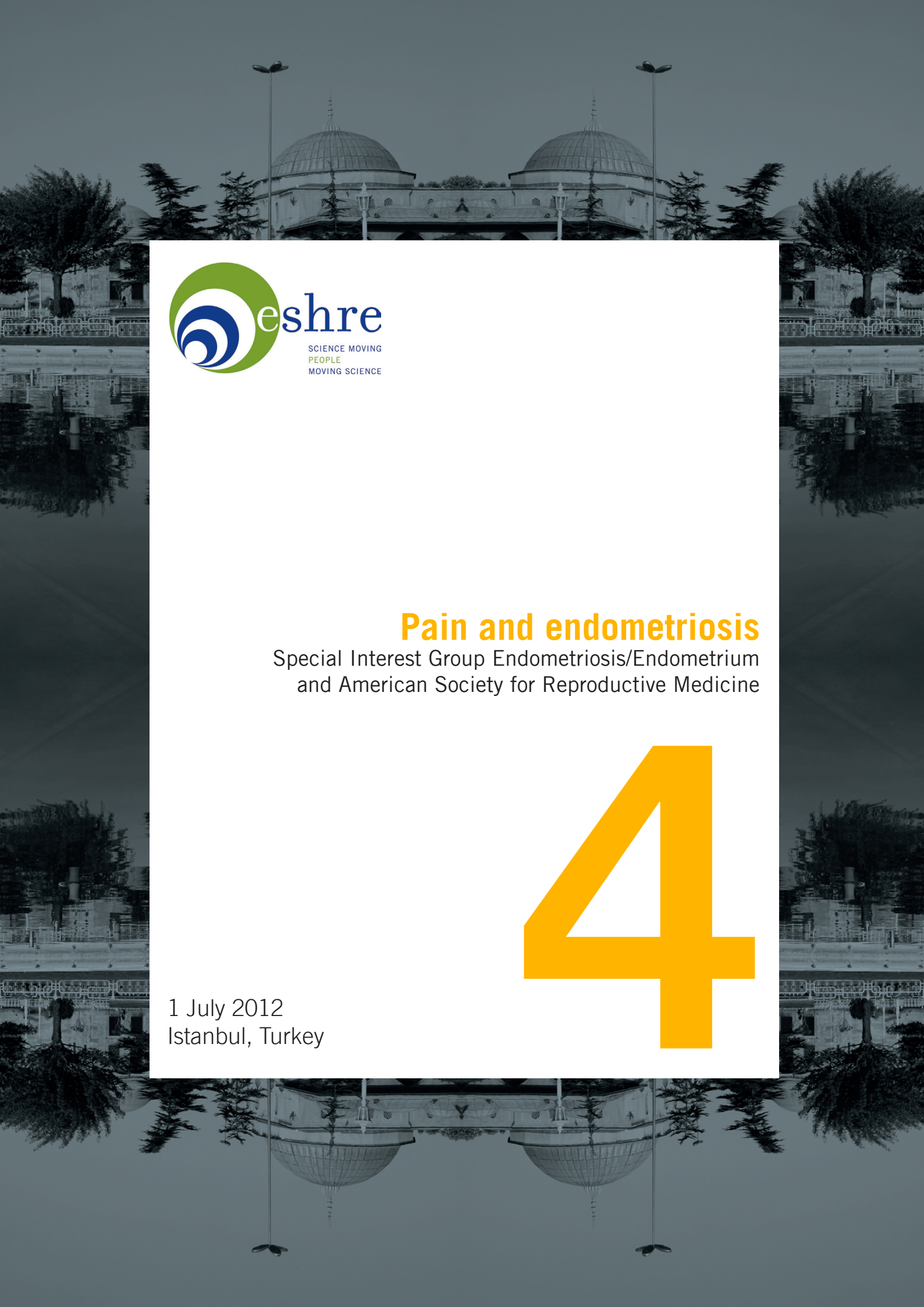


eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

# Pain and endometriosis

Special Interest Group Endometriosis/Endometrium
and American Society for Reproductive Medicine

4

1 July 2012
Istanbul, Turkey


# Pain and endometriosis

**Istanbul, Turkey**
**1 July 2012**

**Organised by**
**the Special Interest Group Endometriosis/Endometriosis and**
**the American Society for Reproductive Medicine**

# Contents

# Course coordinators

Hilary Critchley (United Kingdom), ESHRE SIGEE Coordinator and Pamela Stratton (USA), ASRM representative

# Course description

Pre-congress course will address the area of endometriosis and specifically the symptom of pain. The course will consider clinical issues as well as mechanistic insights and best available evidence for clinical management.

# Target audience

All providers of care for women with endometriosis: including clinicians and scientists (and neuroscientists) with an interest in endometriosis and pain mechanisms. We welcome the attendance of those who provide multi-/ cross-discipline care provision.

# Scientific programme

Chairmen : Hilary Critchley (ESHRE SIG co-ordinator) & Aydin Arici (Turkey)

| | |
|---|---|
| 09.00 - 09.30 | Chronic pelvic pain and endometriosis: Translational evidence of the relationship and implication – **Pamela Stratton (USA)** |
| 09.30 - 09.45 | Discussion |
| 09.45 - 10.15 | Immune-neurovascular interactions in endometriosis – **Robert Taylor (USA)** |
| 10.15 - 10.30 | Discussion |
| 10.30 - 11.00 | Coffee break |
| 11.00 - 11.30 | Progesterone resistance in the endometrium – **Linda Giudice (USA)** |
| 11.30 - 11.45 | Discussion |
| 11.45 - 12.15 | Pain, inflammation, and sex steroids – **Jon Levine (USA)** |
| 12.15 - 12.30 | Discussion |
| 12.30 - 13.30 | Lunch |

Chairmen: Pamela Stratton (ASRM SIG) & Gerard Dunselman (ESHRE SIG-deputy co-ordinator)

| | |
|---|---|
| 13.30 - 14.00 | Myofascial trigger points, pain, and endometriosis: lessons learned from other pain conditions – **Marie Adele Giamberardino (Italy)** |
| 14.00 - 14.15 | Discussion |
| 14.15 - 14.45 | Impact of dyspareunia for women with endometriosis – **Lone Hummelshoj (United Kingdom)** |
| 14.45 - 15.00 | Discussion |
| 15.00 - 15.30 | Coffee break |
| 15.30 - 16.00 | Recommendations for outcome-based clinical trials after surgical treatment of deeply infiltrative endometriosis – **Thomas D'Hooghe (Belgium)** |
| 16.00 - 16.15 | Discussion |
| 16.15 - 16.45 | Medical treatment of endometriosis-associated pain – **Paolo Vercellini (Italy)** |
| 16.45 - 17.00 | Discussion |

ESHRE Pain and Endometriosis :

# Chronic pelvic pain and endometriosis: Translational evidence of the relationship and implications

Pamela Stratton, MD
Head, Gynecology Consult Service
Principal Investigator, Endometriosis Studies

Disclosures: None

## Learning Objectives

At the conclusion of this presentation, participants should be able to

1. Define the terms nociception, sensitization, and myofascial trigger point
2. Describe the role of the central nervous system in pain related to endometriosis
3. Describe ways hormones and surgery may influence pain independent of endometriosis lesions

## Endometriosis in Women:
A hormonally dependent inflammatory disorder

***Symptoms:***

- Subfertility
- Chronic Pelvic Pain:
  - Dysmenorrhea - up to 90%
  - Dyspareunia
  - Non-menstrual Pain
- Dyschezia
- Dysuria
- Pelvic visceral or muscle pain

***Comorbidities or Overlapping Pain Syndromes:***

- Irritable bowel syndrome
- Interstitial cystitis/painful bladder
- Migraines
- Fibromyalgia
- Chronic fatigue syndrome

P. Stratton and K. Berkley, *Hum Reprod Update*, 2011

## Chronic Pelvic Pain Associated with Endometriosis

Character of chronic pelvic pain

- Intermittent or continuous over menstrual cycle
- Dull, throbbing, or sharp
- Exacerbated by physical activity
- Cyclic bladder- and bowel-associated symptoms (nausea, distention, and early satiety)
- Over time, pain worsens or changes in character

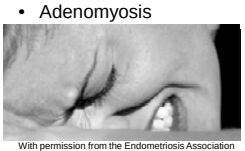
*Infrequently, women report burning or hypersensitivity, symptoms suggestive of neuropathic component*

Giudice L. N Engl J Med 2010
P. Stratton and K. Berkley, *Hum Reprod Update*, 2011

## Chronic Pelvic Pain Associated with Endometriosis Symptoms Overlap

Other gynecologic conditions

- Pelvic inflammatory disease
- Pelvic adhesions
- Ovarian cysts or masses
- Leiomyomata
- Adenomyosis



With permission from the Endometriosis Association

Nongynecologic conditions

- Irritable bowel syndrome
- Inflammatory bowel disease
- Interstitial cystitis
- Myofascial pain
- Depression
- History of sexual abuse

Overlap of symptoms among conditions makes diagnosis of endometriosis difficult, but confounds attributing chronic pelvic pain to endometriosis

P. Stratton and K. Berkley, *Hum Reprod Update*, 2011

## Surgical Treatment of Endometriosis-related Chronic Pelvic Pain

Surgery based on oncologic principle to remove all lesions and restore normal anatomy

- Surgical removal or destruction of lesions alleviates pain
  - Indicates lesions contribute to pain
- Severity of pain or duration of surgical effect does not correlate with extent of disease
  - Patients with least amount of disease experience pain sooner
- Some lesions are more painful than others
  - Surgery benefits those with deeply infiltrating endometriosis
- Complete surgical removal does not relieve symptoms for at least a year in 50% of patients
- In some patients whose pain is relieved, pain returns, without new lesions forming

**P. Stratton and K. Berkley, *Hum Reprod Update*., 2011**

## Hormonal treatments: Endometriosis-related Chronic Pelvic Pain

- Reducing estradiol or influencing progesterone alleviates pain in women with endometriosis
  - Estradiol contributes to pain symptoms
  - Progestagen therapy may decrease pain symptoms
- "Progesterone resistance" important to developing endometriosis
  - Is "progesterone resistance" important in the development of pain from endometriosis?
- Hormone therapy does not alleviate pain in all women
- Leuprolide (GnRH agonist) is effective in relieving pain, regardless of endometriosis

P. Stratton and K. Berkley, *Hum Reprod Update.*, 2011

## Hormonal Treatments
## Effects Beyond the Lesions

Known and studied effects
- Thins endometrium, decreases menstrual flow
- Decidualizes endometrium
- Prevents ovulation
- Decreases uterine contractions

Possible, as yet unstudied effects on pain
- Alterations of CNS activity
- Influences of estrogen and progestagens
- Decreases in blood flow to the uterus or pelvis (GnRH analogues)

P. Stratton and K. Berkley, *Hum Reprod Update.*, 2011

NIH ENDOMETRIOSIS AND PELVIC PAIN STUDY

## Raloxifene: A Designer Estrogen

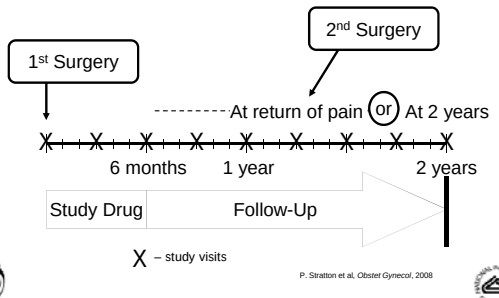
Compare Raloxifene to Placebo after Surgical Excision

- Animal studies- Raloxifene decreases size of endometriosis implants
- Selective estrogen receptor modulator Raloxifene
  - does not stimulate breast or endometrium
  - increases bone mass
  - does not suppress ovarian function
- Raloxifene may inhibit endometriosis growth without lowering estrogen levels

P. Stratton et al, *Obstet Gynecol*, 2008

NIH ENDOMETRIOSIS AND PELVIC PAIN STUDY

## Surgery then Medical Treatment

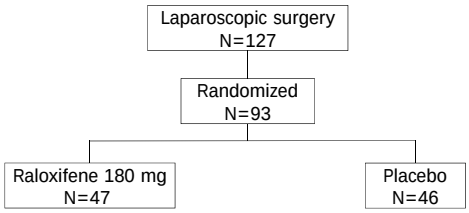



P. Stratton et al, *Obstet Gynecol*, 2008

NIH ENDOMETRIOSIS AND PELVIC PAIN STUDY

## Surgery then Medical Treatment

Study Population



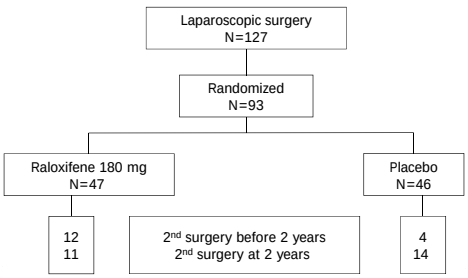

In each group
75% had history of endometriosis
Pain had lasted on average 10 + years
Two-thirds had minimal or mild disease

P. Stratton et al, *Obstet Gynecol*, 2008

NIH ENDOMETRIOSIS AND PELVIC PAIN STUDY

## Surgery then Medical Treatment

Time to Second Surgery



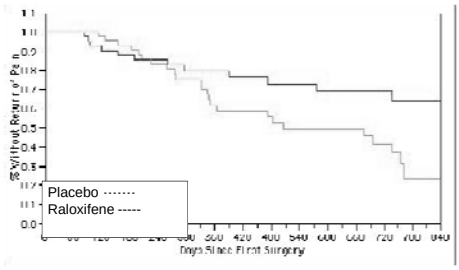

Second surgery sooner with raloxifene p=0.016

P. Stratton et al, *Obstet Gynecol*, 2008

NIH ENDOMETRIOSIS AND PELVIC PAIN STUDY

## Surgery then Medical Treatment

Time to return of pain




P. Stratton, *Obstet Gynecol*, 2008

Return of pain sooner with raloxifene p=0.03

NIH ENDOMETRIOSIS AND PELVIC PAIN STUDY

## Surgery then Medical Treatment

Second surgery findings

| | Biopsy proven Endometriosis | |
|---|---|---|
| | + | - |
| Raloxifene N=23 | 16 | 7 |
| Placebo N=17 | 13 | 4 |

NS

P. Stratton et al, *Obstet Gynecol*, 2008

Biopsy-proven endometriosis NOT associated with return of pain

NIH ENDOMETRIOSIS AND PELVIC PAIN STUDY

## Surgery then Medical Treatment

Conclusions

- Raloxifene taken after complete excision of endometriosis significantly shortened time to return of pain.
- Since many women in both groups had endometriosis at second surgery and endometriosis not associated with return of pain, estrogen and not lesions, per se, may be source of pelvic pain.

P. Stratton et al, *Obstet Gynecol*, 2008

## Endometriosis in Women

- SYMPTOMS:
  - Subfertility
  - Chronic Pain - dysmenorrhea, dyspareunia, dyschezia, pelvic visceral or muscle pain
- Co-occurrence with:
  - Irritable bowel syndrome
  - Interstitial cystitis/painful bladder
  - Migraines
  - Fibromyalgia
  - Chronic fatigue

P. Stratton and K. Berkley, *Hum Reprod Update*, 2011

NIH ENDOMETRIOSIS AND PELVIC PAIN STUDY

### Migraine Headaches

Are women with pelvic pain more likely to have migraine headaches?

- Patients: 108 women with pelvic pain
- Intervention: Headaches classified as migraine or non-migraine using IHS criteria
- Main Outcome: Frequency of migraine headache, non-migraine headache, and without headache in those with and without endometriosis
- Headache cohorts compared for differences in headache frequency and Qol

B. Karp et al, Fertil Steril, 2010

NIH ENDOMETRIOSIS AND PELVIC PAIN STUDY

### Migraine Headaches

Results

- 67% of women with chronic pelvic pain had definite or probable migraine
- An additional 8% of women met criteria for possible migraine
- Migraine no more likely in women with endometriosis than those without
- Lowered quality-of-life, beyond that due to pelvic pain alone, especially likely in women with most frequent headaches
- Strong association suggests common pathophysiology.

B. Karp et al, Fertil Steril, 2010

MRI DIAGNOSIS OF ADENOMYOSIS AND PERSISTENT PAIN

## NIH Endometriosis and Pelvic Pain Study

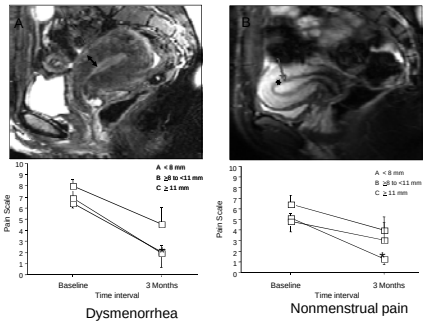
Do women whose pain persists after excision have adenomyosis or a thickened junctional zone on MRI?

- Patients: 53 women with pelvic pain
- Intervention: MRI before surgical excision and histologic diagnosis of endometriosis
- Main Outcome: Junctional zone thickness on preoperative MRIs compared to VAS pain scales at baseline and 3 months

J. Parker, *Fertil. Steril.*, 2006

MRI DIAGNOSIS OF ADENOMYOSIS AND PERSISTENT PAIN

Adenomyosis | Normal Junctional Zone




Dysmenorrhea | Nonmenstrual pain

J. Parker, *Fertil. Steril.*, 2006

MRI DIAGNOSIS OF ADENOMYOSIS AND PERSISTENT PAIN

## Conclusions

- After excision of endometriosis, chronic pelvic pain significantly more likely to persist with JZ thickness > 11mm on preoperative MR imaging.
- Myometrial junctional zone abnormalities or adenomyosis may contribute to chronic pelvic pain in women with endometriosis.

J. Parker, *Fertil. Steril.*, 2006

APPENDICEAL DISEASE IN WOMEN WITH CHRONIC PELVIC PAIN

## NIH Endometriosis and Pelvic Pain Study

Do women with endometriosis have appendiceal disease?

- Patients: 133 women with pelvic pain and possible endometriosis undergoing laparoscopy
- Intervention: Removal of abnormal appendices and literature review
- Main Outcome: Appendiceal abnormalities at laparoscopy

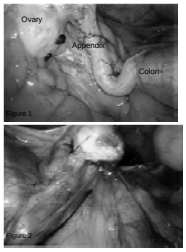
R. Gustofson, *Fertil. Steril.*, 2006

APPENDICEAL DISEASE IN WOMEN WITH CHRONIC PELVIC PAIN

## NIH Endometriosis and Pelvic Pain Study

Results

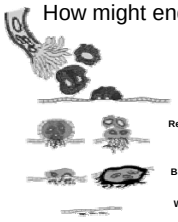
- Of 133, 13 prior appendectomy
- 109 of 120 right lower quadrant pain
- 6 of 109 appendiceal pathology
  - 4 pathology-confirmed endometriosis
  - 1 Crohn's disease
  - 1 chronic appendicitis
- Prevalence this study
  - 4.1% endo (n=97) vs 3.7% RLQ pain
- Prevalence in literature
  - 3.1% biopsy proven endo vs 0.2% general population

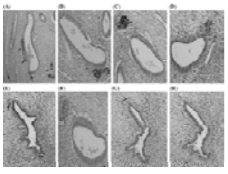





R. Gustofson, *Fertil. Steril.*, 2006

## How might endometriosis be associated with pain?



Tokushige et al. Fertil Steril, 2009
Innervation first reported by Berkley KJ et al, Science, 2005

Endometriosis must be vascularized to survive

Blood vessels innervated by sensory & sympathetic nerves

Do nerves accompany blood vessels as they vascularize, sprouting to innervate endometriosis?

- Yes, both a sensory and a sympathetic supply

## Surgical Treatment of Endometriosis-related Chronic Pelvic Pain

High recurrence of pain symptoms may be due to

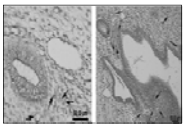
- Remodeling of CNS (some of which occurred before surgery)
- Reproductive tract events reactivating pain
- Incomplete removal (that may also increase pain) due to:
  - Varying technical skill
  - Difficult lesion locations
  - Lack of recognition of variable appearance of lesions
- Recurrence of lesions
- Adhesions
- Pain due to something other than endometriosis

P. Stratton and K. Berkley, *Hum Reprod Update*., 2011

## Endometriosis and Chronic Pelvic pain: Role of the reproductive tract

**Menstruation**
Shed monthly
Heavier in women with endometriosis
Outflow tract obstruction associated with endometriosis

**Endometrium**
May differ in women with endometriosis
Progesterone resistance
Growth factor differences
Nerves or nerve growth factors



Tokushige N, *Fertil Steril*, 2007

Nerves in endometrium of endometriosis patient:
Increased nerve density

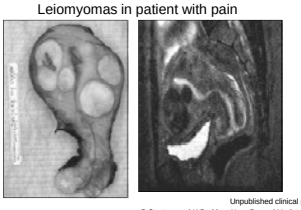
P Stratton and K Berkley, *Hum Reprod Update*, 2011

## Endometriosis and Chronic Pelvic pain Role of the reproductive tract

**Uterus**
Adenomyosis
Leiomyomas

Contractions may differ in women with endometriosis

Leiomyomas in patient with pain

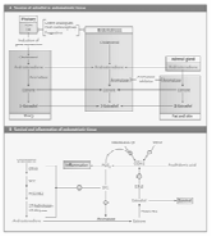


Unpublished clinical photos
P Stratton and K Berkley, *Hum Reprod Update*, 2011

## Endometriosis and Chronic Pelvic pain
### Role of the reproductive tract

**Ovaries and peritoneal fluid**

- Dynamic complex events with ovulation
- Higher peritoneal levels hormonal and inflammatory factors
- May differ in women with endometriosis



Bulun SE. N Engl J Med 2009

P Stratton and K Berkley, *Hum Reprod Update*, 2011

## Endometriosis and Chronic Pelvic pain
### Role of the reproductive tract

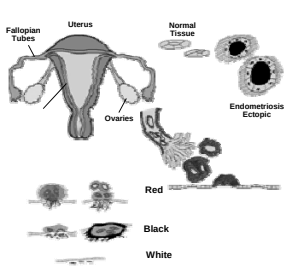
**Pregnancy and delivery**

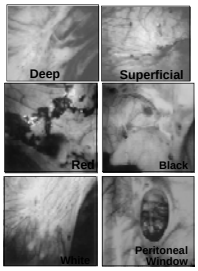
- Pseudopregnancy resolves lesions
- Narrow cervical diameter before delivery
  - May contribute to lesion formation and symptoms
- Wider cervical diameter after delivery
  - may lessen symptoms

Giudice L. N Engl J Med 2010

P Stratton and K Berkley, *Hum Reprod Update*, 2011

## Variable appearance of Endometriosis

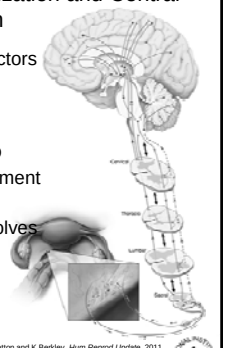



Unpublished clinical photos

- Variable appearance may lead to incomplete removal
- Incomplete removal may increase pain

## Nociception, Peripheral Sensitization and Central Sensitization



Nociceptors - peripheral sensory detectors that respond to noxious stimulus

C-fiber nociceptors - normally 'silent'

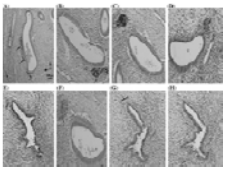
When activated, nociceptors
- convey information to CNS AND
- release factors into local environment

Once activated, C-fibers sensitized
- Not silent after inflammation resolves

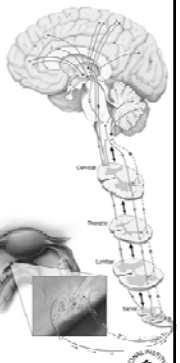
Central sensitization
initiated by peripheral sensitization
maintained by input from sensitized sensory afferent fibers

P Stratton and K Berkley, *Hum Reprod Update*, 2011

## 



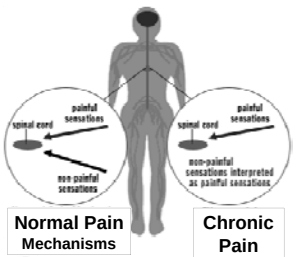
Tokushige et al. Fertil Steril, 2009
Innervation first reported by Berkley KJ et al, Science, 2005



Endometriosis lesions are sometimes innervated
- Two-way communication between lesions and central nervous system initiates and then perpetuates the constellation of pain symptoms
- Engagement of central nervous system results in central sensitization and myofascial dysfunction.

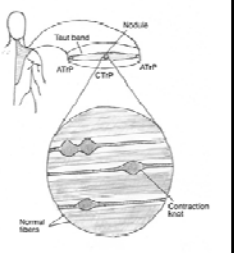
P Stratton and K Berkley, *Hum Reprod Update*, 2011

## Central Sensitization and Myofascial Trigger Points




**Normal Pain Mechanisms**

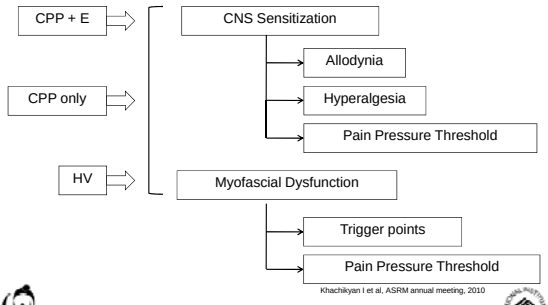
**Chronic Pain**




Trigger Point Complex

NIH NEURAL-IMMUNE STUDY OF ENDOMETRIOSIS AND PELVIC PAIN

## CNS Sensitization and Myofascial Dysfunction




Khachikyan I et al, ASRM annual meeting, 2010

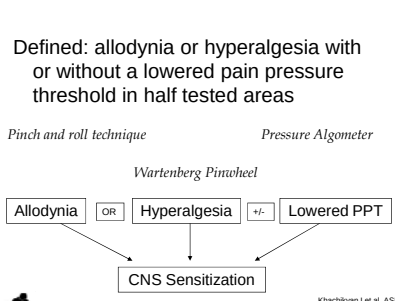
NIH NEURAL-IMMUNE STUDY OF ENDOMETRIOSIS AND PELVIC PAIN

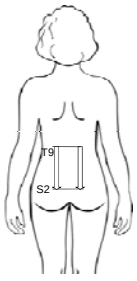
## CNS Sensitization

Defined: allodynia or hyperalgesia with or without a lowered pain pressure threshold in half tested areas

*Pinch and roll technique* *Pressure Algometer*

*Wartenberg Pinwheel*



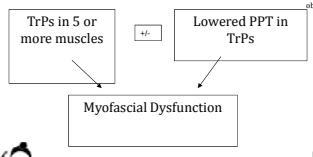

ASRM Fertil Steril 1993

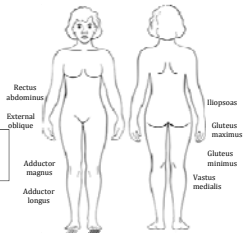
Khachikyan I et al, ASRM annual meeting, 2010

NIH NEURAL-IMMUNE STUDY OF ENDOMETRIOSIS AND PELVIC PAIN

## Myofascial Dysfunction

Defined: myofascial trigger point (TrPs) with or without a lowered pain pressure threshold in 5 or more muscles



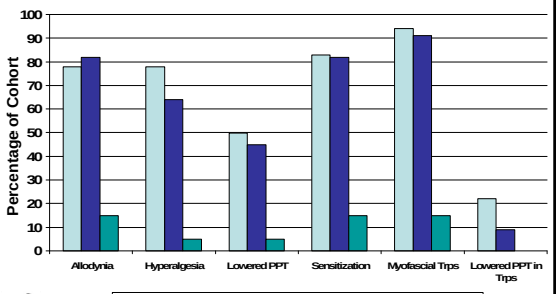




ASRM Fertil Steril 1993

Khachikyan I et al, ASRM annual meeting, 2010

NIH NEURAL-IMMUNE STUDY OF ENDOMETRIOSIS AND PELVIC PAIN

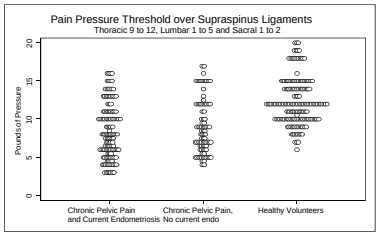
## CNS Sensitization and Myofascial Dysfunction




Khachikyan I et al, ASRM annual meeting, 2010

NIH NEURAL-IMMUNE STUDY OF ENDOMETRIOSIS AND PELVIC PAIN

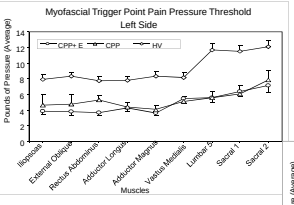
## Supraspinous Ligament Pain Pressure Threshold



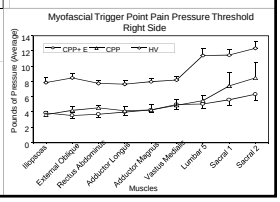

Women with CPP+E and CPP only could tolerate less pressure than healthy volunteers.

NIH NEURAL-IMMUNE STUDY OF ENDOMETRIOSIS AND PELVIC PAIN

## Myofascial Pain Pressure Threshold Results

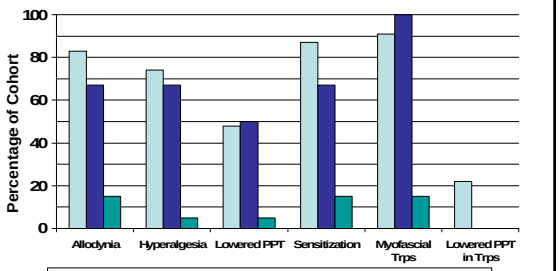



Healthy volunteers have a much higher pain pressure threshold in myofascial trigger points.



NIH NEURAL-IMMUNE STUDY OF ENDOMETRIOSIS AND PELVIC PAIN

## CNS Sensitization and Myofascial Dysfunction




Khachikyan I et al, SGI annual meeting, 2011

## Engaging the Nervous System: Evidence from the ENDO Rat Model

- Uterine horn (ENDO) pieces or fat (shamENDO) transplanted onto abdominal mesentary
- ENDO model develops pain symptoms
  - Vaginal hyperalgesia
  - Increased abdominal muscle activity
- As in women, symptom severity in ENDO rats does not correlate with volume of ectopic growths
- Sensory fibers innervating growths
  - Immunostain with calcitonin gene-related peptide which include C-fiber nociceptors
  - Derived from pre-existing nerve fibers

Vernon and Wilson, Fertil Steril 1985
Berkley et al, Proc Natl Acad Sci 2004

## Engaging the Nervous System: Evidence from the ENDO Rat Model

- In the ENDO model
  - Vaginal hyperalgesia varies with ovarian cycle
  - Paralleled by changes in ectopic cysts
- As severity decreases,
  - Cysts' sympathetic innervation, NGF and VEGF significantly decrease
  - Neural changes do not occur in the rat's eutopic uterus

Cysts directly conveying hormonally modifiable information to the CNS while simultaneously receiving hormonally modifiable information

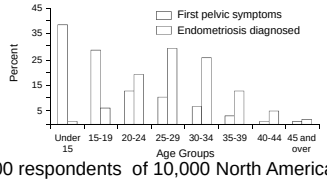
Zhang et al, Am J Physiol Regul Integr Comp Physiol 2008

## Engaging the Nervous System: Evidence from the ENDO Rat Model

- ENDO's effects
  - Greater when estradiol is high
  - Increases ongoing activity in spinal neurons
  - Completely removing cysts abolishes ENDO-induced vaginal hyperalgesia
  - Incompletely removing cysts increases vaginal hyperalgesia
  - Co-existing conditions: Pain behaviors greater in animals with renal stones and ENDO

McGinty et al, Soc Neurosci Abstr, 2009
Zhang et al, Am J Physiol Regul Integr Comp Physiol 2008
McAllister et al, Pain, 2009
Giamberardino et al, Pain 2002

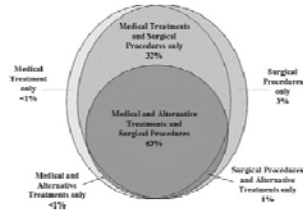
## Endometriosis Association Survey
### Pain – Symptoms to Diagnosis




- ~ 5000 respondents of 10,000 North American members
- Self-reported surgically diagnosed endometriosis
- 67.1% symptoms during adolescence
- Nearly all (98.4%) pelvic pain
- 8 year lag to diagnosis

N Sinai et al. *Hum Reprod 2002*

## Endometriosis Association Survey
### Treatment Utilization for Endometriosis Symptoms

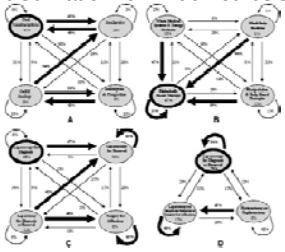



- Of 1,160 women, symptoms average 16 years
- Many (46%) had 3+ medical treatments
- 20% on medication for 10+ years
- Surgical procedures at least 3 times on 42%

N. Sinaii et al, *Fertil.Steril*, 2007

Endometriosis Association Survey

## Treatment Utilization for Endometriosis Symptoms



- 20% hysterectomy or oophorectomy; most successful in improving symptoms N. Sinaii al, *Fertil.Steril*, 2007
- Despite various treatments helpful, women used many types and endured symptoms an average of two decades

Chronic Pelvic Pain associated with Endometriosis:

## Neural network, Innervation, and Pain

- Neural network complex and changeable
  - Alters in response to pain and contributes to symptom chronicity
- For women with endometriosis, nerve fibers
  - Present in endometriosis lesions
  - Increased in myometrium
  - Possibly present in endometrium
- Nerve fibers increased in pain syndromes
  - Lower neuron segments in pelvic pain from other causes
  - Vulvar vestibule in vestibulitis
  - Myometrium in women undergoing hysterectomy for pain
- Other pain syndromes coexist with endometriosis
  - Irritable bowel syndrome
  - Interstitial cystitis
  - Levator spasm

## Other factors affect pain threshold and tolerance

- Menstruation lowers pain threshold and tolerance
- In menopause, women taking estrogen more sensitive to pain than those not taking estrogen
- Women with greater sensitivity to pain in distant sites have less pain relief after surgery
- Higher scores on catastrophization testing associated with poorer outcomes after laparoscopic treatment of endometriosis

## Rethinking the assessment of endometriosis and pain

- Endometriosis differs biologically among women
- Adjacent organ systems share neural networks

Challenge for clinicians

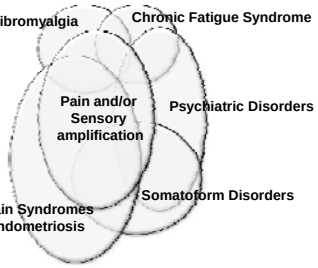
- Think beyond role of endometrial implants
- Take into account multiple factors that can influence pain perception

## Endometriosis and Chronic Pelvic Pain

*…a Central Sensitivity Syndrome*

***Clinical Presentation***

- Multifocal Pain
- Somatic Symptoms:
  - Fatigue
  - Insomnia
  - Cognitive/memory problems
  - Psychological distress
  - Depression
  - Anxiety




***Pathophysiology***

Central Nervous System pain and central sensitization

Clauw and Chrousos, Neuroimmunomodulation. 1997; 4:134-53
Clauw Physical Medicine & Rehabilitation 2010;2:414-430

## Clinical entities currently considered parts of the spectrum of central sensitivity syndrome

- Fibromyalgia
- Chronic Fatigue syndrome (CFS)
- Irritable bowel syndrome and other functional gastrointestinal disorders
- Temporomandibular joint disorder
- Restless leg syndrome and periodic limb movements in sleep
- Idiopathic low back pain
- Multiple chemical sensitivity
- **Primary dysmenorrhea**
- Headache (tension>migraine, mixed)
- Migraine
- Interstitial cystitis/chronic prostatitis/painful bladder syndrome
- **Chronic pelvic pain and endometriosis**
- Myofascial pain syndrome/regional soft-tissue pain syndrome

Clauw Physical Medicine & Rehabilitation 2010;2:414-430

## Any combination may be present in a given individual

| Peripheral (nociceptive) | Neuropathic | Central (non-nociceptive) |
|---|---|---|
| Inflammation or mechanical damage in all tissues | Damage or entrapment of peripheral nerves | Characterized by central disturbance in pain processing (diffuse hyperalgesia) |
| NSAID, opioid responsive | Responds to both peripheral (NSAIDs, opioids, Na channel blockers) and central (TCA's, neuroactive compounds) pharmacological therapy | Tricyclic, neuroactive compounds most effective |
| Responds to procedures | | Behavioral factors more prominent |
| Behavioral factors minor | | Classic examples: Fibromyalgia, Irritable bowel syndrome, Tension headache, Idiopathic low back pain |
| Classic examples: Osteoarthritis, Rheumatoid arthritis, Cancer pain | | |

Which combination exists in women with endometriosis and chronic pelvic pain?
How do hormones or surgery for endometriosis relate to these types of pain?

Clauw Physical Medicine & Rehabilitation 2010;2:414-430

USE OF BOTULINUM TOXIN A TO TREAT CHRONIC PELVIC PAIN

## NIH Endometriosis and Pelvic Pain Study

For women with persistent pelvic floor spasm, will Botulinum toxin a injection treat pelvic pain?

- Patients: 3 women with persistent pelvic pain and pelvic floor spasm
- Intervention: 100 units of Botulinum toxin A injected into muscles with palpable spasm under EMG guidance; 3-5 injection sites
- Main Outcome: Assessment of relief
  - Pain lessened, physical limitations improved, need for narcotics lessened, resumed work

Clinical trial of botulinum toxin A in women with endometriosis will begin soon

M. Merideth, SGI, 2006

## Rethinking the Assessment of Endometriosis and Pain: Implications for practice

- Standard bimanual examination confuses pain signals from the pelvic floor, abdominal wall, bladder and other viscera
- Pain-oriented assessment is mandatory
- Vaginal exam: single digital examination
  - map areas that are tender
  - consider size, shape, mobility of structures

## Pain Syndromes Associated with Endometriosis: Summary

- Treatments have focused on endometriosis lesions assuming lesions correlate with symptoms
- Surgical treatments are aimed at reducing lesions and restoring normal anatomy.
- Surgical treatment helpful in deeply infiltrating lesions
  - Lesions sometimes innervated
- After surgery, patients with least amount of endometriosis experience pain sooner than others
  - Women may be sensitized

## Pain Syndromes Associated with Endometriosis: Summary

- Pain syndromes associated with endometriosis reflect an engagement of the central nervous system.
- The initiation and, over time, the development of peripheral and then central sensitization is likely associated with
  - Endometriosis-associated hormonal changes such as progesterone resistance, aromatase in tissues
  - Higher peritoneal hormone and inflammatory factor levels
  - Innervation of some lesions

## Pain Syndromes Associated with Endometriosis: Summary

- For those undergoing surgery, recurrence of endometriosis-related pain syndromes may be decreased by
  - Complete surgical resection of endometriosis lesions, especially deep lesions that may be innervated
  - Treating potential contributors to pelvic pain noted at surgery, such as removing appendix, lysing adhesions
  - Timing surgery during follicular phase or suppressing reproductive tract events for weeks after surgery to decrease risk of lesion recurrence

## Pain Syndromes Associated with Endometriosis: Summary

- For those using medical approaches, recurrence of endometriosis-related pain syndromes may be decreased by
  - Using hormonal treatments to modify reproductive tract events thereby decreasing local peritoneal inflammation and cytokine production
  - Engaging in multidisciplinary approaches to treat myofascial dysfunction as well as sensitization, such as physical therapy, botulinum toxin a
  - Identifying and treating other chronic pain conditions such as migraines, irritable bowel syndrome, painful bladder syndrome


## Acknowledgments

Reproductive Endocrinology Staff /Fellows
- Barbara Stegmann, MD
- Alicia Armstrong, MD
- Bill Catherino, MD, PHD
- Rose Christian, MD
- Alan Decherney, MD
- John Fratterelli, MD
- Rob Gustofson, MD
- Rhonda Hearns-Stokes, MD
- Mark Leondires, MD
- Andy Levi, MD
- Cindy Murdock, MD
- Adrienne Neithardt, MD
- Jason Parker, MD
- Mark Payson, MD
- James Segars, MD
- Craig Winkel, MD
- Erin Wolff, MD

Data management staff
- Louis Battuello
- Linda Hazlehurst
- Asma Idress
- Shelly Mashburn
- Pat Moyer, PhD
- Tim Stitely

All of the patients who participated to find a new treatment

Endometriosis Association

Operating Room nurses
- Barb Gallagher
- Jose Garcia
- Maureen George
- Jeanne O'Donnell
- Yolanda Redding
- Marru Rodriguez
- Tessa Rodriguez
- Juanita Washington

Research staff
- Albert Hsu, MD
- Barbara Frank, MD
- Julieanne Gemmill
- Heidi Godoy, MD
- Alma Christina Gonzalez
- Rebecca Greene
- Nadine Idress, MD
- Emily Japp
- Izabella Khachikyan, MD
- Shannon Liu
- Nancy Kim
- Somjate Manipalviratn, MD
- Vanessa Lopez
- Sheila Mahoney, CNM
- Kelly Morrissey, MD
- Tam Nguyen
- Katie Plumb
- Clariss Potlog-Nahari, MD
- Stacey Spechler
- Victoria Shanmugan, MD

Statisticians
- Delores Koziol, Ph.D
- Ninet Sinaii, Ph.D
- Robert Wesley, Ph.D

RBMB staff
- George Chrousos, MD
- Lynnette Nieman, MD

Pathology
- Norio Azumi, MD
- Maria Merino, MD

Radiology
- Catherine Chow, MD
- Ahalya Premkumar, MD
- James Reynolds, MD

Neurology
- Barbara Karp, MD

Physiatry
- Jay Shah, MD

Clinical Center nurses
- Janice Wilson, RN
- Donna Hardwick, RN
- Lois Sarachman, RN
- Carolyn Zimmer, RN


## References


- Management of endometriosis in the presence of pelvic pain. The American Fertility Society. Fertility and sterility 1993;60:952-5.
- American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertility and Sterility 1997;67:817-21.
- Berkley KJ, Dmitrieva N, Curtis KS, Papka RE. Innervation of ectopic endometrium in a rat model of endometriosis. Proc Natl Acad Sci U S A 2004;101:11094-8.
- Berkley KJ, Rapkin AJ, Papka RE. The pains of endometriosis. Science (New York, NY 2005;308:1587-9.
- Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 1997;4(3):134-153
- Clauw DJ. Perspectives on fatigue from the study of chronic fatigue syndrome and related conditions. PM & R : the journal of injury, function, and rehabilitation 2010;2:414-30.

# References


- Giamberardino MA, Berkley KJ, Affaitati G, Lerza R, Centurione L, Lapenna D *et al.* Influence of endometriosis on pain behaviors and muscle hyperalgesia induced by a ureteral calculosis in female rats. Pain 2002;95:247-57.
- Giudice LC. Clinical practice. Endometriosis. The New England journal of medicine.2011;362:2389-98.
- Gustofson RL, Kim N, Liu S, Stratton P. Endometriosis and the appendix: a case series and comprehensive review of the literature. Fertility and sterility 2006;86:298-303.
- Herzog AJ, McGinty KA, McAllister SL, Dmitrieva N, Berkley KJ. Endometriosis (ENDO) in the rat: upregulation of ER in spinal cord but not afferent fibers innervating the ectopic growths contribute to estrous differences in the severity of ENDO-induced vaginal hyperalgesia. In: Society for Neuroscience, 2010. Washington, DC, 2010.
- Khachikyan I, Sinaii N, Shah J, Ortiz R, Segars J, Stratton P. CNS sensitization and myofascial dysfunction in patients with endometriosis and chronic pelvic pain Fertility and sterility 2010;94: S40.


# References


- Khachikyan I, Sinaii N, Shah J, Ortiz R, Segars J, Stratton P. CNS sensitization and myofascial dysfunction in patients with endometriosis and chronic pelvic pain. In: Society for Gynecologic Investigation. Miami Beach, FL, 2011.
- McAllister SL, McGinty KA, Resuehr D, Berkley KJ. Endometriosis-induced vaginal hyperalgesia in the rat: role of the ectopic growths and their innervation. Pain 2009;147:255-64.
- McGinty KA, Zhang G, McAllister SL, Herzog AJ, Crampton LJ, Dmitrieva N *et al.* Endometriosis (ENDO) and co-morbidity with bladder dysfunction in the rat: influence of ENDO and shamENDO on spinal c-Fos expression induced by distention of the uninflamed and inflamed bladder. In: Society for Neuroscience. Washington, D.C., 2009.
- Parker JD, Leondires M, Sinaii N, Premkumar A, Nieman LK, Stratton P. Persistence of dysmenorrhea and nonmenstrual pain after optimal endometriosis surgery may indicate adenomyosis. Fertility and sterility 2006;86:711-5.


# References


- Shah JP, Gilliams EA. Uncovering the biochemical milieu of myofascial trigger points using in vivo microdialysis: an application of muscle pain concepts to myofascial pain syndrome. Journal of bodywork and movement therapies 2008;12:371-84.
- Stratton P, Berkley KJ. Chronic pelvic pain and endometriosis: translational evidence of the relationship and implications. Human reproduction update 2011.
- Tokushige N, Markham R, Russell P, Fraser IS. High density of small nerve fibres in the functional layer of the endometrium in women with endometriosis. Human reproduction (Oxford, England) 2006;21:782-7.
- Tokushige N, Markham R, Russell P, Fraser IS. Different types of small nerve fibers in eutopic endometrium and myometrium in women with endometriosis. Fertility and sterility 2007;88:795-803.
- Zhang G, Dmitrieva N, Liu Y, McGinty KA, Berkley KJ. Endometriosis as a neurovascular condition: estrous variations in innervation, vascularization, and growth factor content of ectopic endometrial cysts in the rat. American journal of physiology 2008;294:R162-71.

# References


- Stratton P, Sinaii N, Segars J, Koziol D, Wesley R, Zimmer C, Winkel C, Nieman LK. Return of chronic pelvic pain from endometriosis after raloxifene treatment: a randomized controlled trial. Obstet Gynecol. 2008 Jan;111(1):88-96.
- 22. Karp BI, Sinaii N, Nieman LK, Silberstein SD, Stratton P. Migraine in Women with Chronic Pelvic Pain with and without Endometriosis. Fertil Steril 2011 95(3):895-9; Epub 2010, Dec 8.

# Immune-Neurovascular Interactions in Endometriosis

**Pre-Congress Course**
**ESHRE 2012**

**Robert N. TAYLOR, MD PhD**
**Vice Chair for Research**
**Dept. of Obstetrics and Gynecology**
**Wake Forest School of Medicine**
**Winston-Salem, NC, USA**

## No Conflicts of Interest

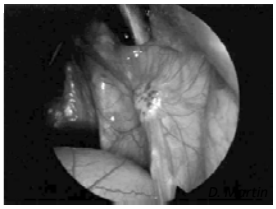
## Objectives

1. **Consider the key cell types: endometrial, immune, neuronal and vascular, that contribute to endometriosis pain and pathophysiology**
2. **Integrate cellular signals and pathways that represent possible targets for novel diagnostics and therapeutics for endometriosis**

## Endometriosis: Definition, Pathogenesis and Prevalence

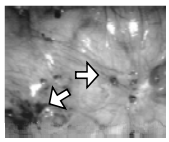
**Islands of hormonally functional endometrial tissue in extrauterine sites; inflammation around implants**

**>176 million cases, >€50 billion in annual global costs**

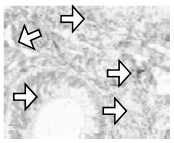


Adamson et al., 2010

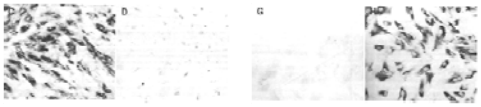
## Endometriosis: Characterization and Isolation of Multiple Cell Types



epithelial stromal

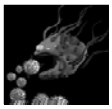


epithelial stromal



**anti-cytokeratin** **anti-vimentin**

## Pathogenesis of Endometriosis

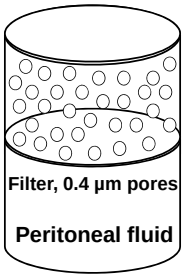


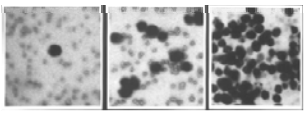



Ryan & Taylor, 1997
Asante & Taylor, 2011

## Boyden Chamber Assay Reveals Chemokine Activity in Peritoneal Fluid

**U937 cells in 0.1% BSA**

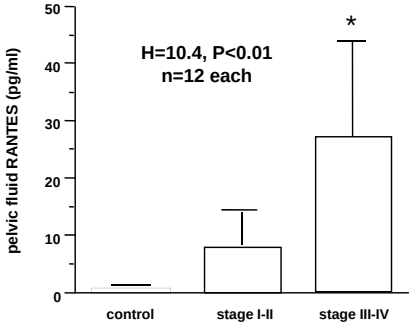


**normal** **stage I** **stage IV**

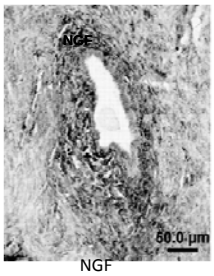
Hornung et al., 2001

## RANTES in Peritoneal Fluid

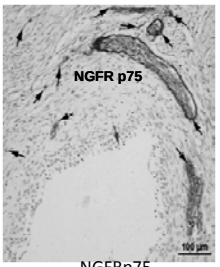



Khorram et al., 1993

## NGF and NGFR p75 are Expressed in Endometriosis Lesions



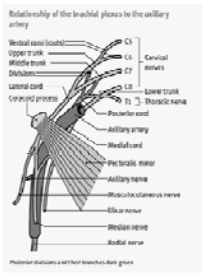

NGF



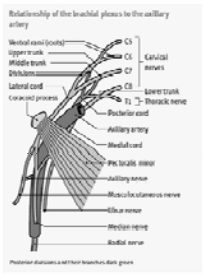

NGFRp75

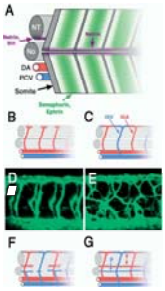
Tokushige et al., 2006

## Brachial Plexus and Zebrafish?



## Brachial Plexus and Zebrafish?





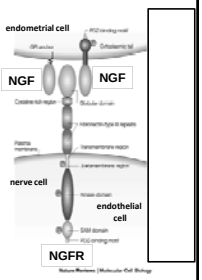

Weinstein, 2005

## "Neuroangiogenic" Ligand-Receptor Pairs Expressed in Endometrium

| Ligand | Receptor | Reference |
|---|---|---|
| NGF | NGFR p75, TrkA | Tokushige et al., 2006 |
| VEGF | VEGFR1/2, neuropilin | Shifren et al., 1996 |
| ephrin A1 | Eph | Kao et al., 2003 |
| SLIT | ROBO | Shen et al., 2009 |
| semaphorin 3c | neuropilin | Kao et al., 2003 |
| netrin | DCC/neogenin | Kato et al., 2004 |

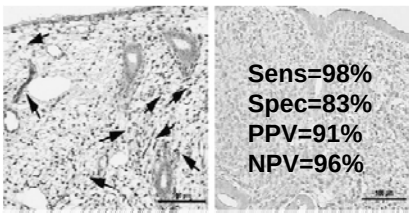
## "Neuroangiogenic" Ligand-Receptor Pairs Expressed in Endometrium

| Ligand | Receptor |
|---|---|
| NGF | NGFR p75, TrkA |
| VEGF | VEGFR1/2, neuropilin |
| ephrin A1 | Eph |
| SLIT | ROBO |
| semaphorin 3c | neuropilin |
| netrin | DCC/neogenin |




axon and vessel guidance

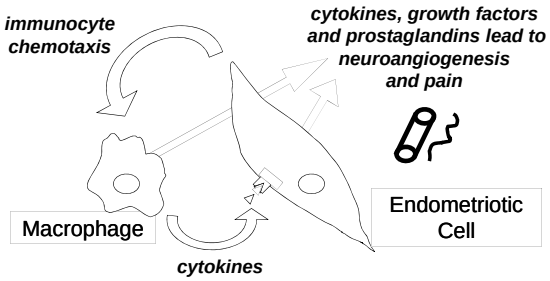
## Nerve Fibers (PGP9.5) are Present in the Eutopic Endometrium of Women with Endometriosis



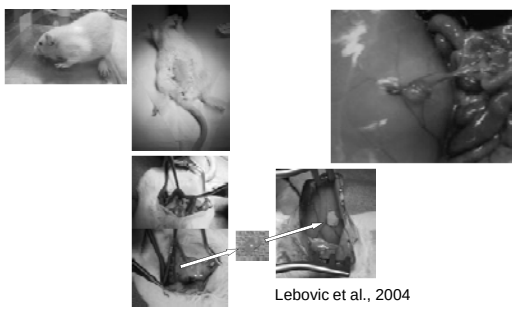

**Endometriosis** **Normal**

Tokushige et al., 2006, Bokor et al., 2009
Al-Jefout et al., 2009

## Pathogenic Vicious Cycle: Multi-Cell Hypothesis

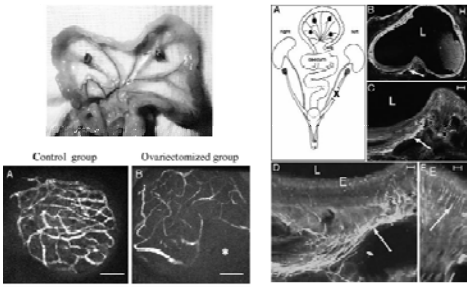


## Surgical Induction of "Endometriosis" in the Rat



Lebovic et al., 2004

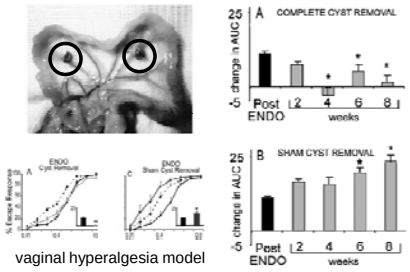
## Evidence of Neuroangiogenesis in Rat "Endometriosis"




intravital fluorescence microscopy
Katayama et al., 2010

PGP9.5-positive nerves
Berkley et al., 2004

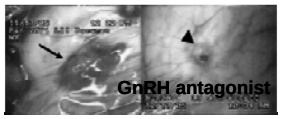
## Removal of "Endometriotic" Lesions Reduces "Dyspareunia" in the Rat

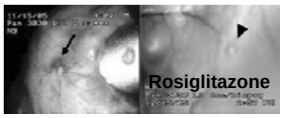



vaginal hyperalgesia model

McAllister et al., 2009

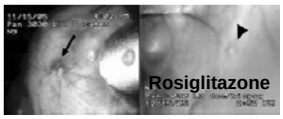
## Baboon Model of Endometriosis: Rosiglitazone Decreases Lesion Size

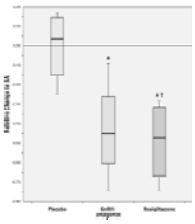



Lebovic et al., 2007

## Baboon Model of Endometriosis: Rosiglitazone Decreases Lesion Size

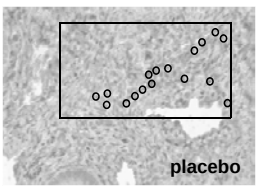



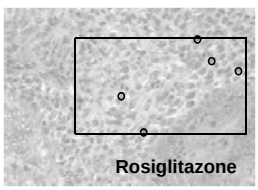



**SA pre-SA post/SA pre**

Lebovic et al., 2007

## Nerve Fiber (PGP9.5) Density in Baboon Endometrium



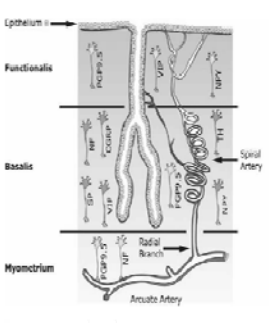




**Thiazolidinediones reduce PGP9.5+ fibers in baboon endometrium (Lebovic, Yu & Taylor, in progress)**

**Endometriosis is cellularly complex and derives via a combination of genetic, biomechanical, endocrine, immune and environmental (epigenetic) mechanisms.**

**Integrated neural and vascular cell recruitment ("neuroangiogenesis") leads to establishment of nociceptive afferents.**

**New therapies targeting neuroangiogenic elements may be promising for pain relief.**




**Supported by NIH/NICHD grant U01-HD66439**

## Endometriosis Research Team

**Wake Forest and Emory University Schools of Medicine**

**References**:

Adamson GD, Kennedy SH, Hummelshoj L. Creating solutions in endometriosis: global collaboration through the World Endometriosis Research Foundation. J Endometriosis 2010;2:3-6.

Al-Jefout M, Dezarnaulds G, Cooper M, Tokushige N, Luscombe GM, Markham R, Fraser IS. Diagnosis of endometriosis by detection of nerve fibres in an endometrial biopsy: a double blind study. Hum Reprod. 2009;24:3019-24.

Asante A, Taylor RN. Endometriosis: the role of neuroangiogenesis. Annu Rev Physiol. 2011;73:163-82.

Berkley KJ, Dmitrieva N, Curtis KS, Papka RE. Innervation of ectopic endometrium in a rat model of endometriosis. Proc Natl Acad Sci U S A. 2004;101:11094-8.

Bokor A, Kyama CM, Vercruysse L, Fassbender A, Gevaert O, Vodolazkaia A, De Moor B, Fülöp V, D'Hooghe T. Density of small diameter sensory nerve fibres in endometrium: a semi-invasive diagnostic test for minimal to mild endometriosis. Hum Reprod. 2009;24:3025-32.

Hornung D, Bentzien F, Wallwiener D, Kiesel L, Taylor RN. Chemokine bioactivity of RANTES in endometriotic and normal endometrial stromal cells and peritoneal fluid. Mol Hum Reprod. 2001;7:163-8.

Kao LC, Germeyer A, Tulac S, Lobo S, Yang JP, Taylor RN, Osteen K, Lessey BA, Giudice LC. Expression profiling of endometrium from women with endometriosis reveals candidate genes for disease-based implantation failure and infertility. Endocrinology. 2003;144:2870-81.

Katayama H, Katayama T, Uematsu K, Hiratsuka M, Kiyomura M, Shimizu Y, Sugita A, Ito M. Effect of dienogest administration on angiogenesis and hemodynamics in a rat endometrial autograft model. Hum Reprod. 2010;25:2851-8.

Kato HD, Kondoh H, Inoue T, Asanoma K, Matsuda T, Arima T, Kato K, Yoshikawa T, Wake N. Expression of DCC and netrin-1 in normal human endometrium and its implication in endometrial carcinogenesis. Gynecol Oncol. 2004;95:281-9.

Khorram O, Taylor RN, Ryan IP, Schall TJ, Landers DV. Peritoneal fluid concentrations of the cytokine RANTES correlate with the severity of endometriosis. Am J Obstet Gynecol. 1993;169:1545-9.

Lebovic DI, Kir M, Casey CL. Peroxisome proliferator-activated receptor-gamma induces regression of endometrial explants in a rat model of endometriosis. Fertil Steril. 2004;82 (Suppl 3):1008-13.

Lebovic DI, Mwenda JM, Chai DC, Mueller MD, Santi A, Fisseha S, D'Hooghe T. PPAR-gamma receptor ligand induces regression of endometrial explants in baboons: a prospective, randomized, placebo- and drug-controlled study. Fertil Steril. 2007;88(Suppl 4):1108-19.

McAllister SL, McGinty KA, Resuehr D, Berkley KJ. Endometriosis-induced vaginal hyperalgesia in the rat: role of the ectopic growths and their innervation. Pain. 2009;147:255-64.

Ryan IP, Taylor RN. Endometriosis and infertility: new concepts. Obstet Gynecol Surv. 1997;52:365-71.

Shen F, Liu X, Geng JG, Guo SW. Increased immunoreactivity to SLIT/ROBO1 in ovarian endometriomas: a likely constituent biomarker for recurrence. Am J Pathol. 2009;175:479-88.

Shifren JL, Tseng JF, Zaloudek CJ, Ryan IP, Meng YG, Ferrara N, Jaffe RB, Taylor RN. Ovarian steroid regulation of vascular endothelial growth factor in the human endometrium: implications for angiogenesis during the menstrual cycle and in the pathogenesis of endometriosis. J Clin Endocrinol Metab. 1996;81:3112-8.

Tokushige N, Markham R, Russell P, Fraser IS. High density of small nerve fibres in the functional layer of the endometrium in women with endometriosis. Hum Reprod. 2006;21:782-7.

Tokushige N, Markham R, Russell P, Fraser IS. Nerve fibres in peritoneal endometriosis. Hum Reprod. 2006;21:3001-7.

Weinstein BM. Vessels and nerves: marching to the same tune. Cell. 2005;120:299-302.

# Progesterone Resistance in the Endometrium

ESHRE Pre-Congress Course 4
*SIG Endometriosis/Endometrium and ASRM*

Linda C. Giudice, MD, PhD
The Robert B. Jaffe MD Endowed Professor and Chair
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Disclosures: Nothing to disclose

## Learning Objectives

- To understand progesterone and progestin actions in endometrial tissue.
- To understand what progesterone resistance is and mechanisms underlying it in endometrium and endometriosis lesions of women with endometriosis.
- To learn about medical therapies containing progestins for management of dysmenorrhea and pelvic pain associated with endometriosis.
- To explore if progesterone resistance has a role in persistent pain associated with endometriosis.

## Endometriosis

- Estrogen-dependent, progesterone-resistant, inflammatory disorder.
- Epidemiology (*Eskenazi 1998; Missmer 2003; 2004a,b*)
  - 6% to 10% of women in general (>100 M women worldwide; teens)
  - **50-70% of women with pelvic pain**
  - **30-50% of women with infertility**
  - 10% of women with endometrioid ovarian cancer
  - **Risks**
    - **increased:** menarche < 10 y.o., low birth wt (<5.5 lb), BMI >25, nullparity, *in utero* DES exposure, + FHx Caucasian, Asian > African American, Hispanic
    - **decreased:** smoking, lactation > 23 mos, parity > 3 children
- time to Dx (surgery): 8-11 yrs from 1st symptoms *(Hadfield et al 1996)*
- estimated U.S. costs for Dx + Rx in 2002 $22B (*Simeons 2012*).
- major health care problem.

*Bulun 2009; Giudice 2010*

## Progesterone Actions in Human Endometrium

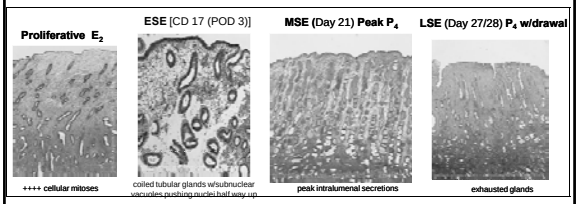
**Progesterone**

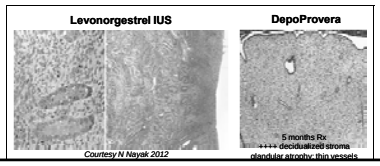
- inhibits actions of $E_2$ in endometrium
- inhibits endometrial cellular DNA synthesis and cell proliferation
- promotes endometrial epithelial differentiation to the secretory phenotype via paracrine actions on stromal fibroblasts
- promotes differentiation (decidualization) of stromal fibroblasts
- anti-inflammatory- inhibition of NfκB, IL-1, RANTES
- inhibits angiogenesis
- acts through PRA, PRB (membrane PR?)
- intersects with PKA/other pathways - uncertain mechanisms

*Bulun 2009*

## Effects of Progesterone and Progestins on Human Endometrium: Histology

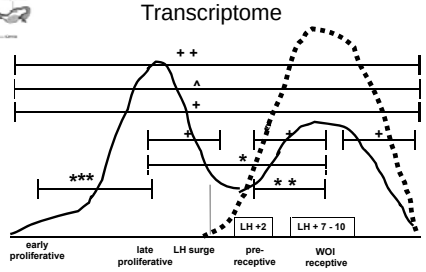
*www.pathologypics.com; Creative Commons License*




*Courtesy N Nayak 2012*

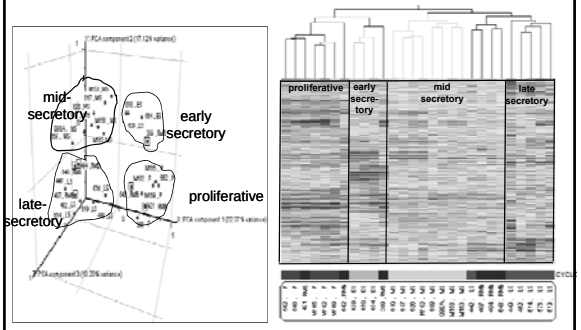
## Steroid Hormone Effects on the Endometrial Transcriptome




* *Kao, et al, 2002, 2003; Borthwick et al, 2003; Ace & Oculicz, 2004*
** *Carson et a 2002; Riesewijk et al, 2003; Horcajadas et al, 2004*
*** *Punyadeera, et al, 2005*
^ *Ponnampalan, et al, 2006*
\+ *Talbi, Hamilton, et al, 2006*
++ *Burney, et al, 2007*

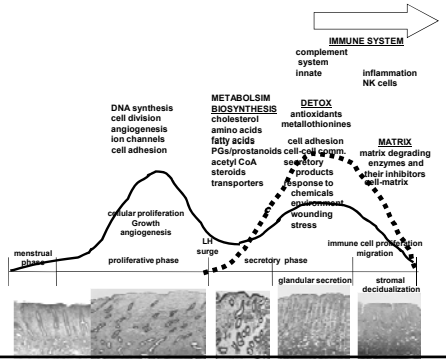
## The Transcriptome of Human Endometrium

Samples Cluster into Cycle Phases; Unique Molecular Profiles

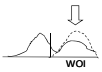



*Talbi, Hamilton, et al, 2006*

## Molecular Events In Response to Progesterone Action and Withdrawal in Human Endometrium



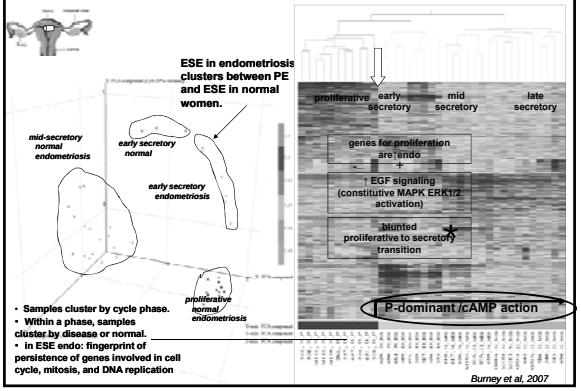

## Early Signs of a Difference of Endometrium in Women with Endometriosis




- altered PR-A:PR-B ratio
- reduced $a_v b_3$ integrin and LIF expression in the window of implantation (WOI).
- lack of IL-11 and IL-1 RA expression in the WOI
- decreased HoxA10 expression due to hyper-methylation of the HoxA10 promoter, reflecting a decrease in $P_4$ action on the endometrium.

*Cakmak & Taylor 2010*

## Endometrial Transcriptome in Endometriosis




- Samples cluster by cycle phase.
- Within a phase, samples cluster by disease or normal.
- In ESE endo: fingerprint of persistence of genes involved in cell cycle, mitosis, and DNA replication

*Burney et al, 2007*

## Persistence of Proliferative Phenotype in ES Phase

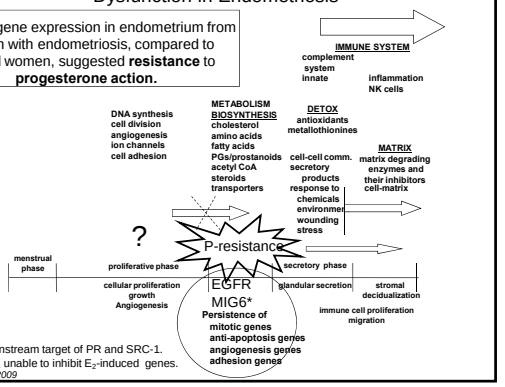
Enriched GO categories in severe endo vs normal subjects

| | Biological Processes | Molecular Functions | Cellular Components |
|---|---|---|---|
| Increased | **N = 53 total processes**<br>Mitotic spindle elongation (100)<br>Spindle checkpoint (50)<br>Spindle organization/biogenesis (50)<br>Traversing start control point (42.8)<br>Mitotic checkpoint (38.5)<br>Deoxyribonucleotide metabolism (25)<br>DNA integrity checkpoint (25)<br>DNA damage checkpoint (25)<br>Chromosome cycle (23)<br>DNA replication initiation (22.7)<br>G2/M transition of cell cycle (18)<br>Mitosis (16.5) | Double stranded DNA binding<br>Nucleotide binding<br>ATP binding<br>ATPase activity<br>Oxidoreductase activity<br>Ribonucleoside diphosphate reductase activity<br>Small protein activating enzyme activity<br>Ubiquitin like activating enzyme activity<br>Protein kinase activity<br>Microtubule motor activity | Chromosome/chromatin<br>Kinetochore<br>Cytoskeleton<br>Microtubule cytoskeleton<br>Spindle microtubule<br>Microtubule associated complex<br>Kinesin complex<br>Intracellular organelle<br>Nucleus<br>Nuclear lamina<br>Non-membrane bound organelle |
| Decreased | Regulation of neurotransmitter lvls<br>Homeostasis: cell, ion, copper, inorganic cation<br>Actin filament bundle formation<br>Cholesterol biosynthesis<br>Protein-cofactor linkage<br>Transport: organic, carboxylic acid | Cadmium ion binding<br>Copper ion binding<br>Monocarboxylate porter activity<br>Transport activity: sulfate, organic acid, carboxylic acid, monocarboxylic acid | Cell fraction<br>Membrane fraction<br>Membrane |

*Burney et al,2007*

## Summary of Events Across the Cycle from Microarray Analyses Dysfunction in Endometriosis

Aberrant gene expression in endometrium from women with endometriosis, compared to normal women, suggested **resistance** to **progesterone action.**




*MIG6 downstream target of PR and SRC-1.
Renders $P_4$ unable to inhibit $E_2$-induced genes.

*Jeong et al, 2009*

## Progesterone Resistance

- **What is is?**

normal $P_4$ levels elicit an abnormal or reduced response to $P_4$

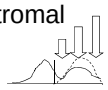
- **What could be causing it?**
- **Where does it occur in the endometrium?**
- **Does $P_4$ resistance have any relevance to pain?**

## Progesterone "Resistance" In Endometriosis

Intrinsic to endometrial cells in both ectopic and eutopic endometrium in women with endometriosis.

- Numerous genes are dysregulated in the WOI *(Kao et al 2002)* and in PE, ESE, MSE in endometrium in women with endometriosis *(Burney et al 2007)*.
- Altered PRA:PRB ratio may account for the variable effectiveness of progestins in the treatment of endometriosis *(Bulun 2009)*
- In vitro treatment of endometrial stromal cells with progestin fails to fully suppress matrix metalloproteinase (MMP) secretion *(Bruner-Tran et al 2002)*.
- Endometrial stromal cells from eutopic endometrium and ectopic lesions have impaired decidualization *in vitro* (IGFBP1 and PRL) in response to cAMP *(Klemmt et al, 2006; Aghajanova et al, 2010a)* and $P_4$ *(Aghajanova et al, 2011)*.
- PR polymorphisms resulting in PR dysfunction *(Treolar et al, 2005).*
- Abnormal regulation of PR co-modulators *(Bulun 2009; Zelenko et al, 2012)*.
- Relationship to $E_2$ and inflammation *(Frank 1996; Bulun 2009).*

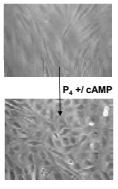
## Decidualization of Endometrial Stromal Fibroblasts



- Endometrial stromal fibroblasts (hESF) undergo decidualization under the influence of P and/or cAMP.
- *In vivo*: $P_4$ from the corpus luteum, PGE2, relaxin.
- *In vitro*: $P_4$, cAMP analogue, $P_4$ + cAMP analogue

**Differentiation of hESF**

- phenotype: fibroblast to epithelial
- shape: spindle to rounded
- unique biomarkers (IGFBP-1, PRL, TIMP-3)
- unique ECM

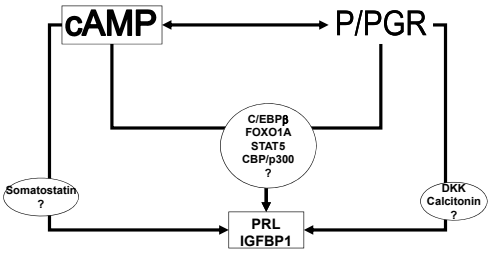



Courtesy J.C. Irwin

There is cross-talk between P and PKA pathways.

*Brar et al., 1997; Velarde 2009*

## cAMP and Progesterone Receptor Crosstalk in Human Endometrium



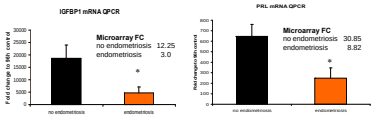

While P4 induces the decidual phenotype in cultured hESF, more rapid didfferentiation requires elevated intracellular cAMP levels and sustained activation of the protein kinase A (PKA) pathway.

*Adapted from: Brar et al., 1997; Velarde et al 2009*

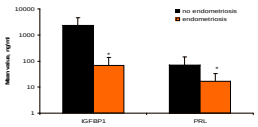
## Reduced cAMP-induced Decidualization Markers in ESF$_{endo\ vs\ nonendo}$

### Microarray and Validation by Q-PCR and ELISA

**Microarray & qRT-PCR**




**ELISA**

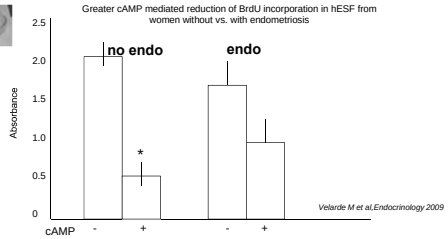



*Aghajanova et al, 2010a*

## Proliferation Potential

**BrdU Incorporation hESF**

Greater cAMP mediated reduction of BrdU incorporation in hESF from women without vs. with endometriosis

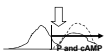



*Velarde M et al,Endocrinology 2009*

**miRNA microarray whole tissue**

hsa miR-9
hsa miR-9*
hsa miR-34c-3p
hsa miR-34c-5p

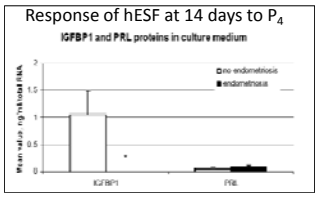
Cell cycle
P53 signaling
DNA replication




*Burney et al, 2009*

## Are hESF Resistant to $P_4$ itself?

Response of hESF at 14 days to $P_4$

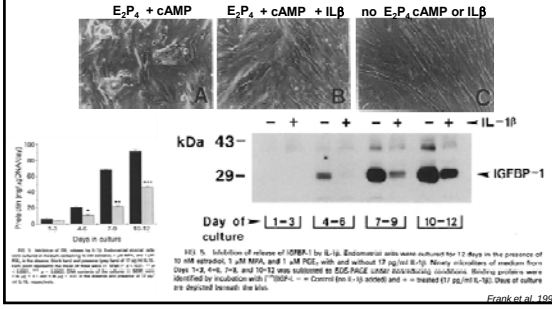



Why might this be?

*Aghajanova et al. 2011*

## Evidence that Inflammation Inhibits hESF decidualization

IL-1β inhibits morphologic transition and blunts response of hESF to $E_2P_4$ and activation of the PKA pathway

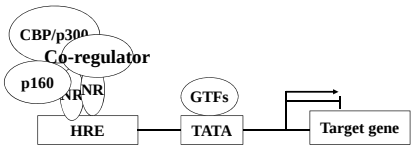



*Frank et al. 1995*

How are inflammation and $P_4$-resistance related?

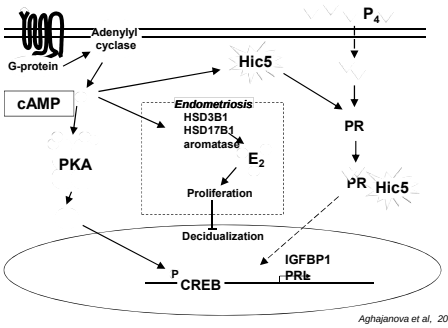
## Progesterone Receptor Co-Regulators

• The function of a transcription cofactor is to interact with nuclear receptor to enhance transcriptional activity; does not bind DNA itself.



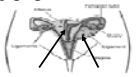

- Co-activators and co-repressors play a vital role in regulating transcription of specific genes.

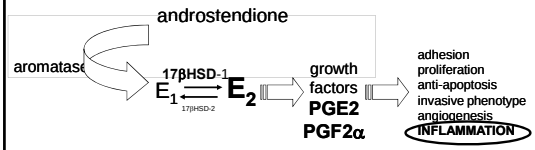
## PR Co-activator Hic5 is Up-regulated by cAMP and $P_4$ in $hESF_{nonendo}$ but not in $hESF_{endo}$




*Aghajanova et al, 2010b*

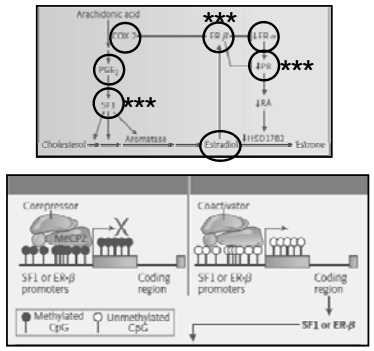
## Ectopic and Eutopic Endometrium in Women with Endometriosis Synthesize $E_2$




*Bulun 2009*

## Progesterone Resistance in Endometriosis and Local Synthesis of Estradiol




*Bulun 2009*

## Whole Genome Co-Regulator Study

- Genes of Interest

| Endometriosis vs No Endometriosis | | |
|---|---|---|
| **Proliferative** | **Fold Change** | **P-Value** |
| HDAC2 | 4.22 | 0.0063 |
| NCOA1 | 3.94 | 0.0072 |
| NCOR1 | 2.88 | 0.0305 |
| HDAC1 | 2.82 | 0.0283 |
| THRA | -2.71 | 0.0210 |
| MTA1 | -2.81 | 0.0299 |

| Early Secretory | Fold Change | P-Value |
|---|---|---|
| HDAC2 | 6.32 | 0.0113 |
| NCOA1 | 5.9 | 0.0142 |
| NCOR1 | 4.32 | 0.0278 |
| HDAC1 | 4.23 | 0.0357 |

-HDACs (Histone deacetylases)
  -Remove acetyl groups causing DNA to wind tighter and repress transcription
-NCOA1 = SRC1 (Nuclear co-activator 1)
  -Has histone acetyltransferase (HAT) activity
  -Interacts with estrogen and progesterone receptors
-NCOR1 (Nuclear co-repressor 1)
  -Repression of thryroid hormone and retinoic acid receptors
-THRA (Thyroid hormone receptor alpha)
  -Localized in stroma, luminal and glandular epithelium (Aghajanova *et al.*, 2005)
  -Present in rat uterus and oviduct (Oner and Oner, 2006)
-MTA1 (Metastasis-associated protein 1)
  -Acts as a potent co-repressor of estrogen receptor

*Zelenko et al 2012*

## Ingeniuty Pathway Analysis

- Disease vs. No Disease
  - All phases
    - **DNA methylation and transcriptional repression signaling most affected canonical pathway**
      - Related genes – HDAC1, HDAC2, MTA1
  - Proliferative Phase
    - Same DNA methylation pathway and same related genes
  - Early Secretory Phase
    - Estrogen receptor and thyroid hormone receptor signaling pathways affected
      - Retaled genes – NCOA1 and NCOR1

*Zelenko et al 2012*

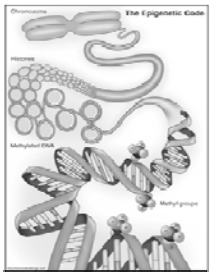
## Persistent Changes in Endometrium in Women with Endometriosis

- $P_4$ and cAMP-resistance is trans-generational in hESF cultured 1-4 passages.
- PR polymorphisms (*Treolar et al, 2005*)
- Altered promoter methylation status in eutopic and ectopic lesions: *(reviewed, Aghajanova 2010b)*
  - hypomethylation of SF1 (increased aromatase and $E_2$ biosynthesis in lesions and eutopic endometrium)
  - hypomethylation of ERβ
  - hypermethylation of HoxA10,
  - hypermethylation of PRB,
  - hypermethylation of E-cadherin.
- DNA methylation,HDAC1, HDAC2, miRNAs.
- Up-regulation of mini-chromosome maintenance genes (*Burney et al 2007*)

## Might endometriosis be an epigenetic disorder?

Guo 2009

- Epigenetics:
  - Changes in methylation Status of promoters of genes for transcription
  - Changes in histones on the chromatin
    - acetylation
    - phosphorylation
    - methylation
    - ubiquitination
    - ADP-ribosylation
- Transgenerational
- Developmental and adult affects




**Gene silening:**
**DNA methylation**
**histone deacetylation**

## Vulnerability of Developing Uterus to EDCs

*the role of ERα and promoter hypermethylation*

- DES changes expression of Wnt 7A, Hoxa10, Hoxa11- genes involved in tissue patterning- and results in altered uterine morphogenesis (*Ma et al, 1998; Miller et al 1998; Block et al, 2000*).
- DES-induced developmental programming requires ERα, suggesting ER-signaling is important to establish developmental programming (*Couse et al, 2001*).
- ***In utero* exposure of mice to DES** (*Bromer et al 2009*) results in:
  - **Hypermethylation Hoxa10 promoter, leading to $P_4$-resistance**
  - Over-expression of DNMT1 and DNMT3B
- DES daughters have abnormal vaginal adenosis (*Jeffries et al, 1984*)
- vaginal adenosis was also found in 80% of stillborns and neonates exposed *in utero* to DES in the first trimester (*Johnson et al, 1979*).
- **Exposure to DES: 80 % increased risk of endometriosis** (*Missmer et al., 2004b).*

## Rodent Studies of Dioxin/PCBs and Endometriosis

- Adult mice exposed to TCDD with subsequent implantation of endometrial tissue:
  - Estrogen level and exposure timing demonstrated significant post-implantation endometrial growth in mice and rats (*Cummings et al. 1996*)
  - Similar findings in mice exposed to combined perinatal and adult TCDD doses (*Cummings et al, 1999*)
- Adult mice exposed to TCDD followed by peritoneal seeding of human endometrial tissue resulted in abnormal **lack of $P_4$ regulation** of MMPs *(Nayyar, et al, 2007)*

## Promotion of Endometriosis by Organochlorines (OCs)

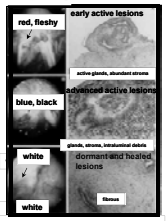
Dioxin (TCDD), pesticides -methoxychlor and DDT, polychlorinated biphenyls

- Evidence is strong in *adult* laboratory animals that endometriosis can be promoted by many OCs.
- Data linking OC exposure and endometriosis in adult women are equivocal. (observational epidemiology studies, limited sample sizes).
- Pre/perinatal period is a susceptible window in which EDCs can induce developmental programming and increase risk for FRT disorders with associated DNA methylation and histone modifications.
- **Adult exposures to EDCs can promote endometriosis and result in $P_4$-resistance observed clinically by mechanisms still to be determined.**

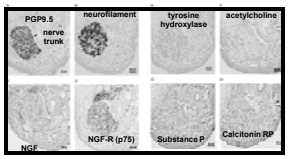
*Guo 2004; Heilier et al 2008*

## Is $P_4$ Resistance Relevant to Endometriosis-Associated Pain?

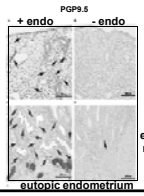
## Endometriosis
(lesion type, histology, and nerves)




Tokushige et al 2006




sensory Aδ/C
sympathetic
para-sympathetic




Pain is related to lesion nerve density, correlates with type of lesion (red>blue>white), depth of invasion and proximity of nerves to lesions.

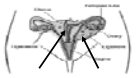
OCPs decrease nerve density in women with endometriosis; nerve density is cycle-dependent.
(*Tokushighe et al, 2009; Wang et al, 2011*)

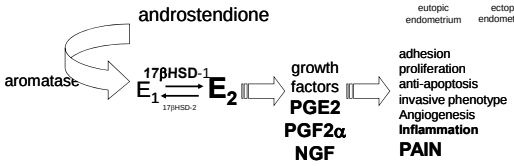
## Pain and Endometriosis

**Activated macrophages and inflammatory response in peritoneal cavity:** secretion of PGs and inflammatory cytokines (e.g., TNFα, IL-1β, IL-8, IL-6)

• **Nociceptor neuron sensitivity** is modulated by mediators in the extracellular space (inflammation, e.g. PGE2, TNF, IL-6,) - many of which are in peritoneal fluid in women with endometriosis.

## Local $E_2$ Production in Endometriosis Lesions and Pain Mechanisms




• Mechanisms contributing to pain:
  • activation of nociceptors by inflammatory mediators in endometriotic tissue.
    $E_2$→ PGs, $E_2$→ NGF.
  • Sprouting of nociceptors leads to a greater number of nociceptive nerve terminals.

**• $P_4$ opposes $E_2$ action. Does it do this in the setting of endometriosis?**

## Medical and Surgical Basis of Treating Symptomatic Endometriosis

*ASSUMPTIONS*

Pain associated with endometriosis will be abated if:

- the establishment, presence, growth, sustenance and dissemination of the disease are inhibited
- pelvic innervation is disrupted
- (peripheral and central nervous systems not considered)

## *Current* Treatments for Endometriosis

**Medical therapies**

- **primarily aim to minimize disease and associated Sx.**
- **inhibit inflammation** (NSAIDs)
- **minimize menstruation volume and frequency** (contraceptive steroids, progestogens/L-IUS, anti-progestogens (RU486, Gestrinone)*(decidualization, followed by atrophy).*
- **oppose estrogen actions throughout cycle** (contraceptive steroids, progestogens/L-IUS, anti-progestogens).
- **create a hypoestrogenic state** (GnRHa, GnRH antagonists; aromatase inhibitors).
- **create a hyperandrogenic state** (similar to progestin actions on endometrium/osis) (e.g., Danazol) and inhibition of gonadotropins.
- **aromatase inhibitors** (inhibit $E_2$ biosynthesis) with a progestogen.

**Surgical therapies**

- surgical removal/ablation of disease gets rid of lesions and innervation and thus pain.
- primarily aim to minimize disease, restore anatomy, minimize pain, increase fertility, detect occult (rare) endometriosis-associated ovarian cancer.

**Sequential therapies** pain, infertility

**Success rates**

**Medical**: most work for a limited time but side effects of the therapies limit their usefulness.
**Surgical**: up to 50% recurrence of pain needing additional surgery within 2-5 years.

*Giudice 2010*

## Pain and Endometriosis

*Why don't medical (and surgical) therapies work long term?*

- What are the roles of $E_2$ and $P_4$ in pain perception, in development and sprouting of nociceptors?
- If inflammation promotes $P_4$ resistance in endometrial cells, is there a similar mechanism occurring in neurons/neuronal pathways?
- Is endometriosis (pain) part of a systemic inflammatory disorder?
- Are progestins functioning optimally in our therapies or are there other opportunities?
- Are immunosuppressive effects of $P_4$ compromised in women with endometriosis?

## Persistent Changes in Endometrium in Women with Endometriosis

- Resistance to actions of cAMP and $P_4$
- PR co-activator Hic-5 dysregulated
- Decreased PRA, PRB
- Local synthesis and decreased metabolism of $E_2$
- Hypomethylated genes (SF1) governing $E_2$ synthesis and ERβ increased expression, and inflammation

↓

**Resistance to action of Progesterone**
**Enhanced sensitivity to $E_2$**

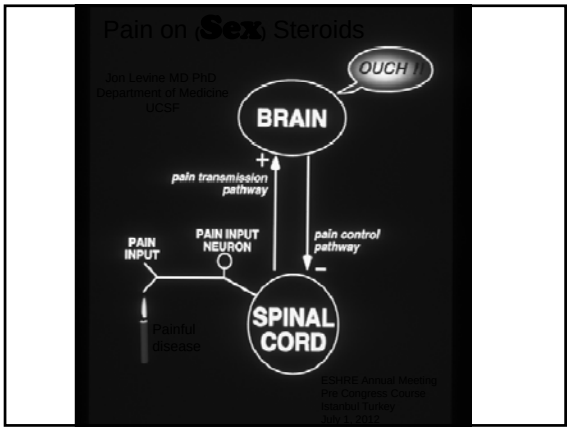
"Estrogen-persistance and Progesterone-resistance"

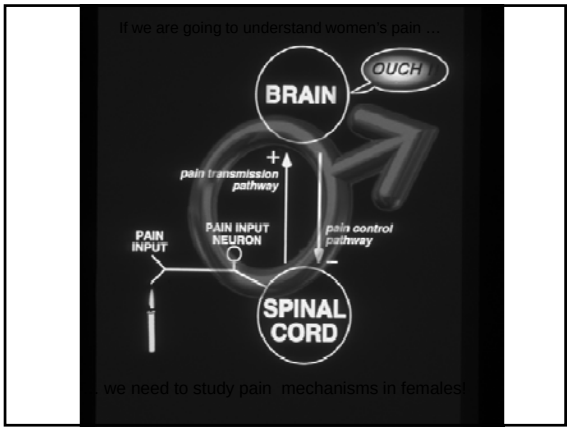
---

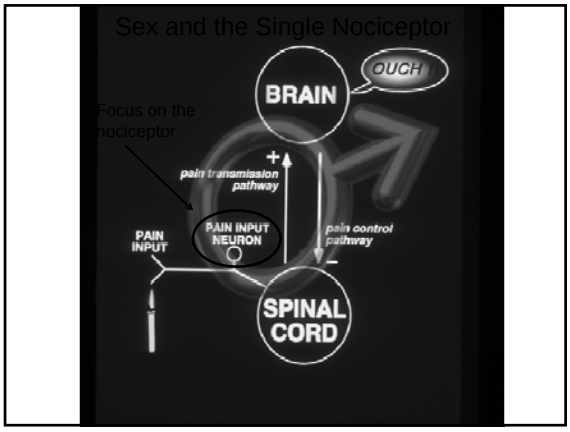
And the question remains:

*Is $P_4$ Resistance Relevant to Endometriosis-Associated Pain?*

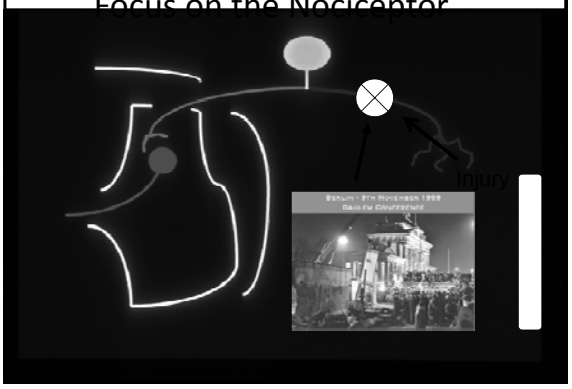
***New Frontier!**

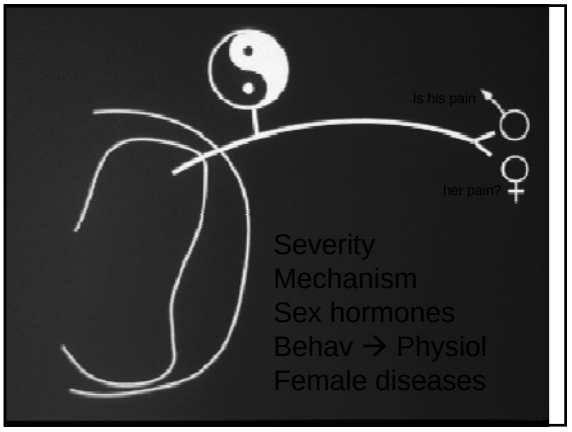

Pain on (Sex) Steroids
Jon Levine MD PhD
Department of Medicine
UCSF
OUCH !
BRAIN
+
pain transmission pathway
PAIN INPUT
PAIN INPUT NEURON
pain control pathway
–
SPINAL CORD
Painful disease
ESHRE Annual Meeting
Pre Congress Course
Istanbul Turkey
July 1, 2012


If we are going to understand women's pain ...
BRAIN
OUCH !
+
pain transmission pathway
PAIN INPUT
PAIN INPUT NEURON
pain control pathway
–
SPINAL CORD
we need to study pain mechanisms in females!


Sex and the Single Nociceptor
BRAIN
OUCH !
Focus on the nociceptor
+
pain transmission pathway
PAIN INPUT
PAIN INPUT NEURON
pain control pathway
–
SPINAL CORD

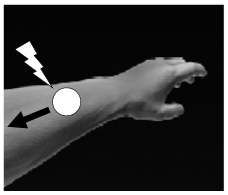
## Focus on the Nociceptor

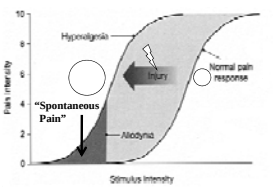


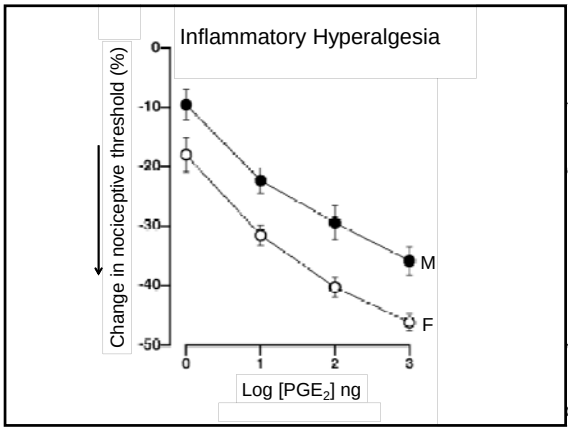

Hallmark of Clinical Pain (Acute & **Chronic**)

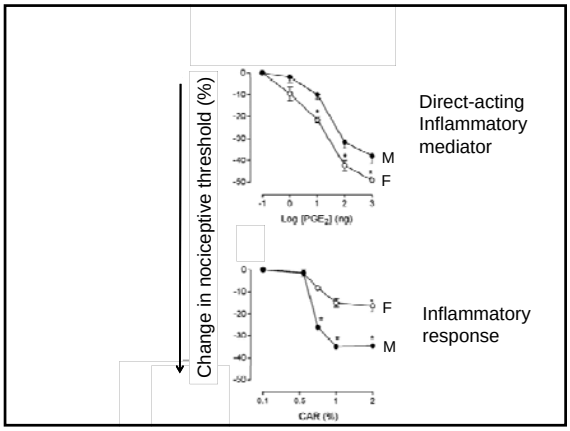
## Sensitization to Mechanical Stimuli



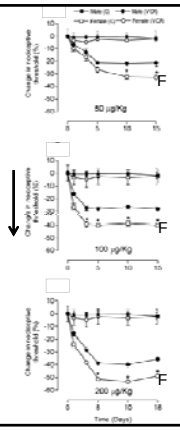


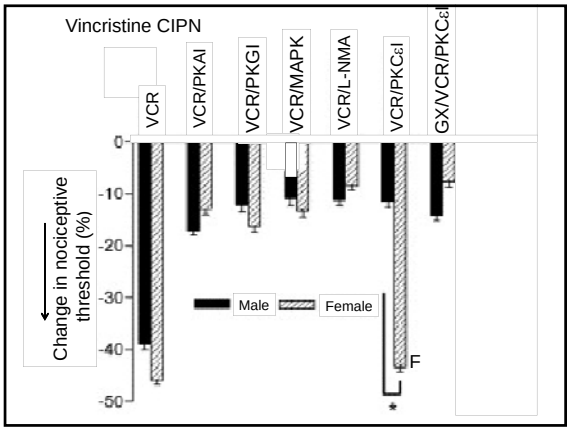

Gebhart / Cervero

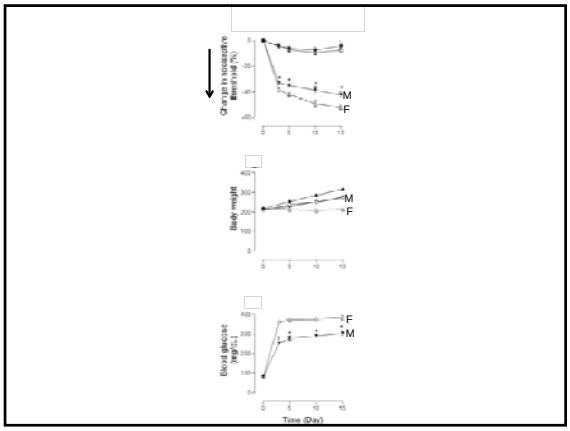


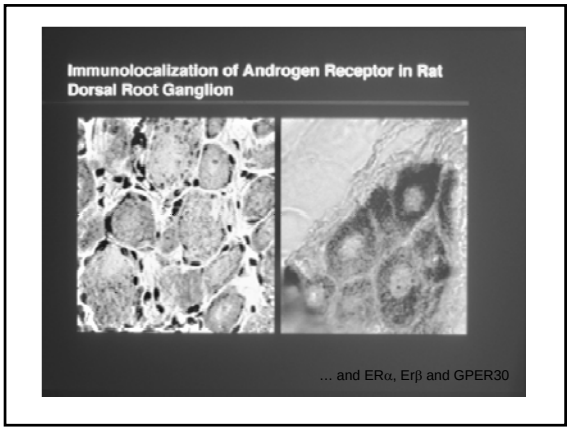



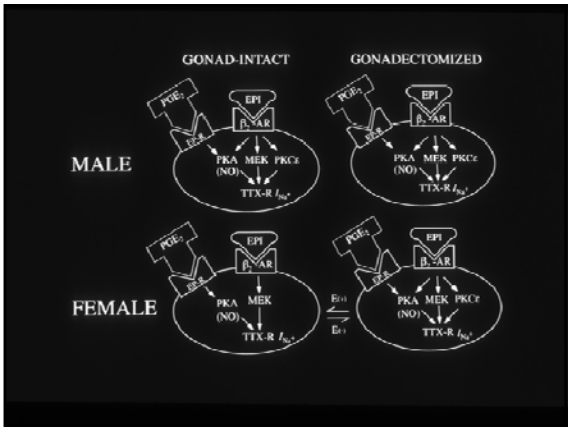

Chemotherapy Neuropathy induced by a vinca alkaloid (vincristine)

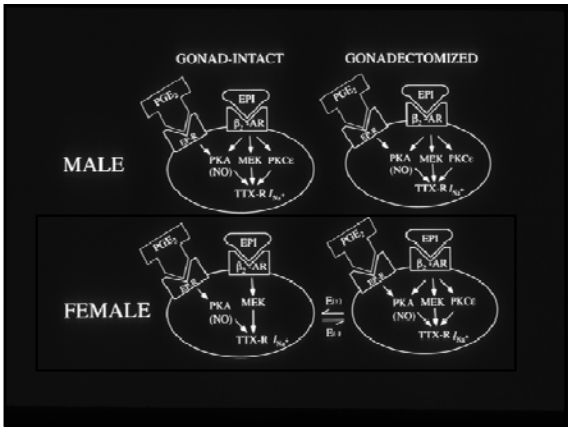



Vincristine CIPN
VCR
VCR/PKAI
VCR/PKGI
VCR/MAPK
VCR/L-NMA
VCR/PKCεI
GX/VCR/PKCεI
Change in nociceptive threshold (%)
0
-10
-20
-30
-40
-50
Male
Female
F
*

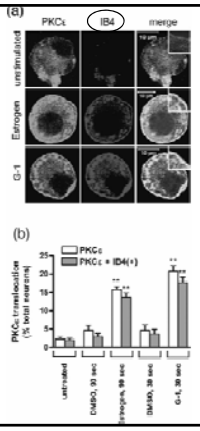

M
F
M
F
F
M
Time (Day)

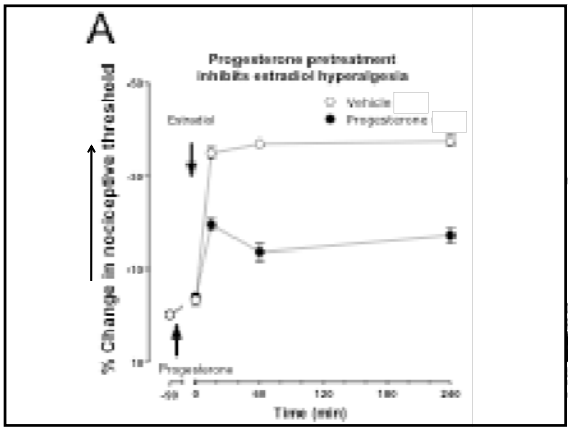

Immunolocalization of Androgen Receptor in Rat Dorsal Root Ganglion
… and ERα, Erβ and GPER30

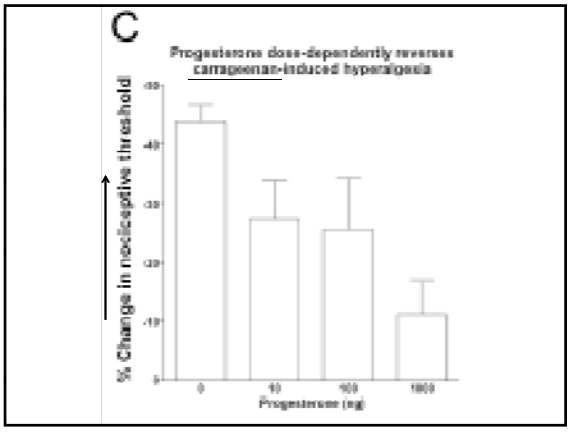


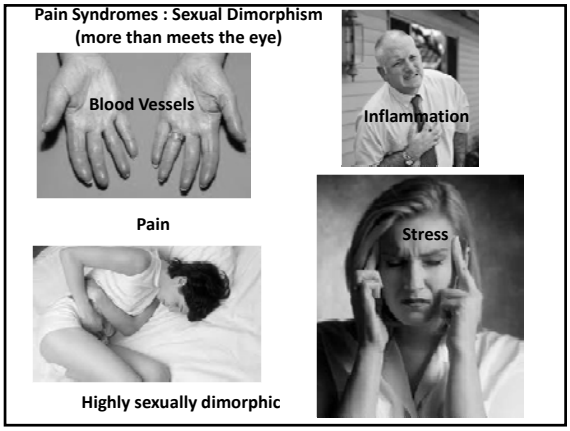



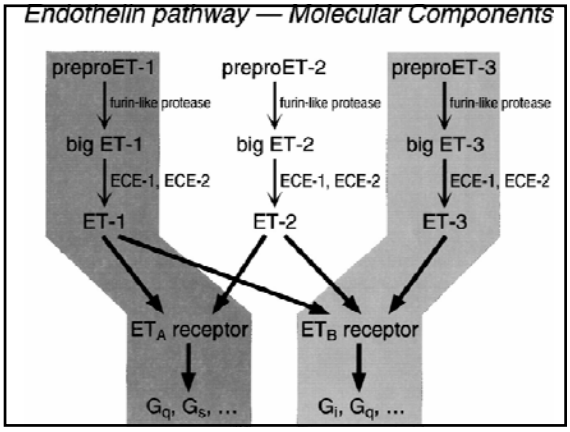

Estrogen also produces hyperalgesia

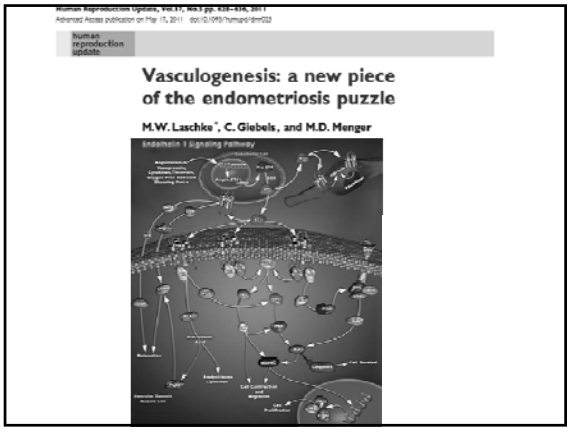


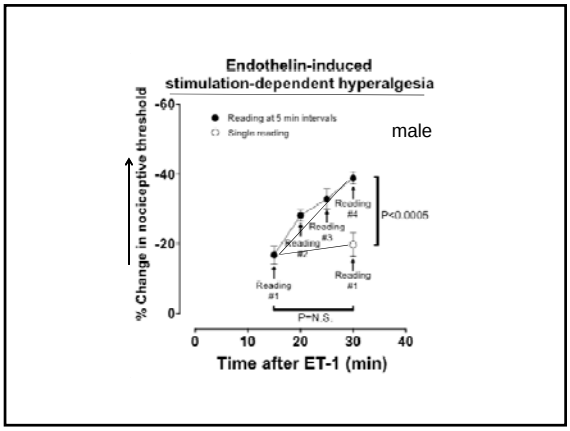

A
Progesterone pretreatment
inhibits estradiol hyperalgesia
Vehicle
Progesterone
Estradiol
Progesterone
% Change in nociceptive threshold
Time (min)

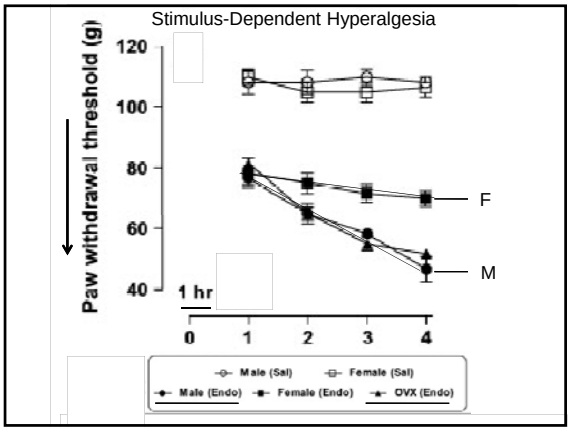

C
Progesterone dose-dependently reverses
carrageenan-induced hyperalgesia
% Change in nociceptive threshold
Progesterone (ng)

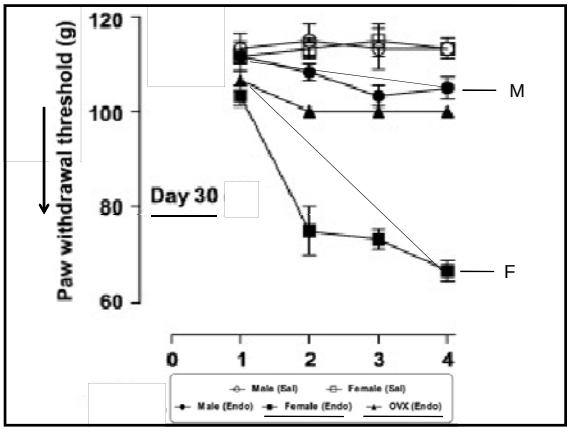

Pain Syndromes : Sexual Dimorphism
(more than meets the eye)
Blood Vessels
Inflammation
Pain
Stress
Highly sexually dimorphic


Endothelin pathway — Molecular Components
preproET-1
preproET-2
preproET-3
furin-like protease
furin-like protease
furin-like protease
big ET-1
big ET-2
big ET-3
ECE-1, ECE-2
ECE-1, ECE-2
ECE-1, ECE-2
ET-1
ET-2
ET-3
ETA receptor
ETB receptor
Gq, Gs, ...
Gi, Gq, ...


human reproduction update
Vasculogenesis: a new piece of the endometriosis puzzle
M.W. Laschke*, C. Giebels, and M.D. Menger


Endothelin-induced stimulation-dependent hyperalgesia
Reading at 5 min intervals
Single reading
male
% Change in nociceptive threshold
-60
-40
-20
0
Reading #4
Reading #3
Reading #2
Reading #1
Reading #1
P<0.0005
P=N.S.
0
10
20
30
40
Time after ET-1 (min)




## Sexual Dimorphism in Endothelin Hyperalgesia

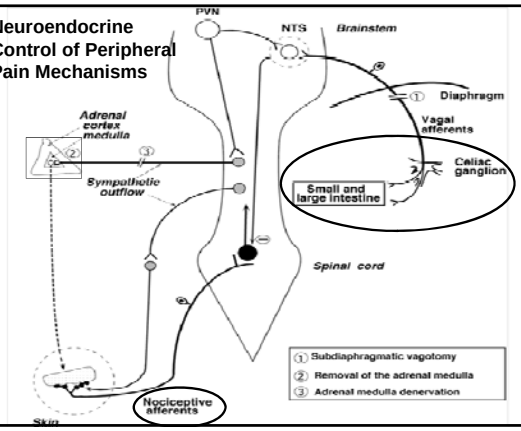
Mechanical hyperalgesia:
delayed onset and longer duration in female

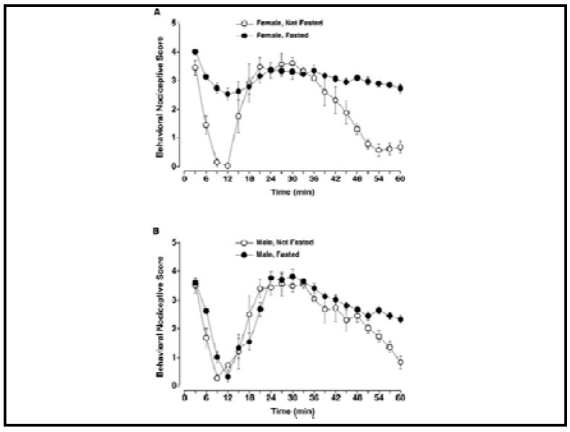
SDH early only in male

Develops in female after **15 (still present at 45)**

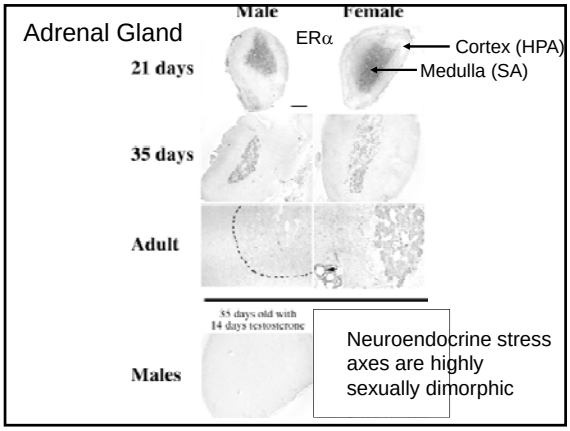
Ovariectomy eliminated sex differences

**Neuroendocrine Control of Peripheral Pain Mechanisms**



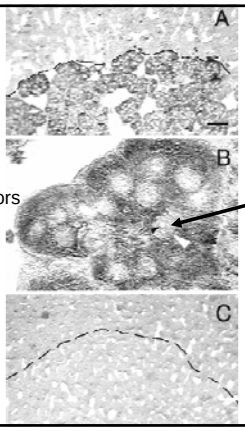




Adrenal Gland




Neuroendocrine stress axes are highly sexually dimorphic

Estrogen Receptors are Nuclear receptors




## Pain (threshold)

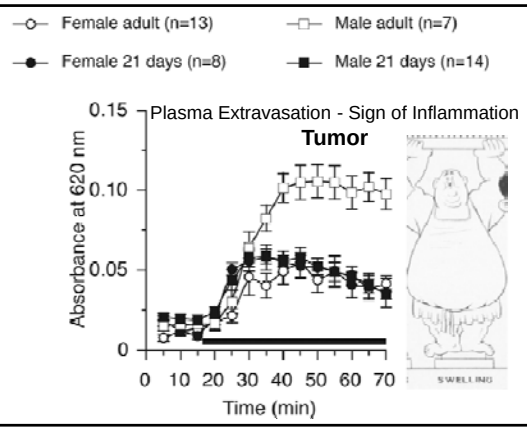
| | Baseline paw-withdrawal threshold | |
|---|---|---|
| | **Male** | **Female** |
| Adult (Naïve) | 107.7 ± 1.1 (36)[2] | 89.8 ± 1.1 (36)[1] |
| Adult AMedx (5 weeks) | 116.3± 1.6 (24) | 117.9 ± 2.2 (24 |
| Adult AMedx + Epi (7 days) | 120.3 ± 4.0 (8) | 101.0 ± 5.8 (8)[1] |
| Adult AMedx + Epi (14 days) | 121.5 ± 2.5 (8) | 86.0 ± 2.4 (8)[1,2] |
| Adult AMdenerv (7 days) | 108.0 ± 1.0 (24)[2,3] | 91.7 ± 1.5 (22)[1] |
| Adult AMdenerv (5 weeks) | 122.6 ± 2.0 (n=24) | 123.8 ± 1.8 (16 |
| Adult AMdenerv + Epi (7 days) | ND | 106.5 ± 2.1 (8)[3] |
| Adult AMdenerv + Epi (14 days) | | 87.8 ± 3.5 (8)[3] |

| | Plasma epinephrine levels (*pg*/ml) | |
|---|---|---|
| | **Male** | **Female** |
| Prepubertal | 226.4 ± 48.0 (15) | 198.7 ± 31.4 (15) |
| Adult (Naïve) | 241.8 ± 42.5 (17) | 606.2 ± 87.2 (23)[1] |
| Adult (Gonadectomy*) | 325.5 ± 73.1 (24) | 333.4 ± 62.8 (25)[2] |

Sexual Dimorphism in Pain Mechanisms:

## *Inflammation*

Many inflammatory diseases are highly sexually dimorphic




**Sexual Dimorphism in Treatment**

***Therapeutic effects occurring more in one sex***

*Toxic affects occurring more in one sex*

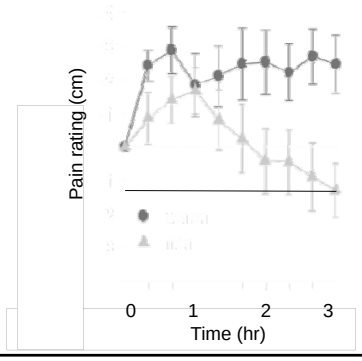
## Labor Pain

Kappa-opioids compared to meperidine:

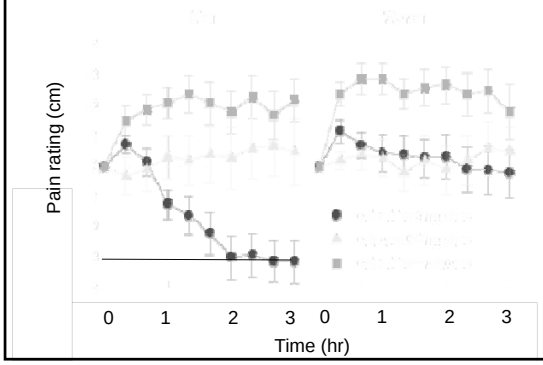
- Equal in effectiveness
- Less nausea
- Greater overall patient satisfaction

(Halpern & Carter, 1996, Anesth & Analg 82:S159)

Nalbuphine (Nubain) 10 mg (PDR dose)




Nalbuphine 5 mg, naloxone 0.4 mg, combo



**COLLABORATORS**

Elizabeth Joseph
Wilfrid Janig
Robert Gear
Tim Hucho
Pedro Alvarez
Luiz Ferrara
Nicole Alessandri-Haber
Oliver Bogen
Sachia Khasar
Olayinka Dina
Paul Green
Julia Kuhn
Xiaojie Chen
Jan Hendrich

**MYOFASCIAL TRIGGER POINTS,
PAIN AND ENDOMETRIOSIS:
LESSONS LEARNED FROM OTHER PAIN CONDITIONS**

**Maria Adele Giamberardino**
**Pathophysiology of Pain Laboratory**
**Department of Medicine and Science of Aging**
**"G. D'Annunzio" University of Chieti - Italy**

**LEARNING OBJECTIVES**

**The participants will learn about**:

-The characteristics and pathophysiology of Myofascial Trigger Points

-The role played by Myofascial Trigger Points in Visceral Pain Syndromes

-The role played by Myofascial Trigger Points in pain from Endometriosis

## Myofascial Trigger Point (TrP)

Spot of exquisite tenderness in a muscle or its fascia, localized in a taut, palpable band of fibers. It mediates a local twitch response under snapping palpation and gives rise to pain, tenderness, autonomic phenomena and dysfunction in an area (target) usually remote from its site.

Simons et al 1999

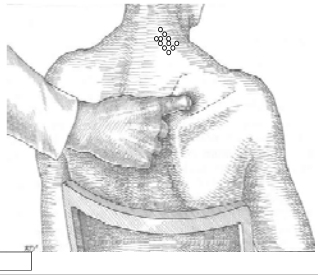
## PALPATION OF THE TRIGGER POINT

Sustained digital pressure over various points of the band. The TrP is the point of maximal tenderness during the manoeuver

**STIMULATION OF THE TrP**

⇩

**PAIN IN THE TARGET AREA**



Simons et al 1999

## Trigger Points

- **Active** Myofascial Trigger Points: responsible for spontaneous pain (MPS)
- **Latent** Myofascial Trigger Points: clinically silent

**Myofascial Pain Syndrome (MPS)**

The sensory, motor, and autonomic symptoms caused by myofascial trigger points

Simons et al 1999

## Myofascial Pain Syndrome

- **Prevalence** in the general population: 38%-48%; increase in frequency with advancing age
- **Risk factors:** incorrect posture, maintaining the same posture for prolonged periods of time, activities that involve repeated use of the same muscle groups, incorrect execution of the athletic movement in sports

Mense e Simons 2001; Bennett 2007; Giamberardino et al 2011

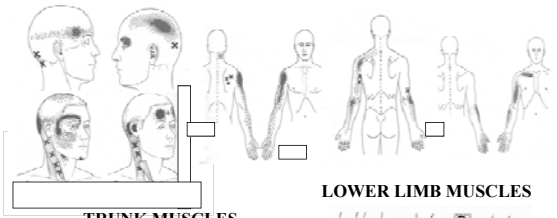
## Myofascial Pain Syndromes as an example of referred pain from a muscle to another somatic structure

***"Referred Pain"***

**Pain perceived in an area other than that in which the noxious stimulation takes place**

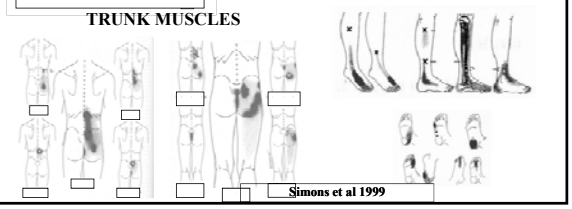
**H. Head 1893**

**HEAD AND NECK MUSCLES** **UPPER LIMBS MUSCLES**



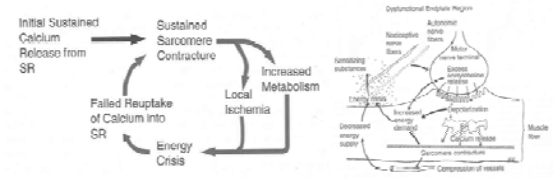
**LOWER LIMB MUSCLES**

**TRUNK MUSCLES**



**Simons et al 1999**

## PATHOPHYSIOLOGY OF THE TrP
## The *"integrated" hypothesis*

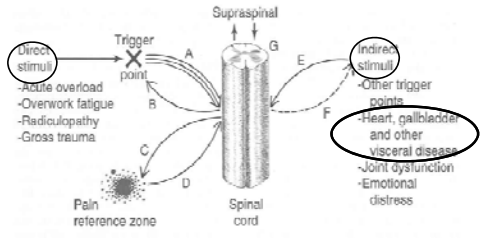



**An active TrP is the site of release of algogenic substances that sensitize nerve terminals**

*Microdialysis in active TrP areas:* significantly higher levels of bradykinin, substance P, protons, calcitonin gene-related peptide, tumor necrosis factor- α, interleukin-1β, serotonin and norepinephrine, compared to areas of normal muscle and of latent TrPs

**Shah et al 2005; Hong 2006**

## PATHOPHYSIOLOGY OF THE TrP




***Direct stimuli:*** **Traumas or repeated microtraumas**
***Indirect stimuli:*** **Referred pain processes from internal organs**

**Gerwin, 2005**

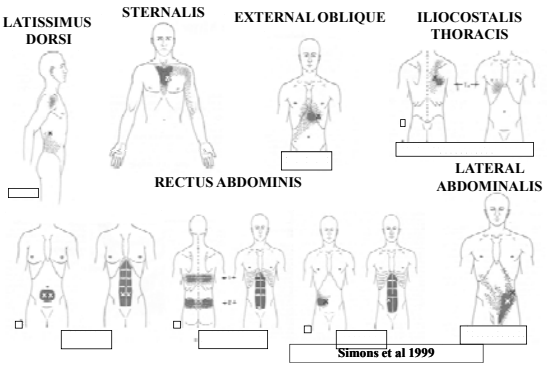
## VISCERAL PAIN SYNDROMES

## AND TRIGGER POINTS

**(1) Primary Trigger Points**
***mimicking Visceral Pain Syndromes***

**(2) Secondary Trigger Points**
***in areas of Referred Pain from Viscera***

## PRIMARY TRIGGER POINTS MIMICKING VISCERAL PAIN SYNDROMES




**Simons et al 1999**

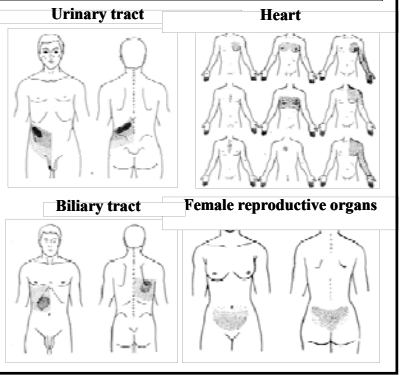
**SECONDARY TRIGGER POINTS**

***in areas of referred pain from viscera***

## VISCERAL PAIN

**- Pain from internal organs is typically referred to somatic structures**

**- Muscle hyperalgesia most often develops in the referred area**




**REFERRED MUSCLE HYPERALGESIA**
***from***

**<u>One visceral district</u>**

**REFERRED MUSCLE HYPERALGESIA FROM ONE VISCERAL DISTRICT**

- **Urinary tract**
  Vecchiet et al 1989-1992; Giamberardino et al 1994, 2007-2012
- **Digestive tract**
  Vecchiet et al 1996; Giamberardino et al 1998-2012; Caldarella et al 2006; Stawowy et al 2004
- **Female reproductive organs**
  Wesselmann et al 1997; Giamberardino et al 1997-2012

REFERRED MUSCLE HYPERALGESIA FROM VISCERA

Assessment of pain thresholds through:

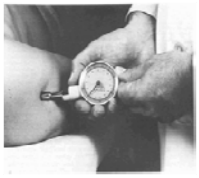
- Electrical stimulation
- Pressure stimulation
- Chemical stimulation

Arendt-Nielsen et al 1998-2012; Vecchiet et al 1989-1992
Giamberardino et al 1994-2012

**PAIN THRESHOLDS TO ELECTRICAL STIMULATION**

- **SKIN** Pricking pain
- **SUBCUTIS** Linearly radiating prickling pain
- **MUSCLE** Cramplike pain

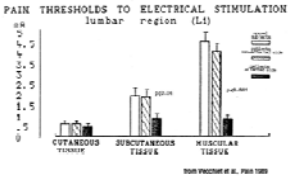
---



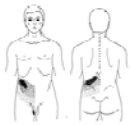
**PAIN THRESHOLDS TO PRESSURE STIMULATION**

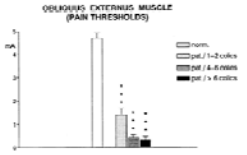
**REFERRED MUSCLE HYPERALGESIA from:**
**-One visceral district (urinary tract)**

## URINARY COLICS




**Single episode**

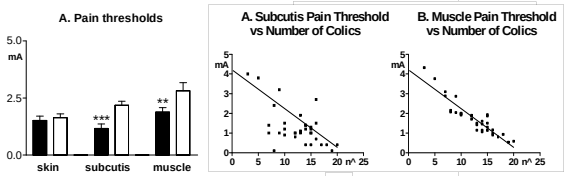




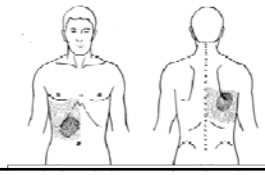

**Multiple episodes**

**Vecchiet et al 1989, 1990**

**REFERRED MUSCLE HYPERALGESIA from:**
**-One visceral district (digestive tract)**




## BILIARY COLICS



**Giamberardino et al 2005**

# Endometriosis
# Clinical Presentation

**Sub-fertility/ Infertility**
**Vaginal Hyperalgesia**
**Dyschezia**

**1. "Silent endometriosis" *or***

**2. Secondary Dysmenorrhea *or***

**3. Chronic Pelvic Pain**

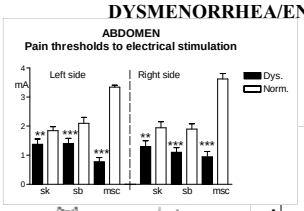
***Somatic abdominopelvic hyperalgesia***

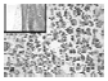
***No correlation between extent of the lesions and presence and intensity of painful symptoms***

**Farquhar 2000; Frackiewicz 2000; Giudice and Kao 2004; Bajaj et al 2003 Laursen et al 2004,2005; Selak et al 2007** Selak et al 2007; Berkley 2010

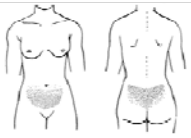
**REFERRED MUSCLE HYPERALGESIA from:**
**-One visceral district (female reproductive organs)**

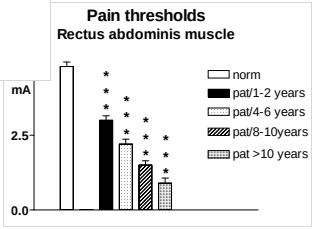
**DYSMENORRHEA/ENDOMETRIOSIS**



Giamberardino et al
1997, 2001, 2010






## REFERRED HYPERALGESIA FROM VISCERA
**(Repetitive visceral attacks)**

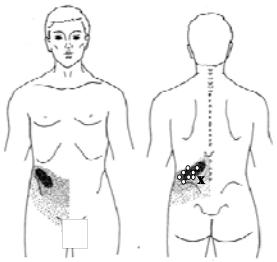
- ♦ mostly a muscle phenomenon
- ♦ an early process
- ♦ accentuated by repetition of visceral painful episodes
- ♦ outlasting the spontaneous pain
- ♦ **persisting, though to a lesser extent, after elimination of the visceral focus**

**Vecchiet et al 1989, 1992; Giamberardino et al 1994-2011**

**Previous studies have shown that 22% of patients with urinary calculosis who have spontaneously eliminated the stone still present colic-like symptoms and 88% of them still have residual lumbar muscle hyperalgesia**
***3 years afterwards***

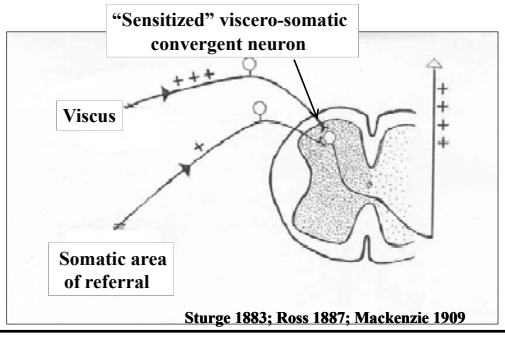
**Vecchiet et al 1992; Giamberardino et al 1994**

**Physical examination of the referred area in these cases reveal the presence of Trigger Points - developing as a consequence of the visceral process - whose stimulation reproduces the typical visceral pain attack and extinction with local treatment reverts the visceral pain symptomatology**



## MECHANISMS OF REFERRED HYPERALGESIA

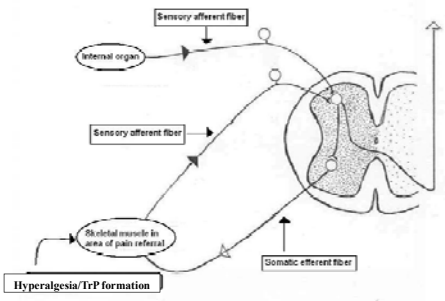
### Convergence-Facilitation Theory




Sturge 1883; Ross 1887; Mackenzie 1909

## MECHANISMS OF REFERRED HYPERALGESIA

### Reflex arc theory




Penfield 1925; Davis & Pollock 1930; Galletti et al 1963; Procacci 1969; Zimmermann 1974

**REFERRED HYPERALGESIA FROM VISCERA**
**(Acute/inflammatory visceral attack)**

In acute cholecystitis:

-hypersensitivity to pinprick, heat, cold, pressure and single and repeated cutaneous electrical stimulation in the referred pain area and in the contralateral control area of the abdomen

- hypersensitivity normalized after cholecystectomy

Stawowy et al 2004

**Repeated visceral attacks**
**are probably necessary**
**to activate the circuit that leads**
**to the development of**
**a TrP in the referred muscle area**

**PAIN AND**
**REFERRED MUSCLE HYPERALGESIA**
***from:***
**Two visceral districts**

## VISCERO- VISCERAL HYPERALGESIA

Phenomena of symptom enhancement between different viscera which share part of their sensory innervation

---------- Giamberardino 2001,2010

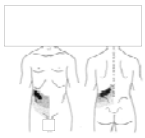
1. Ischemic Heart Disease - Gallbladder Calculosis
[Heart - Gallbladder (T5)]

2. Irritable Bowel Syndrome- Dysmenorrhea/Endometriosis
[Colon -Uterus (T10-L1)]

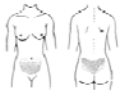
3. Dysmenorrhea/Endometriosis - Urinary Calculosis
[Uterus - Urinary Tract (T10-L1)]

## DYSMENORRHEA

primary or secondary to endometriosis



***plus***

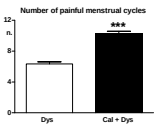


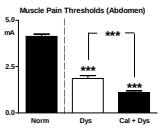
## URINARY CALCULOSIS

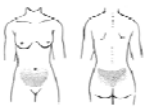
**[Uterus - Urinary Tract (T10-L1)]**

**Giamberardino et al 2001,2010**

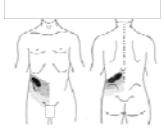
**IMPACT OF URINARY CALCULOSIS ON PAIN FROM DYSMENORRHEA**

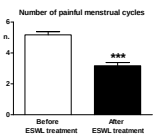


**EFFECTS OF CALCULOSIS TREATMENT ON PAIN FROM DYSMENORRHEA**






## VISCERO-VISCERAL HYPERALGESIA

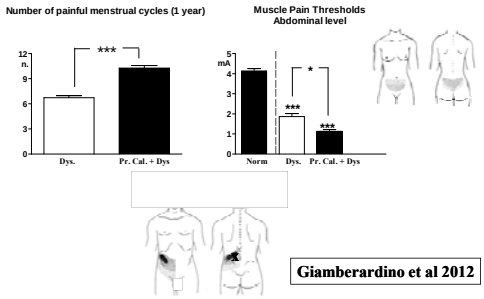
POSSIBLE MECHANISMS

- ***Central sensitization***
  (viscero-viscero-somatic convergent neurons)
- ***Reflex arc activation***
  (Increased extent and/or duration of muscle contraction in the referred area – **TrP formation** - sensitization of muscle nociceptors)

**Twenty-two per cent of patients with urinary calculosis who have spontaneously eliminated the stone still present colic-like symptoms and 88% of them still have residual lumbar muscle hyperalgesia several years afterwards.**

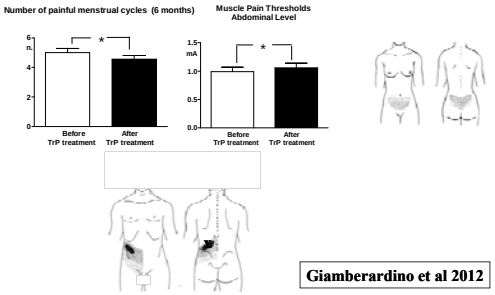
***Physical examination in the lumbar region of these patients reveals the presence of active myofascial Trigger Points***

**IMPACT OF PREVIOUS URINARY CALCULOSIS ON PAIN FROM DYSMENORRHEA/ENDOMETRIOSIS**




Giamberardino et al 2012

**EFFECTS OF TREATMENT OF THE LUMBAR TrP ON PAIN FROM DYSMENORRHEA/ENDOMETRIOSIS**




Giamberardino et al 2012

**The presence of Trigger Points in a referred pain area from an internal organ can modify pain perception not only from that organ but also from other neuromerically connected organs**

**Pain from endometriosis can be deeply influenced/modulated by the presence of Trigger Points in the area or referred pain from the female reproductive organs and/or in referred areas from other pelvic organs with partially overlapping innervation**

# Impact of dyspareunia for women with endometriosis

Lone Hummelshoj
Publisher/Editor-in-chief, Endometriosis.org
Secretary General, World Endometriosis Society (WES)
Chief Executive, World Endometriosis Research Foundation (WERF)

Endometriosis affects an estimated 1 in 10 women during their reproductive years [1]. According to the World Bank it is projected that in 2010 there were 1,761,687,000 women in the world aged between the ages of 15 and 49. If 10% of these have endometriosis, it equates to 176 million women worlwide who have this disease during the prime and most productive years of their lives [2].

## Dyspareunia

Endometriosis has been described as the "3D Syndrome" [3]:

- dysmenorrhea (defined according to loss of work productivity and need for bed rest)
- dyspareunia (defined according to limitation of sexual activity), and
- dyschezia (defined according to frequency of the complaint).

Sexual activity – or rather the lack of it in women with endometriosis – is the focus of the talk today, and thus let's define dyspareunia as pain experienced inside the vaginal canal, at the level of the cervix, in the pelvic/uterine/abdominal region, pain in the vulvar region, and/or the vaginal introitus [4]. Some like to classify these pains as "deep" or "superficial", but the thing with sex is: if it hurts – it hurts!

And, if sex hurts it is a problem. Full stop.

Whereas severe dysmenorrhea contributes to absence from work and/or reduced productivity [5,6], painful intercourse engenders substantial psychological and relational distress contributing to infidelity, relationship dissolution, and divorce. Furthermore, dyspareunia is an ideal candidate for doctor shopping, uncoordinated multiple treatment attempts, and low adherence to strategies that do not show immediate effects [7]. Thus both dysmenorrhea and dyspareunia have a financial and personal cost associated with the complaint.

## Defining sexual health through reproductive health

In 2002 the WHO published a "Report of a technical consultation on sexual health" [8]. In this "reproductive health" was defined as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and to its functions and processes. Reproductive health therefore implies that people are able to have a satisfying and safe se life and that they have the capacity to reproduce and the freedom to decide if, when, and how often to do so".

In other words: sexual rights are reproductive rights. And, according to WHO, these sexual rights embrace human rights that are already recognised in national law, including the right of all persons to pursue a satisfying and pleasurable sexual life [8].

## Rights are one thing – reality another

Sexual rights may have been established on a piece of paper, but if it doesn't work in the bedroom – due to pain – a woman with endometriosis can be left with issues concerning her body image and self esteem, consequent psychological issues, and further consequential relationship problems. None of these issues are aided with today's perpetual bombardment through the popular press and/or glamour magazines when it comes to the improbable promotion of body images and what sex should and/or could be like.

## Impact of dyspareunia in women with endometriosis

Three recent studies have indicated that >50% of women list one of the biggest impact that the symptoms of endometriosis has on these women's lives is how it affects their sex lives and pose a threat to their relationships [9,10,11].

In one study, 64% of women indicated that they would interrupt intercourse due to pain, and 73% would avoid intercourse all together [11]. Thus dyspareunia doesn't just affect women with endometriosis – it affects their partners as well.

This impact should at all times be considered when determining therapeutic options for women with endometriosis, including performing unnecessary bowel resections, which can adversely contribute to an impaired sex-life [12].

## Conclusions

Dyspareunia is a symptom of endometriosis rarely studied or addressed in research reports. In our paper published last year [3] we urge everyone to stop studying symptomatic endometriosis patients as an undifferentiated population. In doing so you may mask important distinctions between sub-groups with specific symptoms, such as dyspareunia, which may interfere with clinical understanding and therapeutic decision-making. Dyspareunia should at all times be viewed in a broader clinical perspective, considering potential psychological and interpersonal consequences.

Dyspareunia affects mainly young women in their most sexually active years. This may, of course, also compromise their fertility. What physicians need to be mindful of, however, is that many women would not

voluntarily disclose what is very personal and intimate information. Even caring and inquisitive physicians may have difficulty explicitly exploring this aspect of a woman's medical history.

However, please do not les this discourage you as clinicians: you are there to help the woman and, by asking probing (and potentially awkward) questions, you may hone in faster on the real problem and thus be in a better position to advise on appropriate solutions long term, including a multi-disciplinary approach and self-help resources. In doing so, it is worth bearing in mind that *improving* symptoms may not be sufficient when dealing with dyspareunia. To use the analogy of being hit by a hammer – it hurts. It hurts less, however, to be hit by stick, but it still hurts – and you'd want to avoid that pain if at all possible. Thus reducing the pain alone is not necessarily enough when it comes to improving the sex lives of women with endometriosis and their partners.

## References

1. Rogers PA, et al. Priorities for endometriosis research: recommendations from an international consensus workshop. Reprod Sci 2009;16:335-346.
2. Adamson GD, et al. Creating solutions in endometriosis: global collaboration through the World Endometriosis Research Foundation. J of Endometriosis 2010;2(1):3-6.
3. Vercellini P, et al. Priorities for endometriosis research: a proposed focus on deep dyspareunia. Reprod Sci 2011;18(2):114-118.
4. Meana M and Binik YM. Dyspareunia: causes and treatments. In: Vercellini P, ed. Gynecology in Practice. Chronic Pelvic Pain. Oxford, UK: John Wiley & Sons; 2011:125-136.
5. Nnoaham KE, et al. Impact of endometriosis on quality of life and work productivity: a multi-center study across ten countries. Fertil Steril 2011;96(20):366-373.
6. Simoens S, et al. The burden of endometriosis: costs and quality of life of women with endometriosis treated in referral centres. Hum Reprod 2012 [epub ahead of publication].
7. Meana M, et al. The relevance of dyspareunia. In: Goldstein AT, Pukall CF, and Goldstein I, eds. Female sexual pain disorders. Oxford, UK: Wiley-Blackwell; 2009:9-13.
8. WHO. Defining sexual health: a report of a technical consultation on sexual health. 28-31 January 2002, Geneva. http://www.who.int/reproductivehealth/topics/gender_rights/defining_sexual_health.pdf [accessed 9 April 2012].
9. Bernuit D, et al. Female perspectives on endometriosis: findings from the uterine bleeding and pain women's research study. J of Endometriosis 2011;3(2):73-85.
10. Fagervold B, et al. Life after a diagnosis of endometriosis - a 15-year follow-up study. Acta Obstet Gynecol Scand 2009;88(8):914-919.
11. WERF EndoCost Study. Data on file.
12. Roman H, et al. Delayed functional outcomes associated with surgical management of deep rectovaginal endometriosis with rectal involvement: giving patients an informed choice. Hum Reprod 2010;25(4):890-899.

UNIVERSITY HOSPITALS LEUVEN

Leuven Consensus Terms and Definitions for Surgical Research in Women with Deeply Infiltrative Endometriosis with Colorectal and Urological extension

**Vanhie A, MD; Meuleman C, MD, PhD; Tomassetti C, MD; D'Hooghe T, MD, PhD**

Leuven University Endometriosis Center of Expertise,
Division of Reproductive Medicine

ESHRE 2012 ISTANBUL, TURKEY, PCC ENDOMETRIOSIS ENDOMETRIUM

UNIVERSITY HOSPITALS LEUVEN

## *Teaching objective:*

- *To present and discuss*
  *an evidence- and consensus-based process*
  *to reach agreement*
  *on terms and definitions*
  *in surgical endometriosis research*

## Conflict of interest/potential bias

Full Professor Leuven University
Merck Serono Chair (2005-15) /Ferring Chair (2010-2013) Reproductive Medicine (Leuven University)

Research Associate and Chair International Advisory Board, Institute of Primate Research, Kenya

Fundamental Clinical Investigator for endometriosis, Belgian Research Foundation (1998-2009), Leuven University Hospital Clinical Research Fund (2010-2015)

Consultant/advisor: Merck Serono, Bayer, Astellas, Novartis, Ferring, MSD, Karolinska Development, Proteomika, Preglem

*http://www/eshre.com*

UNIVERSITY HOSPITALS LEUVEN

- *Introduction*
- Methods
- Results
- Conclusion

UNIVERSITY HOSPITALS LEUVEN

## Introduction

- **Surgical treatment** of deeply infiltrating endometriosis with colorectal involvement. (Meuleman et al, 2011)
- 49 studies (3894 patients)
- **Conclusion: " Data were reported in such a way that comparison of different surgical techniques was not possible"**

UNIVERSITY HOSPITALS LEUVEN

## Basis of checklist

- IDEAL-recommendations (McCulloch et al. Lancet 2009)
- CONSORT-statement (Begg et al. JAMA 1996, Moher et al. Lancet 2001)

UNIVERSITY HOSPITALS LEUVEN

- Introduction
- *Methods*
- Results
- Conclusion

UNIVERSITY HOSPITALS LEUVEN

## Methods

- Literature search
- ICD-11 definitions
- Expert review Leuven Endometriosis Team
- Planned: peer review by endometriosis experts worldwide

UNIVERSITY HOSPITALS LEUVEN

- Introduction
- Methods
- *Results*
- Conclusion

UNIVERSITY HOSPITALS LEUVEN

## Results

I. Reporting pre-and postoperative important data
II. Primary outcome measures
III. Secondary outcome measures
IV. Recovery and complications

UNIVERSITY HOSPITALS LEUVEN

## Results

I. Reporting pre-, per- and postoperative important data
II. Outcome measures: Pain and QOL
III. Outcome measures: Sexual, urological and GI function
IV. Recovery and complications

UNIVERSITY HOSPITALS LEUVEN

- Patient characteristics
- Pre-operative work-up & staging
- Surgical data

UNIVERSITY HOSPITALS LEUVEN

## Patient characteristics

- **Age, BMI, demographics,…**
- **Relevant medical history and treatment:**
- **Previous use of hormonal treatment**
- **Previous gynecological surgery:**
  - **Type (diagnostic, therapeutic) & number**
  - **Laparoscopy or laparotomy**
  - **Endometriosis-related or not**
- **Child wish completed/ child wish uncompleted/ child wish absent**

UNIVERSITY HOSPITALS LEUVEN

## Pre-operative work-up (1)

- Investigations: standardized report
  - Bimanual palpation
  - TRUS (transrectal ultrasound)
  - TVUS (transvaginal ultrasound)
  - Intravenous Urography (cystoscopy)
  - Double contrast barium enema
  - MIR
- Indications for surgery:
  - Pain: specify menstrual, nonmenstrual, dyspareunia, chronic nature
  - Infertility: type of child wish!
  - Others

UNIVERSITY HOSPITALS LEUVEN

## Pre-operative work-up (2)

- Intestinal DIE characteristics (Chapron et al, 2004):
  - Location of intestinal DIE lesions
  - Number of different intestinal DIE lesions (multifocality +++)
  - Largest diameter of lesions/nodules
  - Extent of DIE lesion(s) in the intestinal wall
  - Depth of intestinal DIE lesion(s) in the intestinal wall
  - Distance between intestinal DIE lesion(s) and the linea dentata
  - Existence of other associated DIE lesions (multifocality +++)
  - Number of other associated DIE lesions (multifocality +++)
  - Existence and extent of associated pelvic adhesions

UNIVERSITY HOSPITALS LEUVEN

## Surgical data (1)

- Operation time
- Length of hospital stay
- Detailed description of surgery, including name, experience and contribution of surgeon(s)
- Status pre- and post- surgery (ASRM, 1997; Adamson et al, 2011)
- Type of surgery:
  - Reconstructive versus ablative (Hysterectomy,Oophorectomy)
  - Laser, Ultracision, Unipolar, Scissors
  - Excision versus Vaporization/Coagulation

UNIVERSITY HOSPITALS LEUVEN

## Surgical data (2)

- Clear description of the surgical technique according to the following definitions (Meuleman et al 2011):
  - Shaving: superficial peeling of bowel serosal and subserosal endometriosis (with diathermy or laser)
  - Superficial excision: selective excision of the bowel endometriosis lesion without opening of the bowel wall
  - Full thickness disc excision: selective excision of the bowel endometriosis lesion with opening followed by closure of the bowel wall

UNIVERSITY HOSPITALS LEUVEN

## Surgical data (3)

- Bowel resection anastomosis: resection of a bowel segment affected by endometriosis followed by anastomosis.
  - Level of end-to-end anastomosis *(Davalos et al, 2007)*:
    - *High anterior resection: anastomosis >10cm from anal verge*
    - *Low anterior resection: anastomosis 6-10cm from anal verge*
    - *Ultra-low anterior resection/rectum resection: anastomosis <6cm from anal verge*

UNIVERSITY HOSPITALS LEUVEN

## Results

I. Reporting pre-and postoperative important data
II. Outcome measures: pain and QOL
III. Outcome measures: sexual, urological and GI function
IV. Recovery and complications

UNIVERSITY HOSPITALS LEUVEN

Primary outcome measures: Pain and QoL

- Essential publications:
  - IMMPACT recommendations (Turk et al, 2003; Dworkin et al, 2005.)
    - IMMPACT: Initiative on Methods, Measurement and Pain Assessment in Clinical Trials.
  - Pain scoring in endometriosis: entry criteria and outcome measures for clinical trials. Report from the Art and Science of Endometriosis meeting. (Vincent et al, 2010.)
- Checklist

UNIVERSITY HOSPITALS LEUVEN

IMMPACT-recommendations
Turk et al. Pain, 2003

Core domains for clinical trials of chronic pain treatment efficacy and effectiveness

Pain
Physical functioning
Emotional functioning
Participant ratings of global improvement
Symptoms and adverse events
Participant disposition (including adherence to the treatment regimen and reasons for premature withdrawal from the trial)

UNIVERSITY HOSPITALS LEUVEN

## IMMPACT-recommendations
## Dworkin et al. Pain, 2005

Recommended core outcome measures for clinical trials of chronic pain treatment efficacy and effectiveness

Pain
- 11-point (0–10) numerical rating scale of pain intensity
- Usage of rescue analgesics
- Categorical rating of pain intensity (none, mild, moderate, severe) in circumstances in which numerical ratings may be problematic

Physical functioning (either one of two measures)
- Multidimensional Pain Inventory Interference Scale
- Brief Pain Inventory interference items

Emotional functioning (at least one of two measures)
- Beck Depression Inventory
- Profile of Mood States

Participant ratings of global improvement and satisfaction with treatment
- Patient Global Impression of Change

Symptoms and adverse events
- Passive capture of spontaneously reported adverse events and symptoms and use of open-ended prompts

Participant disposition
- Detailed information regarding participant recruitment and progress through the trial, including all information specified in the CONSORT guidelines

UNIVERSITY HOSPITALS LEUVEN

## Art and Science of Endometriosis meeting (Vincent et al, 2010)

- Entry criteria
- Primary outcome measures
- Secondary outcome measures
- Tertiary outcome measures

UNIVERSITY HOSPITALS LEUVEN

## Entry criteria

- Surgical diagnosis of endometriosis within the last 5 years
- Pain symptoms
- Data capture at baseline:
  - ASRM-classification
  - Baseline pain scores over at least two menstrual cycles
  - EHP-30
- Previous treatments and responses

UNIVERSITY HOSPITALS LEUVEN

## Primary outcome measures

- Daily ratings of pelvic pain
- Daily ratings of dysmenorrhea
- Ratings on an 11-point NRS, anchored by
  0= no pain and 10=worst pain you can imagine, based on a recall of the worst pain experienced over the previous 24 hours
- Daily record of bleeding as none, spotting, light or heavy as compared with a normal period

UNIVERSITY HOSPITALS LEUVEN

## Secondary outcome measures (1)

- Biberoglu and Behrman (B&B) scale, administered weekly for 6 weeks, then monthly until 6 months then at 9,12,18,24 months
- EHP-30 (same time points as B&B)
- Use of rescue analgesia / therapies
- Study specific adverse event questionnaires (same time points as B&B)

UNIVERSITY HOSPITALS LEUVEN

## Secondary outcome measures (2)

- Detailed information as per the CONSORT guidelines including:
  - The recruitment process
  - The number of candidate participants who chose not to enter the trial and why
  - The use of prohibited concomitant medications and other protocol deviations
  - The number and reason for withdrawal from each treatment group
  - The types, rates and reasons for nonadherence with treatment in each group

UNIVERSITY HOSPITALS LEUVEN

## Tertiary outcome measures

- Daily NRS (or not applicable) of 3 symptoms important to the patient
- For example:
  - Dyspareunia
  - Dyschezia
  - Fatigue
  - etc

UNIVERSITY HOSPITALS LEUVEN

## The Endometriosis Health Profile-30

- EHP-30 (Jones et al, 2001)
- Disease specific questionnaire
- Measurement of the dimensions of health related QOLimportant to women with endometriosis

UNIVERSITY HOSPITALS LEUVEN

## Pain outcome measures: checklist

**Pain measurement (1):**

- Define the method used for pain measurement:
  - Pre- and/or post-surgery
  - Patient-based or doctor-based
  - Recommended use of 11-point numerical scale(NRS)
  - *Separate pain assessments for dysmenorrhea, nonmenstrual pelvic pain (and dyspareunia)*
  - Use of other methods (interviews, questionnaires): provide full details.
  - *Record and report concomitant use of other drugs/analgesics/therapies*
    - *E.g.: N patients using hormonal treatment at the time of pain assessment*
    - *Obtain an NRS before administration*
    - *Record indication for administration*

UNIVERSITY HOSPITALS LEUVEN

## Pain outcome measures: checklist

**Pain measurement (2)**

- *Address cyclicity:*
  - *Daily rating of bleeding*
  - *Recommended reporting categories: none, spotting, light or heavy (compared with a normal period)*
- *Obtain baseline data:*
  - *Baseline pain scores over at least two menstrual cycles*
  - *Baseline bleeding rating over at least two menstrual cycles*

UNIVERSITY HOSPITALS LEUVEN

## QOL

**QOL measurement:**

- Define the method used for QOL measurement (e.g. EHP-30, SF-36, EQ-5D)
  - *Recommended use of the EHP-30 (report separate scores and total scores)*
  - *Proposed timing: baseline, weekly the first 6 weeks after intervention, then monthly until 6 months and then at 9,12,18,24 months.*

UNIVERSITY HOSPITALS LEUVEN

## Results

I. Reporting pre-and postoperative important data
II. Outcome measures: pain
III. Outcome measures: sexual, urological and GI function
IV. Recovery and complications

UNIVERSITY HOSPITALS LEUVEN

## Outcome measures

- Female sexual dysfunction
- Bladder and urinary dysfunction
- Gastro-intestinal dysfunction

UNIVERSITY HOSPITALS LEUVEN

## Female sexual dysfunction: ICD-11

**All disorders to be classified into:**

- **-lifelong or acquired (after a period of normal sexual functioning)**
- **-Generalized (ie not limited to a specific partner or situation) or situational**
- **-caused by psychological or medical factors**

- **Sexual desire disorders (hypoactive or inhibited sexual desire and sexual aversion):**

**Hypoactive sexual desire disorder (HSDD)**

**Recurrent deficiency or absence of sexual fantasies or thoughts or desire for sexual activity causing marked distress and interpersonal difficulty**

- **Orgasmic disorders:**

**Orgasmic dysfunction**

**Persistent or recurrent delay in or absence of orgasm following a normal sexual excitement phase, resulting in distress or interpersonal difficulty**

- **Sexual pain disorders**

**Vaginismus**

**Recurrent or persistent involuntary contraction of the perineal muscles surrounding the outer third of the vagina when vaginal penetration with a penis, finger, tampon, or speculum is attempted**

UNIVERSITY HOSPITALS LEUVEN

## Bladder and urinary dysfunction

- **Evaluation of FLUTS (female lower urinary tract symptoms)**
  - **Symptoms tell the physician what bothers the patient.**
  - **Urodynamics defines the underlying pathophysiology.**
- **Subjective**
  - **History**
  - **Self-report instruments/questionnaires**
- **Semi-objective/quantitative**
  - **Clinical examination**
  - **Micturition diary**
  - **Pad test**
- **Objective**
  - **Urodynamics**
  - **Imaging**

UNIVERSITY HOSPITALS LEUVEN

## Gastro-intestinal dysfunction

- Anamnestic
  - E.g.: dyschezia, cyclic RBPA, IBS-complaints
  - Rome III-questionnaires
- Clinical examination
- Technical examinations
  - Radiological imaging
  - Colonoscopy

UNIVERSITY HOSPITALS LEUVEN

## Results

I. Reporting pre-and postoperative important data
II. Primary outcome measures
III. Secondary outcome measures
IV Recovery and complications

UNIVERSITY HOSPITALS LEUVEN

## Essentials from literature

- Complications:
  - The Clavien-Dindo Classification of surgical complications (Dindo et al, 2004)
- Recovery:
  - Systematic review on recovery specific quality of life instruments (Kluivers et al, 2008)

UNIVERSITY HOSPITALS LEUVEN

# Recovery: patient centered

- **Benefits of recovery-specific QoI instruments:**
  - **Quantitative feedback for the impact of complications**
  - **Measures the impact of new processes of care (surgical technology adoption)**
  - **When similar effectiveness in the cure of the underlying disease is expected**
- Possible instruments:
  - Quality of recovery-40 (Myles et al, 2000)
  - Convalescence and recovery (Hollenbeck et al, 2008)
  - Surgical recovery scale (Paddison et al, 2010)

UNIVERSITY HOSPITALS LEUVEN

# Complications: doctor based

Definitions of negative outcomes:

- **Complications**: any deviation from the normal post-operative course
  - Also asymptomatic complications
- **Sequelae**: an 'after-effect' of surgery that is inherent to the procedure
  - E.g. inability to walk after an amputation of the leg
- **Failure to cure**: if the original purpose of surgery has not been achieved
  - E.g. residual tumor after surgery
- Sequelae and failure to cure should not be included in the classification of complications.

UNIVERSITY HOSPITALS LEUVEN

Clavien-Dindo classification of surgical complications

| Grade | Definition |
|---|---|
| **Grade I** | Any deviation of the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside |
| **Grade II** | Requiring pharmacological treatment with drugs other than such allowed for grade I Blood transfusions and TPN are also included |
| **Grade III** | Requiring surgical, endoscopic or radiological intervention |
| **Grade IIIa** | Intervention not under general anesthesia |
| **Grade IIIb** | Intervention under general anesthesia |
| **Grade IV** | Life-threatening complication (including CNS complications) requiring IC/ICU management |
| **Grade IVa** | Single organ dysfunction (including dialysis) |
| **Grade IVb** | Multi-organ dysfunction |
| **Grade V** | Death of a patient |
| **Suffix D** | **If the patient suffers from a complication at the time of discharge the suffix 'D' (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication** |

UNIVERSITY HOSPITALS LEUVEN

- Introduction
- Methods
- Results
- *Conclusion*

UNIVERSITY HOSPITALS LEUVEN

## CONCLUSION

- Meuleman et al, HRU 2011: proposed checklist
- Current presentation: evolved checklist representing Leuven consensus
- Next step: external expert review → submission for publication → basis for international consensus

## References (1)


- Adamson GD. Endometriosis classification: an update. Curr Opin Obstet Gynecol 2011; 23: 213-220
- Chapron Ch, Chopin N, Borghese B, et al. Surgical Management of DIE: An Update. Ann. NY. Acad. Sci. 2004; 1034: 326–337.
- Clavien et al. The Clavien-Dindo classification of surgical complications: five year experience. Ann Surg 2009; 250: 187-196.
- De Cicco C, Corona R, Schonman R, Mailova K, Ussia A, Koninckx P. Bowel resection for deep endometriosis: a systematic review. BJOG 2011; 118: 285–291.
- Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240: 205-13.
- Dworkin RH et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005; 113: 9–19.
- Hedgepeth RC, Stuart Wolf J, Dunn RL, Wei JT and Hollenbeck BK. Patient-Reported Recovery After Abdominal and Pelvic Surgery Using the Convalescence and Recovery Evaluation (CARE): Implications for Measuring the Impact of Surgical Processes of Care and Innovation. Surg Innov. 2009; 16(3): 243–248.

# References (2)


- Hollenbeck BK, Dunn RL, Stuart J, Wolf J et al. Development and Validation of the Convalescence And Recovery Evaluation (CARE) for Measuring Quality of Life after Surgery. Qual Life Res. 2008; 17(6): 915–926.
- Jones G, Kennedy S, Barnard A, Wong J and Jenkinson C. Development of an Endometriosis Quality-of-Life Instrument: The Endometriosis Health Profile-30. Obstet Gynecol 2001;98:258–64
- Kluivers KB, Riphagen I, Vierhout ME, Brölmann HAM and de Vet HCW. Systematic review on recovery specific Quality-of-life instruments. Surgery 2008; 143: 206-15
- Kluivers KB et al. Clinimetric properties of 3 instruments measuring postoperative recovery in a gynecologic surgical population. Surgery 2008; 144: 12-21.
- McCulloch et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet 2009; 374: 1105-1112
- Meuleman Ch, Tomassetti C, D'Hoore A, Van Cleynenbreugel B, Penninckx F, Vergote I, D'Hooghe Th. Surgical treatment of deeply infiltrating endometriosis with colorectal involvmenet. Hum Reprod update 2011; doi 10.1093/humupd/dmq057.


# References (3)


- Moher et al. The CONSORT-statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001; 357: 191-194
- Myles PS, Weitkamp B, Jones K, Melick J and Hensen S. Validity and reliability of a postoperative quality of recovery score: the QoR-40. Br J Anaesth 200; 84: 11-15.
- Paddison JS, Sammour T, Kahokehr A, Zargar-Shoshtari K and Hill AG. Development and Validation of the Surgical Recovery Scale (SRS). J Surg Res 2001;167: e85–e91.
- Ret Davalos ML, De Cicco C, D'Hoore A, De Decker B, Koninckx PR. Ouctome after rectum or sigmoid resection: a review for gynaecologists. J Minim Inv Gynecol 2007;14:33-38
- Turk DC et al. Core outcome domains for chronic pain clinical trials: IMMPACT Recommendations. Pain 2003; 106: 337–345.
- Vincent K, Kennedy S and Stratton P. Pain scoring in endometriosis: entry criteria and outcome measures for clinical trials. Report from the Art and Science of Endometriosis meeting. Fertil Steril 2010; 93: 62–7.

28th ESHRE Annual Meeting
Pre-congress Course 4
Pain and Endometriosis

# Medical treatment of endometriosis-associated pain

Paolo Vercellini, M.D. & Maria Pina Frattaruolo, M.D.
Istituto Ostetrico Ginecologico "Luigi Mangiagalli"
Università degli Studi di Milano, Italy

## CONFLICT OF INTEREST

Paolo Vercellini has no conflict of interest to disclose

## LEARNING OBJECTIVES

1. Understand the general biologic background on which to base the indications for the use of medical therapies
2. Identify the drugs suitable for long-term treatments and evaluate their effect on various pelvic pain symptoms
3. Define therapeutic strategies aimed at reducing the risk of postoperative symptom and lesion recurrence, as well as of malignant degeneration of ovarian endometriosis

## GENERAL BACKGROUND

- Drugs used in the treatment of endometriosis are not cytoreductive
- Quiescent implants have been demonstrated in nearly all women treated with danazol, GnRH agonists and progestogens

## GENERAL BACKGROUND

- At restoration of ovulation and of physiological levels of estrogens, the endometrium, both eutopic and ectopic, resumes its metabolic activity
- Therefore, medical therapy is symptomatic and pain relapse at treatment suspension is the rule

## GENERAL BACKGROUND

- Drugs that are administered for relatively few months only, due to their poor tolerability, severe metabolic side-effects or high costs, do not greately benefit women with symptomatic endometriosis
- Progestogens alone or combined with estrogens are instead generally well-tolerated, have a more limited metabolic impact than danazol or GnRH agonists, are inexpensive and may be used on a long-term basis

PAIN SYMPTOM SCORES IN PATIENTS WITH ENDOMETRIOSIS BEFORE, AT THE END OF TREATMENT AND AT THE END OF FOLLOW-UP ACCORDING TO A LINEAR ANALOG SCALE

| Type of symptom | Goserelin | OC |
|---|---|---|
| Dysmenorrhea (*n*) | ( *n* = 26) | ( *n* = 24) |
| Baseline | 8.1 ± 2.4 * | 8.0 ± 1.9 |
| End of treatment | - | 3.7 ± 2.1 |
| End of follow-up | 7.5 ± 2.5 | 7.4 ± 1.7 |
| Dyspareunia (*n*) | ( *n* = 22) | ( *n* = 21) |
| Baseline | 6.4 ± 3.0 | 6.1 ± 3.3 |
| End of treatment | 2.1 ± 2.5 | 3.9 ± 2.9 |
| End of follow-up | 5.2 ± 3.0 | 5.6 ± 2.7 |
| Non-menstrual pain (*n*) | ( *n* = 26) | ( *n* = 24) |
| Baseline | 4.4 ± 3.2 | 4.2 ± 3.0 |
| End of treatment | 2.1 ± 2.2 | 1.9 ± 2.5 |
| End of follow-up | 3.9 ± 3.0 | 3.6 ± 2.6 |

* Values are means ± SDs

*Vercellini et al., 1993*

## IS MENSTRUATION REALLY NATURAL?

- Women and health professionals are conditioned to think of monthly menstruation as the holy grail of womanhood
- Monthly menstruation for decades on end is not the historical norm
- Current menstrual patterns are new and unproven as to their health effects

*Thomas & Ellertson, 2000*

VARIATION IN MENSTRUAL AND REPRODUCTIVE FACTORS OVER THE PAST CENTURY

| Variable | Foremothers | Modern women |
|---|---|---|
| Age at menarche (y) | 16 | 12 |
| Age at first birth (y) | 19 | 24-30 |
| Pregnancies (*n*) | 6 | 1-2 |
| Breast feeding | Years | Months |
| Ovulations and menstruations | 30-160 | 450 |

*Vercellini et al., 2010*

## IS MENSTRUATION REALLY NATURAL?

- There is plenty of modern evidence that amenorrhoea is often healthier then the alternative
- Disease directly caused by menstruation such as endometriosis would improve
- Health professionals and women ought to view menstruation as they would any other naturally occurring but frequently undesirable condition

*Thomas & Ellertson, 2000*

## ORAL CONTRACEPTIVE FOR SYMPTOMATIC ENDOMETRIOSIS

"The 7- day pill-free interval in each cycle has historical rather than medical justification.

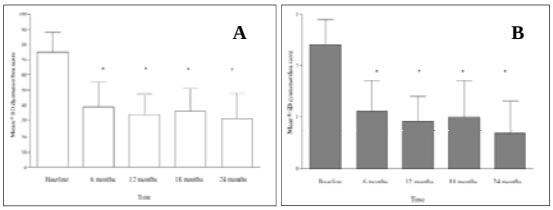
It is tempting to speculate that oral contraceptives may achieve greater control of endometriosis when administered continuously."

*Duleba et al., 1996*

## MENSTRUAL PATTERN IN 50 WOMEN DURING LONG-TERM CONTINUOUS OC USE

| | *n* | (%) |
|---|---|---|
| Amenorrhea | 19 | (38) |
| Spotting | 18 | (36) |
| Breakthrough bleeding | 13 | (26) |
| Mean ± SD no. of 1-week OC suspension | 5.5 | - |

*Vercellini et al., 2003*




Variations of intensity of dysmenorrhea after switch from cyclic to continuous oral contraceptive use. (**A**) Visual Analog Scale score. (**B**) Verbal Rating Scale score. Values are mean ± SD. ** p <.001* compared with corresponding baseline value, paired *t* test.

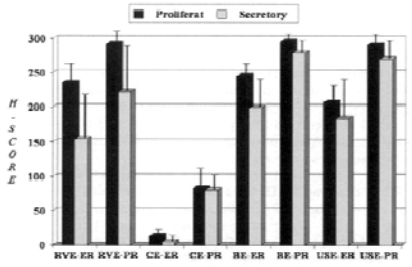
*Vercellini et al., 2003*

SATISFACTION WITH TREATMENT IN 50 WOMEN ON CONTINUOUS OC USE FOR ENDOMETRIOSIS ASSOCIATED RECURRENT DYSMENORRHEA

| | *n* | (%) |
|---|---|---|
| Very satisfied | 13 | (26) |
| Satisfied | 27 | (54) |
| Uncertain | 1 | ( 2) |
| Dissatisfied | 8 | (16) |
| Very dissatisfied | 1 | ( 2) |

*Vercellini et al., 2003*

Median H-score ± SE of estrogen (ER) and progesterone (PR) receptors in the smooth muscle component of rectovaginal (RVE), colonic (CE), bladder (BE), and uterosacral (USE) endometriosis




*Noel et al., 2009*

SUMMARY OF STUDY CHARACTERISTICS AND INTERVENTIONS FROM INDIVIDUAL REPORTS INCLUDED IN SYSTEMATIC REVIEW OF MEDICAL TREATMENT FOR RECTOVAGINAL ENDOMETRIOSIS

| Author | Year | Study design | No. of subjects | Diagnostic modality | Intervention | Duration of treatment | Criteria for pain evaluation |
|---|---|---|---|---|---|---|---|
| Fedele et al. | 2000 | Prospective non-comparative | 15 | US, MRI, histology | Leuprolide acetate 3.75 mg i.m./28d | 6 months | VRS |
| Fedele et al. | 2001 | Prospective non-comparative | 11 | US, MRI, histology | Levonorgestrel-releasing IUD | 12 months | VRS |
| Heller et al. | 2005 | Prospective non-comparative | ? | US, MRI, histology | Vaginal anastrozole 0.25 mg/d | 6 months | VAS |
| Vercellini et al. | 2005 | Randomised controlled trial | 90 | US, histology | Ethinyl estradiol 0.01 mg + cyproterone acetate 3 mg/d vs norethindrone acetate 2.5 mg/d per os | 12 months | VAS and VRS |
| Bazot et al. | 2007 | Prospective non-comparative | 21 | US, histology | Vaginal danazole 200mg/d | 12 months | VRS |
| Remorgida et al. | 2007 | Prospective non comparative | 12 | US, MRI histology | Oral letrozole 2.5 mg/d plus 2.5 mg/d norethisterone acetate | 6 months | VAS |
| Vercellini et al. | 2009 | Patient preference study | 58* | US, histology | Vaginal ethinylestradiol 0.015 mg + etonogestrel 0.12 mg/d vs transdermal ethinyl estradiol 0.02 mg + norelgestromin 0.15 mg/d | 12 months | VAS and VRS |

VAS = visual analogue scale. US = ultrasonography. MRI = magnetic resonance imaging. IUD = intrauterine device. VRS = verbal rating scale.
*Only subjects with rectovaginal endometriosis are considered.

*Vercellini et al., 2009*

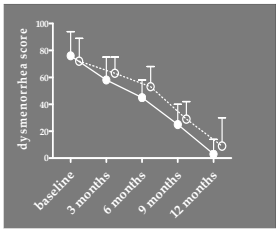
## STUDY CHARACTERISTICS

- Women with persistent rectovaginal endometriotic plaques after conservative surgery
- Parallel-group, randomized controlled trial
- Etynil Estradiol + Cyproterone acetate 0.01 mg + 3 mg
- Norethindrone acetate 2.5 mg
- Continuos oral administration of treatments
- 12 months follow-up

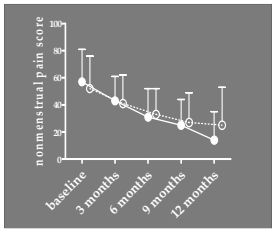
*Vercellini et al., 2005*

## PAIN SYMPTOMS VARIATIONS

DYSMENORRHEA




NONMENSTRUAL PAIN

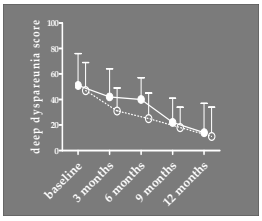



EE+CA NETA

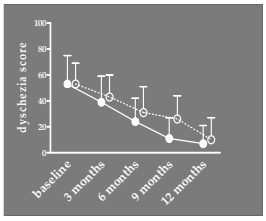
*Vercellini et al., 2005*

## PAIN SYMPTOMS VARIATIONS

DEEP DYSPAREUNIA



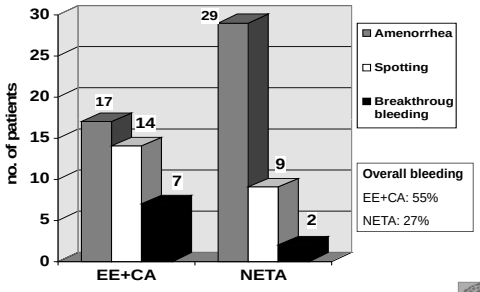

DYSCHEZIA




EE+CA NETA

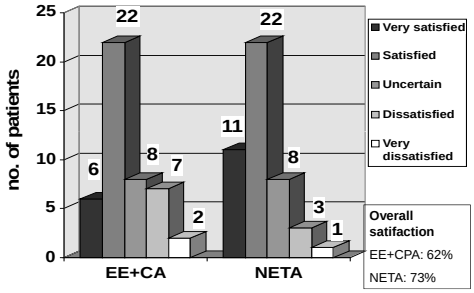
*Vercellini et al.,2005*

## BLEEDING PATTERN




*Vercellini et al., 2005*

## DEGREE OF SATISFACTION




*Vercellini et al., 2005*

## PROGESTINS FOR RECTOVAGINAL ENDOMETRIOSIS

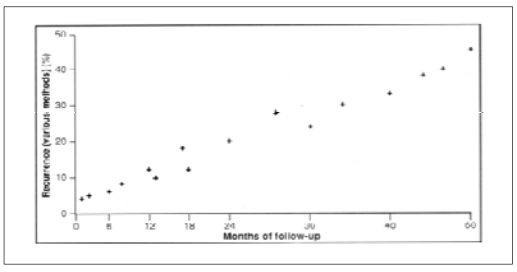
Low-dose oral norethisterone acetate (2.5 mg/day) should be considered the first-line option for medical treatment of rectovaginal endometriosis due to a very favourable efficacy/safety/tolerability/cost ratio.

## PROGESTINS FOR RECTOVAGINAL ENDOMETRIOSIS

Women's consent to surgery should no longer be sought based solely on the purposed uselessness of pharmacological therapies.

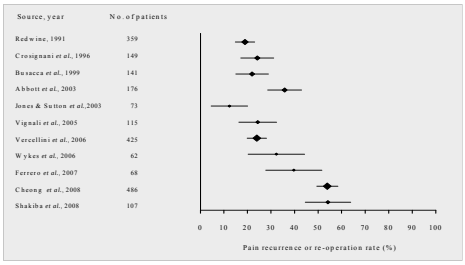
*Vercellini et al., 2005*

Cumulated literature data from studies reporting recurrence of endometriosis showing a gradual but steady increase in recurrence figures over the first five years of follow up.



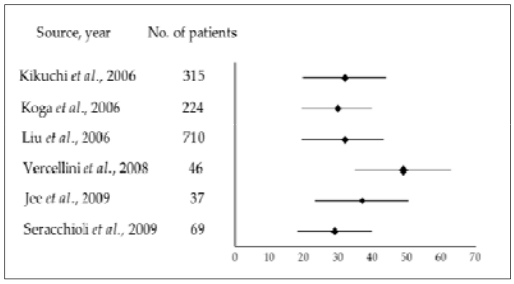

*Evers et al., 1991*

PAIN RECURRENCE OR RE-OPERATION RATES REPORTED AFTER FIRST-LINE CONSERVATIVE SURGERY FOR SYMPTOMATIC ENDOMETRIOSIS. LITERATURE DATA, 1991-2008, OBSERVATIONAL AND RETROSPECTIVE STUDIES.




*Vercellini et al., 2009*

REPORTED INCIDENCE OF POSTOPERATIVE ENDOMETRIOMA RECURRENCE. LITERATURE DATA, 2006-2009



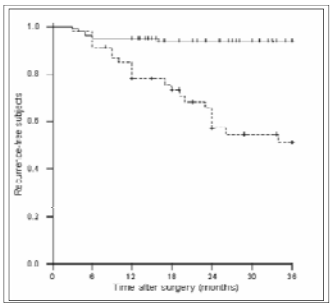

## MEDICAL TREATMENT OF ENDOMETRIOSIS

If ovulation is causally related to endometriotic cyst development, ovarian suppression after conservative surgery for endometrioma would greatly reduce the risk of lesion recurrence

## POSTOPERATIVE OC EXPOSURE AND RISK OF ENDOMETRIOMA RECURRENCE

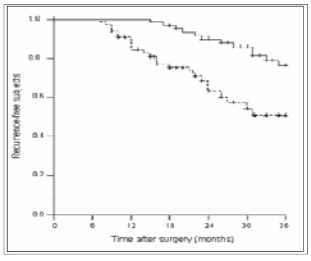
After conservative surgery for endometriomas, patients not seeking pregnancy were offered long-term oral contraception with a cyclic, low-dose, monophasic OC containing EE 0.02 mg and desogestrel 0.15 mg

*Vercellini et al., 2008*




36-month endometrioma recurrence-free survival analysis after conservative laparoscopic surgery according to the treatment modality adopted: (——) oral contraception for the entire follow-up period ($n$ = 102); (- - -) expectant management ($n$ = 46) (log-rank test, $\chi^2_1$ = 36.2; $P$ < .001)

*Vercellini et al.,2008*




36- month endometrioma recurrence-free survival analysis after conservative laparoscopic surgery according to duration of postoperative oral contraceptive use: (——) 12 months or more ($n$ = 62); (-------) less than 12 months ($n$ = 67) (long rank test, $\chi^2_1$ = 11.9; $P$ <.001)

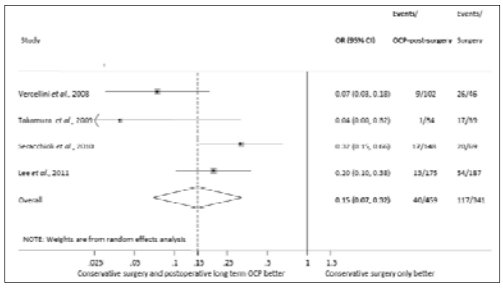
*Vercellini et al.,2008*

## POSTOPERATIVE OC EXPOSURE AND RISK OF ENDOMETRIOMA RECURRENCE

| | |
|---|---|
| Relative Risk Reduction: | 80% |
| Absolute Risk Reduction: | 47% (95% CI , 37-57) |
| Number Needed to Treat: | 2 (95% CI , 0.2-7) |

*Vercellini et al.,2008*

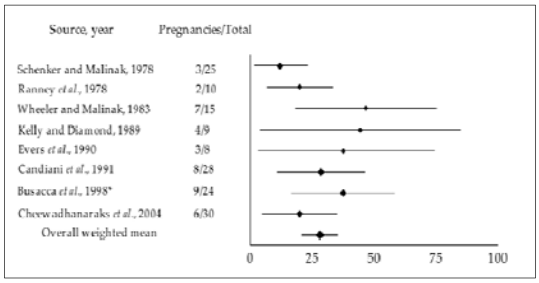
## RESULTS OF STUDIES COMPARING CONSERVATIVE SURGERY FOR OVARIAN ENDOMETRIOMAS WITH OR WITHOUT POSTOPERATIVE LONG-TERM ORAL CONTRACEPTIVE USE




*Horizontal lines* indicate 95%CIs; *boxes* show the study-specific weight; *rhombi* represent combined effect sizes; *dashed line* indicates the overall estimate.

*Vercellini et al.,2012*

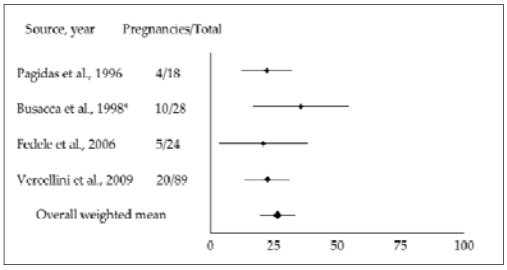
## STUDIES REPORTING PREGNANCY RATE AFTER REPETITIVE SURGERY FOR ENDOMETRIOSIS AT LAPAROTOMY.




* Only women operated at laparotomy are considered.

*Vercellini et al.,2009*

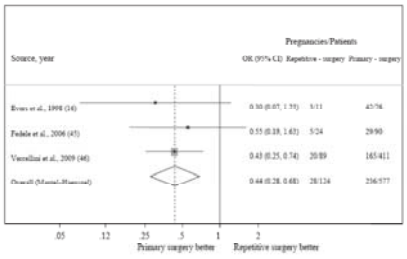
STUDIES REPORTING PREGNANCY RATE AFTER REPETITIVE SURGERY FOR ENDOMETRIOSIS AT LAPAROSCOPY.




* Only women operated at laparoscopy are considered.

*Vercellini et al.,2009*

RESULTS OF STUDIES COMPARING REPETITIVE SURGERY FOR RECURRENT ENDOMETRIOSIS WITH FIRST-LINE SURGERY FOR PRIMARY DISEASE




Horizontal lines indicate 95%CIs; boxes show the study-specific weight; rhombi represent combined effect sizes; dashed line indicates the overall estimate. Breslow-Day test for heterogeneity: $\chi^2 = 0.45$, $P = 0.79$.

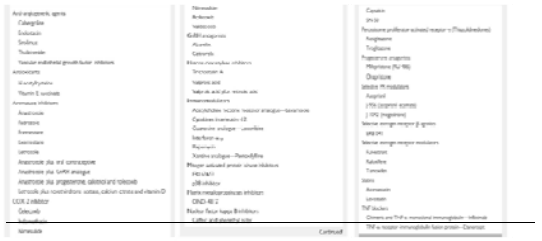
*Vercellini et al.,2009*

MEDICAL TREATMENT OF ENDOMETRIOSIS

Prevention of recurrences and repeat surgery should be mainstays in long-term therapeutic strategies for women with endometriosis, especially in those seeking pregnancy in the future

## MEDICAL TREATMENT FOR ENDOMETRIOSIS

Experimental drugs and proposed future therapeutic schemes for endometriosis (literature data 1987-2010)



*Vercellini et al., 2011*

Human Reproduction, Vol.24, No.6 pp. 1267–1275, 2009
Advanced Access publication on March 4, 2009 doi:10.1093/humrep/dep045

human reproduction NEW DEBATE

# A call for more transparency of registered clinical trials on endometriosis

**Sun-Wei Guo[1,7], Lone Hummelshoj[2], David L. Olive[3], Serdar E. Bulun[4], Thomas M. D'Hooghe[5], and Johannes L.H. Evers[6]**

[1]Renji Hospital, and the Institute of Obstetric and Gynecologic Research, Shanghai Jiao-Tong University School of Medicine, Shanghai 200001, China [2]Endometriosis.org, 89 Southgate Road, London N1 3JS, England [3]Wisconsin Fertility Institute, Madison, WI, USA [4]Division of Reproductive Biology Research, Department of Obstetrics and Gynecology, Northwestern University, Chicago, IL, USA [5]Department of Obstetrics and Gynaecology, Leuven University Fertility Center, UZ Gasthuisberg, B-3000 Leuven, Belgium [6]Division of Reproductive Medicine, Research Institute GROW, Maastricht University Medical Center, NL 6202 AZ Maastricht, The Netherlands

[7]Correspondence address. Institute of Obstetric and Gynecologic Research, Shanghai Jiao Tong University School of Medicine, Renji Hospital, 145 Shandong Zhong Road, Shanghai 200001, China. Fax: +86 21 53 88 23 77; E-mail: hmm610@gmail.com

Human Reproduction, Vol.26, No.1 pp. 1–11, 2011
Advanced Access publication on November 11, 2010 doi:10.1093/humrep/deq303

human reproduction DEBATE

# 'Waiting for Godot*†': a commonsense approach to the medical treatment of endometriosis

**Paolo Vercellini[1,*], PierGiorgio Crosignani[1], Edgardo Somigliana[2], Paola Viganò[3], Maria Pina Frattaruolo[1], and Luigi Fedele[1]**

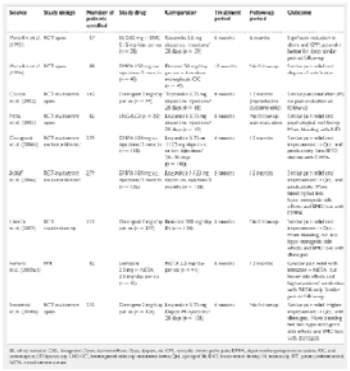
[1]Department of Obstetrics and Gynaecology, Istituto Luigi Mangiagalli, University of Milan, Milan, Italy [2]Infertility Unit, Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy [3]Centre for Research in Obstetrics and Gynaecology (C.R.O.G.), Milan, Italy

*Correspondence address. E-mail: paolo.vercellini@unimi.it

MEDICAL TREATMENT FOR ENDOMETRIOSIS

" The general principles that should guide medical management of endometriosis are not different from those applicable to other chronic inflammatory disorders: achievement of long phases of disease remission is the reasonable goal, and reappearance of symptoms at drug discontinuation must not be considered as a demonstration of inefficacy of therapy"

Effect of OCs and progestins as assessed in controlled trials on the treatment of symptomatic endometriosis (literature data, 1990-2010)



*Vercellini et al.,2011*

Cost of 12 months of continuous medical treatment of rectovaginal endometriosis; Italy, 2009

| Medication | Cost | | |
|---|---|---|---|
| | € | £ | $ |
| Letrozole 2.5 mg/day* | 2104 | 1868 | 2713 |
| Anastrozole 1 mg/day* | 2046 | 1817 | 2638 |
| Depot GnRHagonist | 1804–2160 | 1602–1918 | 2372–2784 |
| Danazol 600 mg per os/day | 821 | 729 | 1068 |
| Danazol 200 mg per vaginam/day | 274 | 243 | 353 |
| Vaginal ring† | 233 | 206 | 297 |
| Transdermal patch† | 220 | 195 | 280 |
| Low-dose monophasic OC† | 80–260 | 71–230 | 101–331 |
| Levonorgestrel-releasing IUD | 38 | 34 | 49 |
| Norethisterone acetate 2.5 mg/day** | 18 | 16 | 22 |

*Cost probably higher owing to the need for combination with other standard regimens inhibiting ovulation.
**Partly reimbursed by the Italian National Health System with an overall yearly patient cost of €9–£2.6–$6.
†Cost potentially higher owing to the need for system removal/replacement when treatment is ceasing.
‡The least expensive OCs contain 30 μg of EE and are partly reimbursed by the Italian National Health System with an overall yearly patient cost of €18–£16–$20.

*Vercellini et al., 2011*

## MEDICAL TREATMENT FOR ENDOMETRIOSIS

Scientific glasnost

- Outcome selection
- Placebo-controlled design
- Monophasic OCs taken continuously or low-dose NETA as the reference comparator
- Satisfaction with treatment vs pain relief
- Duration of study
- Intention-to-treat analysis

## ORAL CONTRACEPTIVE (OC) USE AND OVARIAN CANCER RISK IN WOMEN WITH ENDOMETRIOSIS

Women with endometriosis are at increased risk of ovarian cancer.
(OR, 1.32; 95% CI, 1.06-1.65)

OC use for > 10 years is associated with a substantial reduction in risk among women with endometriosis.
(OR, 0.21; 95% CI, 0.08-0.58)

*Modugno et al.,2004*

## ENDOMETRIOSIS, OCS, AND OVARIAN CANCER

"To date, only OCs have emerged as chemopreventive agents against ovarian cancer. OCs are prescribed commonly for women with endometriosis. Our data suggest that this clinical practice may have an added benefit: protection against ovarian cancer. When women with endometriosis are being treated, the use of OCs, especially long-term use, should be encouraged."

*Modugno et al., 2004*

## CONCLUSIONS

- Medical treatment plays a role in the therapeutic strategy for women with endometriosis only if it can be administered over a prolonged period of time
- Progestogens are effective in controlling pain symptoms in appoximately 3 out of 4 women with symptomatic endometriosis

  Their effect does not seem to be significantly inferior to that obtained with other drugs habitually used in treating the disease
- Given their good tolerability, minor metabolic side effects and low cost, progestogens should be considered as first-line drugs

## MEDICAL TREATMENT FOR ENDOMETRIOSIS CONCLUSIONS

The revolution of concepts in the last 30 years:

From the maximum tolerable treatment

To the minimum effective treatment

Umberto Veronesi, 2012

## REFERENCES I


- Duleba AJ, Keltz MD, Olive DL. Evaluation and management of chronic pelvic pain. J Am Assoc Gynecol Laparosc 1996;3:205-27.
- Evers JL, Dunselman GA, Land JA, Bouckaert PX. Is there a solution for recurrent endometriosis? Br J Clin Pract Suppl 1991;72:45-50; discussion 51-3.
- Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG, Goodman MT. Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. Am J Obstet Gynecol 2004;19:733-40.
- Noël JC, Chapron C, Bucella D, Buxant F, Peny MO, Fayt I, Borghese B, Anaf V. Estrogen and progesterone receptors in smooth muscle component of deep infiltrating endometriosis. Fertil Steril 2010;93:1774-7.
- Thomas SL, Ellertson C. Nuisance or natural and healthy: should monthly menstruation be optional for women? Lancet 2000;355:922-4.
- Vercellini P, Trespidi L, Colombo A, Vendola N, Marchini M, Crosignani PG. A gonadotropin releasing hormone agonist versus a low-dose oral contraceptives for pelvic pain associated with endometriosis. Fertility and Sterility 1993;60:75-9.

## REFERENCES II


- Vercellini P, Frontino G, De Giorgi O, Pietropaolo G, Pasin R, Crosignani PG. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to cyclic pill regimen. Fertility and Sterility 2003;80:560-563.
- Vercellini P, Pietropaolo G, De Giorgi O, Pasin R, Chiodini A, Crosignani PG. Treatment of symptomatic rectovaginal endometriosis with an estrogen-progestogen combination versus low-dose norethindrone acetate. Fertil Steril 2005;84:1375-87.
- Vercellini P, Somigliana E, Daguati R, Viganò P, Meroni F, Crosignani PG. Postoperative oral contraceptive exposure and risk of endometrioma recurrence. American Journal of Obstertics and Gynecology 2008;198:504.e1-5.
- Vercellini P, Crosignani PG, Abbiati A, Somigliana E, Viganò P, Fedele L. The effect of surgery for symptomatic endometriosis: the other side of the story. Human Reproduction Update 2009;15:177-188.
- Vercellini P, Crosignani PG, Somigliana E, Berlanda N, Barbara G, Fedele L. Medical treatment for rectovaginal endometriosis: what is the evidence? Human Reproduction 2009;24:2504-2514.


## REFERENCES III


- Vercellini P, Crosignani PG, Somigliana E, Viganò P, Consonni D, Barbara G, Fedele L. The effect of second-line surgery on reproductive performance of women with recurrent endometriosis. Acta Obstetricia et Gynecologica Scandinavica 2009;88:1074-1082.
- Vercellini P, Somigliana E, Viganò P, De Matteis S, Barbara G, Fedele L. Postoperative endometriosis recurrence: a plea for prevention based on pathogenetic, epidemiologic, and clinical evidence. Reproductive Bio Medicine Online 2010;21:259-265.
- Vercellini P, Crosignani PG, Somigliana E, Viganò P, Frattaruolo MP, Fedele L. “Waiting for Godot”. A commonsense approach to the medical treatment of endometriosis. Human Reproduction 2011;26:3-13.
- Vercellini P, De Matteis S, Somigliana E, Buggio L, Frattaruolo MP, Fedele L. Postoperative medical therapy for the prevention of endometrioma recurrence. Acta Obstetricia et Gynecologica Scandinavica 2012, in press.

**Mark your calendar for the upcoming ESHRE Campus events**

- Basic Semen Analysis Course in Greek Language
  4-7 September 2012 - Athens, Greece
- Basic Genetics for ART practitioners
  7 September 2012 - Rome, Italy
- Regulation of quality and safety in ART – the EU Tissues and Cells Directive perspective
  14-15 September 2012 - Dublin, Ireland
- Basic Semen Analysis Course in Spanish language
  18-21 September 2012 - Galdakano,Vizcaya
- GnRH-antagonists in ovarian stimulation
  28 September 2012 - Hamburg, Germany
- The best sperm for the best oocyte
  6-7 October 2012 - Athens, Greece
- Basic Semen Analysis Course in Italian language
  8-11 October 2012 - Rome, Italy
- Accreditation of a preimplantation genetic diagnosis laboratory
  11-12 October 2012 - Istanbul, Turkey
- Endoscopy in reproductive medicine
  21-23 November 2012 - Leuven, Belgium
- Evidence based early pregnancy care
  29-30 November 2012 - Amsterdam, The Netherlands

www.eshre.eu
(see "Calendar")

Contact us at info@eshre.eu

eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

# NOTES

# NOTES

# NOTES

# NOTES

# NOTES

# NOTES

# NOTES

# NOTES