PRE-CONGRESS COURSE 5

Impact of pelvic pain and uterine bleeding on quality of life.

Special Interest Group Endometriosis/Endometrium
London - UK, 7 July 2013
Impact of pelvic pain and uterine bleeding on quality of life

London, United Kingdom
7 July 2013

Organised by
The ESHRE Special Interest Group Endometriosis/Endometrium
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Upcoming ESHRE Campus Courses  

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Course coordinators

Hilary Critchley (United Kingdom)

Course description

Multidisciplinary content addressing:
- what we know now about pain and uterine bleeding
- what we need to know to improve treatment outcomes
- how to prioritise basic research that can be translated into patient benefit
- the impact of pelvic pain and menstrual bleeding disturbances on quality of life for women. This topic will encompass (but not exclusively) the clinical conditions of endometriosis, fibroids, and HMB (heavy menstrual bleeding) – the focus will be upon symptoms and impact of interventions on the patient from a multidisciplinary perspective.
- medical, surgical, and complementary therapy outcomes will be addressed in terms of morbidity, mortality, quality of life (pain & bleeding), and fertility.
- future research priorities proposed by each speaker for discussion at the end of each presentation

Target audience

All providers of care for women with the complaints of pelvic pain and unacceptable menstrual bleeding. This will include care-providers of women with endometriosis, fibroids, and HMB: including clinicians, scientists (especially those with an interest in bleeding and pain mechanisms) and psychologists with an interest in quality of life and the impact of pelvic pain and bleeding. We welcome the attendance of those who provide multi-/cross-discipline care provision.
Scientific programme

Chairman: Andrew Horne - United Kingdom

09:00 - 09:30  Pain and bleeding and quality of life – the evidence  
   Cindy M. Farquhar - New Zealand
09:30 - 09:45  Discussion
09:45 - 10:15  "From basic research to clinical management - are we improving women's quality of life?"  
   Peter Rogers - Australia
10:15 - 10:30  Discussion

10:30 - 11:00 Coffee break

11:00 - 11:30  Endometrialgia: Neuronal pathways in the perception of endometriosis-associated pain  
   Thomas Lundeberg - Sweden
11:30 - 11:45  Discussion
11:45 - 12:15  Pelvic pain and bleeding – the impact on female sexuality  
   Brigitte Leeners - Switzerland
12:15 - 12:30  Discussion

12:30 - 13:30 Lunch

13:30 - 14:00  Medical management and patient benefit  
   Khalid Khan - United Kingdom
14:00 - 14:15  Discussion
14:15 - 14:45  Pelvic surgery and patient benefit  
   Philippe Koninckx - Belgium
14:45 - 15:00  Discussion

15:00 - 15:30 Coffee break

15:30 - 16:00  Psychologically-informed pain management and pain self-management  
   Amanda Williams - United Kingdom
16:00 - 16:15  Discussion
16:15 - 16:45  Quality of life outcomes and trial regulation: influence on future clinical study design  
   Stephen Kennedy - United Kingdom
16:45 - 17:00 Discussion
Pain and bleeding and quality of life – the evidence

Professor Cindy Farquhar
MBChB MD FRANZCOG FRCOG CREI MPH MNZM
National Women’s and University of Auckland
ESHRE Precongress Course
London
July 2013

Declaration

• No commercial conflicts of interest for the past 15 years
• Co-ordinating editor of Cochrane Menstrual Disorders and Subfertility Group

Objectives

• Describe the problem of pain and bleeding for women in the reproductive age group
• Quality of life – what is it? How do we measure it?
• How can we improve the way we consider quality of life in women with pain and bleeding?
The evidence base.....

- Electronic searches of Medline and Embase and the Cochrane Library
- Google Scholar
- Dates – up to February 2013
RCTs for chronic pelvic pain, asthma, back pain, menorrhagia and fibroids

• Unfunded report from Pain Australia and the Faculty of Pain Medicine at the Australian and New Zealand College of Anaesthesia 2011
• Authors: Deborah Bush (EndometriosisNZ), Dr Susan Evans and Prof Theirry Vancaille

Professor Michael Cousins...

"However, pelvic pain has suffered from particularly inappropriate stigmatisation and neglect, with resulting disastrous effects on women and young girls. Thus I am very pleased to see this report giving due emphasis to the special needs of pelvic pain."

Chairman of the IASP International Pain Summit Montreal 2010

The $8 Billion Women and the $800 Million Girl
Food for thought in this report......

- Reluctance of women to seek medical care
  - Patients often given uninformed explanations of pain
  - Often feel dismissed
- Gynaecology may be slow to pick up on some of the advances in pain research
  - New nerve growth in endometriotic lesions
  - Chemical stimulation of inflammatory processes
  - Inadvertent nerve damage as a result of surgery

Chronic pelvic pain

- Definition
  - Chronic pain is defined as “pain that lasts for more than three months”
  - Pelvic pain is defined as “abdominal pain occurring below the level of the umbilicus”
    International Association for the Study of Pain
- Chronic pelvic pain is defined as “abdominal pain occurring below the level of the umbilicus that lasts for more than three months”
- In a report of 101 studies on CPP only 44% mentioned duration (Williams et al 2004)

Chronic pelvic pain

- Recognised pathologies
  - Endometriosis/adenomyosis*
  - Adhesions
  - Ovarian remnant*
  - Residual ovary*
  - Cyclical pattern
- No obvious pathologies
  - Pelvic congestion*
  - Primary dysmenorrhea*
  - Midcycle pain*
  - Irritable bowel syndrome
  - Entrapped nerve syndrome
  - Neuropathic pain
  - Painful bladder syndrome
Some Patterns of Pain in Women

Abdomino-pelvic pain

• Common
  – 20-25% of all gynaecological outpatient consultations include some aspect of chronic or recurring pain
  – 30-50% of diagnostic laparoscopies are for pain
  – 5-10% of all hysterectomies

WHO systematic review 2006: “a neglected reproductive health morbidity”
WHO review on chronic pelvic pain 2006

- 106 studies of dysmenorrhoea
  - 17%-81% prevalence
- 54 studies of dyspareunia
  - 8-22% prevalence
- 18 studies of non cyclical pain
  - 2% to 24% prevalence
  - Higher in developed countries
    - US: 15% of women between the ages of 18 and 50 years (did not include mid cycle pain) (Mathias 1996)
    - UK: 24% (Zondervan 2001)
    - NZ: 25% (Grace 2004)

The burden of disease of chronic pelvic pain

- Pelvic pain lasting > 6 months occurs in 38/1000 women in primary care
  - asthma 37/1000 and chronic back pain 41/1000
  - Zondervan et al 1999
- “The impact significantly disrupts quality of life and causes major downstream problems for individuals, families, communities, health and welfare costs and productivity”
  - $6 Billion Dollar report

The cost of chronic pelvic pain

- Is mostly about endometriosis....
- Major cause of workplace absenteeism and presenteeism
- Cost of managing women with chronic pelvic pain is estimated at £3-600 M per year (2005)
- In 2011 – World Endometriosis Research Fund report
  - In Ireland, USA, UK, and Italy: the average extra cost/week/woman to the employer is $200 - $250/week in absenteeism
The $6 Billion refers just to women with endometriosis in Australia and is direct costs only (estimates of 1 in 10 women).

The $6 million refers just to adolescents.

Back to this...

World Endometriosis Research Foundation - report 2011

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Mean number of episodes per woman with and without endometriosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endometriosis (n = 396)</td>
</tr>
<tr>
<td>Mean episode frequency (0-7)</td>
<td>4.2 (4.0)</td>
</tr>
<tr>
<td>% No episode (%)</td>
<td>3.0 (3.0)</td>
</tr>
<tr>
<td>% 1 episode (%)</td>
<td>7.0 (7.0)</td>
</tr>
<tr>
<td>% 2 episodes (%)</td>
<td>7.0 (7.0)</td>
</tr>
<tr>
<td>% 3 episodes (%)</td>
<td>7.0 (7.0)</td>
</tr>
<tr>
<td>% 4 episodes (%)</td>
<td>7.0 (7.0)</td>
</tr>
<tr>
<td>% 5 episodes (%)</td>
<td>7.0 (7.0)</td>
</tr>
<tr>
<td>% 6 episodes (%)</td>
<td>7.0 (7.0)</td>
</tr>
<tr>
<td>% 7 episodes (%)</td>
<td>7.0 (7.0)</td>
</tr>
</tbody>
</table>

Ninoaham et al 2011

Evidence report published in 2012

- Key points
  - Difficulty with lack of uniform definition of CPP
  - Study populations vary widely
  - Treating symptoms not a condition
  - Poor evidence base for either surgical or medical interventions
Bleeding problems

• FIGO definition of abnormal uterine bleeding
  – bleeding from the uterine body that is abnormal in duration, volume, and/or frequency and has been present for the majority of the last 6 months
  – Prevalence is 11-13% increasing to 24% in women aged 36-45 years old
  – Related to likelihood anemia

The impact of heavy periods...

<table>
<thead>
<tr>
<th></th>
<th>LNG – IUS</th>
<th>Thermal balloon ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of bleeding (mean (SD))</td>
<td>7.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Number of days of heavy bleeding (mean (SD))</td>
<td>3.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Number of days of painful bleeding (mean (SD))</td>
<td>3.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Unable to leave house on heaviest days</td>
<td>17 (40%)</td>
<td>12 (29%)</td>
</tr>
<tr>
<td>Number of days housebound*</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Sleep disturbed</td>
<td>39 (95%)</td>
<td>39 (95%)</td>
</tr>
<tr>
<td>Number of nights disturbed* (mean (SD))</td>
<td>2.9</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*Only includes women who were housebound or had nights disturbed

Quality of Life
Quality of Life is a uniquely personal perception, denoting the way that individual patients feel about their health status and/or non-medical aspects of their lives.

Editorial in The Lancet 1995

“Quality of life in clinical medicine represents the functional effect of an illness and its consequent therapy upon the patient as perceived by the patient.”

Schipper et al 1996

When is QoL assessment a relevant endpoint?

- When it is the main endpoint (Palliative care or an incurable disease)
- Treatments may be expected to be equivalent in efficacy
- A treatment may show a small benefit that might be offset by adverse effects on QoL
- A treatment might be associated with potential adverse events
- Overall failure rate of treatment is high
Patient-based Outcome Measures for clinical trials

- Appropriateness
  – Is the content appropriate to answer the question posed by the trial?
- Reliability
  – Are the results reproducible and internally consistent?
- Validity
  – Does the instrument measure what it claims to measure?
- Responsiveness
  – Does the instrument detect changes over time?

Patient-based Outcome Measures for clinical trials

- Precision
  – How precise are the scores of the instrument?
- Interpretability
  – How interpretable are the scores?
- Acceptability
  – Is the instrument acceptable to patients?
- Feasibility
  – Can it be easily administered and processed?

Does the instrument assess what it purports to assess?
The selection of a patient-based measure for a trial therefore remains to some extent a matter of judgement and as much an art as a science

Fitzpatrick et al. HTA Assessment 1998

Patient related outcome measures (PROM)
RCOG Paper 31 April 2012
- Consists of a series of questions which patients are asked...with the aim of gauging their views on their own health
- Not a measure of symptoms but should also include an assessment of function and health related quality of life

Patient Reported Outcome Measures
- General/generic measures
  – eg Euro-Qol Group 1990 (EQ-5D)
  – Eg SF-36
- Disease-specific measures
  – Eg Uterine Fibroid Symptom and Quality of Life (UFS-QOL)
Potential benefits and limitations of PROM data

**Benefits**
- Inform patient choice by getting patients to compare their outcomes against PROM scores of others
- Assess the impact of an intervention based on PROM data rather than a surrogate marker
- Appraise the quality of care provided
- Use PROM data to triage referrals

**Limitations**
- A change in PROM can not be attributed to the intervention
- Low response rates
- Cost
- Data security

Generic Instruments

**Advantages**
- Assess a broad range of health problems.
- Useful if no disease-specific instrument exists
- Allows comparison across treatments and conditions
- Provides normative data
- They can assess the health status of individuals not recruited because they have a specific disease
- May identify outcomes that were not anticipated
- When used for many conditions gives strong body of evidence that enhances value of interpretation

**Disadvantages**
- Sacrifices some level of detail
- Questionnaire items less relevant
- Less sensitive to change
SHORT FORM 36 (SF 36)

- previously validated questionnaire
- used to assess health status
- 36 questions assessing 8 dimensions of health
  - PHYSICAL
  - EMOTIONAL
  - SOCIAL

Variables of the SF 36
- PF: Physical functioning
- RP: Role limitation as a result of physical problems
- BP: Bodily pain
- GH: General health
- VI: Vitality
- SF: Social functioning
- RE: Role limitation resulting from emotional problems
- MH: Mental health

SF 36

- Low back pain
- Menorrhagia
  - Validated by Garrett et al 1993
- Peptic ulcer disease
- Varicose veins

EQ5D

- 5 questions with 3 different response categories
  - Mobility
  - Self care
  - Usual activity
  - Pain/anxiety
  - Anxiety/depression
Disease Specific Measures

- Advantages
  - Items developed to assess a particular health problem
  - Likely to detect change with time
  - Likely to be acceptable

- Disadvantages
  - Can only be administered to an individual with that particular disease
  - Cannot be compared with general population or those with different conditions
  - Will not capture unexpected outcomes

The problem of assessing QoL in women with pain and bleeding

- Cyclical nature problem
- Generic instruments less valuable
- Need to assess impact of symptoms themselves
- What is most important to the patient? (e.g. clots, flooding etc)

Disease or condition specific measures

- Examples
  - Uterine Fibroid Symptom – Quality of Life
  - Ruta Menorrhagia Questionnaire
  - Menorrhagia Utility Scale
  - Menorrhagia Outcomes Questionnaire
Uterine Fibroid Symptom – Quality of Life

- Spies 2004
  - 37 questions on fibroid symptoms
    - 8 symptoms questions
    - 29 health related quality of life
  - Usefulness tool for detecting differences in symptom severity and health related quality of life amongst women with fibroids
  - Suggested that it may be used to monitor treatment of women with fibroids

UFS-QOL

- Has been compared with
  - SF-36
  - Menorrhagia Questionnaire
  - Revicki-Wu Sexual Function Scale
  - Clinical variables
  - Self-rated symptom severity

Report on PROM by the University of Oxford

- Disease Specific measures
  - Concluded that the UFS-QOL was an instrument with "good supportive evidence for use for women with fibroids..."
- Generic measures
  - Recommended EQ-5D and SF-36
- Noted that there is no instruments for women with menorrhagia
Randomized controlled trials and quality of life measures

From the Cochrane Register of Trials
• Chronic pelvic pain: 21 rcts
• Fibroids: 16
• Menorrhagia: 48

Studies with heavy menstrual bleeding including fibroids

Reporting using UFS-QOL for fibroids
Quality of life measures for heavy menstrual bleeding

Table 4. Quality of life (SF-36) at randomisation and at 3, 12 and 24 months (including treatment failures). Values are given as mean (SD).

<table>
<thead>
<tr>
<th>SF-36 scores</th>
<th>Overall (n = 79)</th>
<th>TBA (n = 31)</th>
<th>LNG+US (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomisation</td>
<td>63.7 (19.0)</td>
<td>63.7 (14.4)</td>
<td>63.7 (22.7)</td>
</tr>
<tr>
<td>3 months</td>
<td>77.9 (15.7)</td>
<td>78.2 (14.7)</td>
<td>77.7 (17.0)</td>
</tr>
<tr>
<td>17 months</td>
<td>79.1 (14.6)</td>
<td>76.0 (16.0)</td>
<td>79.5 (16.6)</td>
</tr>
<tr>
<td>24 months</td>
<td>76.2 (13.6)</td>
<td>74.0 (18.0)</td>
<td>77.5 (20.1)</td>
</tr>
</tbody>
</table>

TBA, thermal balloon ablation.

MEA versus TCRE

Fig. 5.1. Short Form 36 scores

REST Study
“Among existing QoL instruments there is good compliance with the quality criteria for measurement properties but not those for clinical validity. There is a need to develop methodologically sound disease specific QoL instruments in menorrhagia focussing on both face validity and measurement properties”.

Clark et al 2002

What’s next?

• RCOG has embarked on PROM development for heavy menstrual bleeding
• No progress in the assessment of women with chronic pain
From basic research to clinical management – are we improving women's quality of life?

Peter AW Rogers PhD
Professor of Women's Health research
University of Melbourne
Dept Obstetrics and Gynaecology
Royal Women's Hospital

Commercial relationships and potential conflicts of interest: Nil

Learning Objectives

From basic research to clinical management
are we improving women's quality of life?

- Translation of basic research to clinical practice in women's health
- Examples of successful translation
- Current basic research - the potential for translation
One of the most consistent findings from clinical and health services research is the failure to translate research into practice and policy. McGlynn and colleagues observed that patients in the USA received 55% of recommended care, and that quality varied by medical condition ranging from 79% of recommended care for senile cataract to 11% of recommended care for alcohol dependence [McGlynn et al NEJM 2003]. Similar findings have been reported globally in both developed and developing settings, in both primary care and specialty-provided care and in care provided by all disciplines [Grol, 2001].

From basic research to clinical management are we improving women's quality of life?

- Impact of pelvic pain and uterine bleeding on quality of life
- Clinical conditions of endometriosis, fibroids, and HMB
- How to prioritise basic research that can be translated into patient benefit?

From basic research to clinical management are we improving women's quality of life?

- Translation of basic research to clinical practice in women's health
- Examples of successful translation
- Current basic research - the potential for translation

From basic research to clinical management are we improving women's quality of life?

**Clinical Advances** (endometriosis, fibroids, HMB)

- Surgical technology/minimally invasive
- Anaesthetics
- Diagnostic Imaging
- Steroid hormone formulations
Progestin effects on endometrium
Progesterone and progestins
Progesterone receptors
The nuclear receptor superfamily
PR co-activators & co-repressors

From basic research to clinical management are we improving women’s quality of life?

Clinical Advances (endometriosis, fibroids, HMB)
• Surgical technology/minimally invasive
• Anaesthetics
• Diagnostic Imaging
• Steroid hormone formulations
• Mirena
• Patient reported outcomes

From basic research to clinical management are we improving women’s quality of life?

Not as much as we would like …
From basic research to clinical management are we improving women's quality of life?

- Translation of basic research to clinical practice in women's health
- Examples of successful translation
- Current basic research - the potential for translation

From basic research to clinical management are we improving women's quality of life?

- Impact of pelvic pain and uterine bleeding on quality of life
- Clinical conditions of endometriosis, fibroids, and HMB
- How to prioritise basic research that can be translated into patient benefit?

Original Article

Defining Future Directions for Endometriosis Research: Workshop Report From the 2011 World Congress of Endometriosis in Montpellier, France

Peter A. W. Rogers, BSc, PhD¹, Thomas M. D’Hooghe, MD, PhD²,³, Asgerally Fazilebasi, PhD⁴, Linda C. Giudice, MD, PhD, MSc⁵, Grant W. Montgomery, PhD⁶, Felice Petraglia, MD⁷, and Robert N. Taylor, MD, PhD⁸

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Defining Future Directions for Endometriosis Research: Workshop Report From the 2011 World Congress of Endometriosis in Montpellier, France

• A total of 56 recommendations for research have been developed, grouped under 6 subheadings: (1) diagnosis, (2) classification and prognosis, (3) clinical trials, treatment, and outcomes, (4) epidemiology, (5) pathophysiology, and (6) research policy.

• By producing this consensus international research priorities statement, it is the hope of the workshop participants that researchers will be encouraged to develop new interdisciplinary research proposals that will attract increased funding support for work on endometriosis.
Genome-wide association meta-analysis identifies new endometriosis risk loci

In addition:
- rs4141819 at 2p14
- rs13394619 in GREB1
- Rs7739264 at 6p22.3
- rs10859871 at 12q22 near VEZT.

Confirm:
- rs7521902 at 1p36.12 near WNT4.
- rs12700667 at 7p15.2
- rs1537377 at 9p21.3

Evidence for association with all endometriosis from the GWA meta-analysis for 1p36.12, 2p25.1 and 12q22 regions following imputation using the 1000 Genomes Project reference panel. Diamond and circle symbols represent genotyped and imputed SNPs, respectively. The most significant genotyped SNP is represented by a purple diamond. All other SNPs are color coded according to the strength of LD with the top genotyped SNP (as measured by $r^2$ in the European 1000 Genomes data). From Nyholt et al. 2012.

WNT4 region of chromosome 1

Single probe for WNT4 on Illumina HT12 Chips.
88% of GWAS "hits" are in introns or intergenic
ENCODE data show 12% overlap transcription factor binding sites and 34% overlap DHS sites
For SNPs in LD 31% overlap transcription factor binding sites and 71% overlap DHS sites

The closest gene, NFE2L3 highly expressed in placenta
HOXA10 and HOXA11 play a role in uterine development and peak expression at the time of implantation does not occur in women with endometriosis

Most GWAS hits probably affect gene expression
- 1,509 published GWAS; >210 traits (Feb 2013)
- >88% variants are located in intronic and intergenic regions (challenges current understanding of how genome works!)
- Likely that trait-associated alleles exert their effects through gene expression
  - transcript levels and splicing
- Much to learn about control of gene regulation

Freedman (2011) Nature Genetics 43: 513

• So, how far from the bedside are we??
Translating GWAS Results into Disease Mechanisms and Drugable Targets

- Better understanding of the pathophysiology of endometriosis
- New clinical interventions
- As of February 2013, there were 1509 publications and 8523 significant SNPs reported (US National Human Genome Research Institute NHGRI; Bethesda, MD; http://www.genome.gov/gwasstudies).

Published GWA Reports, 2005 – 6/2012

Published Genome-Wide Associations through 07/2012
Published GWA at p≤5X10⁻⁸ for 18 trait categories

NHGRI GWA Catalog
www.genome.gov/GWAStudies
www.ebi.ac.uk/ippt/gwas/
Value of GWAS studies

- While GWAS results provide valuable biological insights for many common diseases, the translation of the genetics findings from GWAS into the clinic remains limited and a topic of intense debate.
- Out of 991 GWAS genes, 212 (21%) were considered druggable, and 469 (47%) potentially biopharmable.
- 1,089 genes (6% of the genome) being pursued as a target by a launched product, a candidate in clinical phase or in preclinical development. Of 991 GWAS genes, 155 (15.6%) had an associated drug project
- Provides evidence that GWAS data not only give insights into the biology of diseases, but may lead to immediate translational opportunities for drug discovery and development.

Sanseau et al. VOLUME 30 NUMBER 4 APRIL 2012 NATURE BIOTECHNOLOGY

The road from a gene target to an approved marketed drug takes in general more than ten years and most GWAS results have only been obtained over the past four years.

Ie: For endometriosis, new drugs based on current GWAS work are 10-20 years away.

Sanseau et al. VOLUME 30 NUMBER 4 APRIL 2012 NATURE BIOTECHNOLOGY

From basic research to clinical management are we improving women’s quality of life?

- Impact of pelvic pain and uterine bleeding on quality of life
- Clinical conditions of endometriosis, fibroids, and HMB
- How to prioritise basic research that can be translated into patient benefit?
A genome wide association study identifies three loci associated with susceptibility to uterine fibroids

Bar-Chama E1, Akinci T2, Johnston JJ3, Leal SM4, Tuvat C5, Gotay P6, Mercado E7, Leal SM4, Kao H8, Mieczkowska E8, Barrasso D9, Nishida N9, Wieland S10, Tanaka M11, Pycock I12, Leal SM4, Tuvat C2. Estrogen-Receptor beta is a common feature of the female genital tract. We conducted a genome wide association study in 6,674 black (with serum estradiol in 1,683 individuals) and 1,683 white women, with uterine leiomyoma (Mendelian randomization analysis). A single nucleotide polymorphism (SNP) in the long arm of chromosome 6 (rs2106661) showed evidence for association with the risk of uterine leiomyoma in African Americans and White women. This SNP was associated with susceptibility to uterine leiomyoma in women, with serum estradiol levels, and with uterine leiomyoma in women with estradiol levels above the median. This study supports the hypothesis that estrogen receptor beta is a common feature of the female genital tract and that the risk of uterine leiomyoma is increased in women with high serum estradiol levels.

RESULTS

- High levels of variability occur both with fibroid ultrasound appearance and differential gene expression.
Figure 3. Molecular mechanisms of GnRHa (FDA approved) and LNG-IUS (FDA approved for IUD users only), mifepristone, asoprisnil, CDB-2914, CDB-4124, epigallocatechin gallate, pirfendine, and aromatase inhibitors (under clinical trial) on fibroid regression and symptomatic improvement.

Islam et al., J Clin Endocrinol Metab, March 2013, 98(3):921–934

Medical treatment = tiadifinexac, mefendamicid acid, combined estrogen–progestogen, or progesterone alone.

CONCLUSIONS
In women with menorrhagia who presented to primary care providers, the Iud nonprogestin-IUS was more effective than usual medical treatment in reducing the effect of heavy menstrual bleeding on quality of life.

Mirena: IUD with LNG, a progestin from the 1960’s, still better than any of the more recent medical approaches for treating HMB.
Success rate in translating basic research into clinical practice is generally poor, and
Time lag from bench to bedside is long.

Current fundamental research in Women’s Health is discovering significant new information on pathophysiology
Translation still a major challenge
Endometrialgia: neuronal pathways in the perception of endometriosis-associated pain

Irène Lund and Thomas Lundeberg
Department of Physiology and Pharmacology, Karolinska Institutet
FAAB, Sabbatsbergshospital,
Stockholm
Sweden

Relating Pelvic Pain Location to Surgical Findings of Endometriosis.

Obstet Gynecol. 2011 August; 118(2 Pt 1): 223-230
A Pilot Study of the Prevalence of Leg Pain Among Women with Endometriosis


From the Periphery to the Brain

Ascending Pathways

<table>
<thead>
<tr>
<th>Prefrontal Cortex</th>
<th>Sensory Cortex</th>
<th>Limbic Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>PAG</td>
<td>Hypothalamus</td>
</tr>
<tr>
<td>Brain stem</td>
<td>Formatio reticularis NRAM</td>
<td></td>
</tr>
</tbody>
</table>
Hypothetical scenario for endometriosis: the 'brain-body-brain cross talk'.

Central projections

Prefrontal Cortex
Cognitive

Sensory Cortex

Fear analysis:
1. Fear avoidance
2. Catharticizing

Limbic structures
Affective

Illness responses:
1. Decreased deep sleep
2. Altered food intake
3. Social isolation
4. Depression

Descending Pathways

Cortex
Hypothalamus

Brain stem

Neurotransmitters:
Serotonin Noradrenaline Endorphins

Facilitation
Inhibition

Neurotransmitters
CCK Serotonin
Pain classification - aetiology

ADAPTIVE
- Nociceptive pain (adhesion)
- Inflammatory pain (cyst)

MALADAPTIVE
- Neuropathic pain (postsurgical nerve, lesion)
- Idiopathic/Functional pain (central sensitisation, disinhibition, central facilitation)

Pain classification

ADAPTIVE - Nociceptive pain

Adhesions - traction, distension - activation of nociceptive mechanoreceptors in the viscera results in an increased sympathetic tone and muscular activity.

Influence of endometriosis on visceromotor and cardiovascular responses induced by vaginal distention in the rat.

Pain classification

ADAPTIVE: Inflammatory pain (cyst)

Neuroendocrine-immune disequilibrium in endometriosis

Chiu et al., Nat Neurosci. 2013 February 01.

Chiu et al, Nat Neurosci. 2013 February 01.
Distance of pain from border of lesion.


Interstitial Cystitis and Endometriosis in Patients With Chronic Pelvic Pain: The “Evil Twins” Syndrome


Pain classification

MALADAPTIVE
- Neuropathic pain (postsurgical nerve lesion)

1. Stimulus evoked - Hyperphen.
2. Allodynia
3. Spontaneous
Pain classification
MALADAPTIVE
• Idiopathic/Functional pain (central sensitisation, central facilitation)

Target sites for pain treatment
Periphery
Spinal cord
Brain stem
Brain

Endometrialgia: Holistic treatment
Polytherapy
Fear/Anxiety
Pain
Sleep/ fatigue
Function
Pain inhibiting factors:
- Compassion, positive expectation, happiness, relaxation, warmth, breathing exercise, visualisation
- Acupuncture, low frequency TENS, exercise, opioids, antidepressants, antiepileptics
- High frequency TENS, massage, vibration, warmth, NSAIDS
- Local anaesthetics, NSAIDs, paracetamol, NAC, Acupuncture, LLLT

Periphery

Central
Brain stem

Promises for the future?
Endocannabinoid involvement in endometriosis

Pain as a reward: Changing the meaning of Pain from negative to positive co-activates opioid and cannabinoid systems


Pain is a negative emotional experience.

When the meaning of the pain experience is changed from negative to positive through verbal suggestions, the opioid and cannabinoid systems are co-activated and these, in turn, increase pain tolerance.
Pelvic pain and bleeding
the impact on female sexuality?

Learning objectives

• Understand the impact of pelvic pain and bleeding on female sexuality
• Get an insight on the underlying pathophysiological mechanisms
• Receive a differentiated understanding of the interaction between endometriosis-associated pain and female sexuality on the background of first evaluations of the „Zurich Endometriosis- Quality of life study”
• Learn the state of the art on the correlation of bleeding and female sexuality
• Increase the competence in patient counselling for sexual disorders associated with pelvic pain and bleeding

Psycho-social/sexual pre-conditions

Specific individual/ female needs
Sexual competence
Quality of partnership
Socio-cultural influences
Hormone

Female sexuality

Physical pre-conditions

Perception of own attractiveness
Genital anatomy
Vascularisation/ Lubrication
Neuronal regulation
Genetical influences
General disease/ mental diseases

Brigitte Leeners, Division for Reproductive Endocrinology, University Hospital Zurich

- No conflicts of interests -
Dyspareunia - vaginism

Causes of pelvic pain

Gynaecological
- Endometriosis
  - Pain
    - Dysmenorrhea 70%
    - General pelvic pain 70%
    - Dyspareunia 40%
    - Pain at defaecation & micturition
  - Fatigue
  - PID/adhesions
  - Pelvic varicosity
  - Ovarian retention syndrome

Psychosomatic chronic pelvic pain
Non-gynaecological disorders
- Irritable bowel syndrome
- Bladder pain syndrome
- Myofascial pain syndromes
- Fibromyalgia

Pelvic pain and sexuality

- Independent from the actual cause of CPP it leads to a significant reduction of sexual satisfaction
- Patients with CPP: more sexual problems than patients with any other type of chronic pain
- Anxiety and depression may mediate the effect of CPP on sexual problems

Collett, 1998; Howard, 2012; Jan Kuile, 2010; Tripoli, 2011
Swelling of endometriotic lesions
Bleeding into surrounding tissues
Secretion of inflammatory substances
Cognitive evaluation of pain
Attitude towards occurrence and control of pain
Subjective pain threshold
Generalized hypersensitivity
Dysfunctional behavior
Physical tension

Endometriosis-associated pain

Zurich Endometriosis - Quality of life study

• Swiss-German Multicenter Study
  • Questionnaire
    - Socio-demographic data
    - Endometriosis
    - Pain (modified version BPI and PDI)
    - Resources (SOC), STI (PSQ20)
    - Stress perception (PSQ20)
    - Education and profession
    - Satisfaction with medical support
    - Childhood experiences (Modified version CTQ)
    - Lifestyle, daily life
    - Partner (PFB)
    - Sexuality (modified version BISF, GSF)
    - Anxiety, Depression (PHQ, GAD)

• Confirmation of Endometriosis/ASRM Stage according to medical charts

First Symptoms

<table>
<thead>
<tr>
<th>ASRM</th>
<th>&lt; 1 year</th>
<th>1-5 years</th>
<th>6-10 years</th>
<th>&gt; 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (N=44)</td>
<td>4/9.1</td>
<td>8/16.8</td>
<td>15/31.9</td>
<td>15/31.9</td>
</tr>
<tr>
<td>II (N=53)</td>
<td>3/5.7</td>
<td>8/15.1</td>
<td>13/25.1</td>
<td>23/45.3</td>
</tr>
<tr>
<td>III (N=74)</td>
<td>5/8.1</td>
<td>10/19.1</td>
<td>23/47.6</td>
<td>50/73.0</td>
</tr>
<tr>
<td>IV (N=106)</td>
<td>5/8.7</td>
<td>12/23.2</td>
<td>32/60.4</td>
<td>56/59.8</td>
</tr>
<tr>
<td>Unknown (N=89)</td>
<td>4/6.5</td>
<td>7/12.2</td>
<td>19/33.3</td>
<td>45/50.6</td>
</tr>
<tr>
<td>Total (N=366)</td>
<td>18/4.9</td>
<td>26/5.2</td>
<td>78/21.1</td>
<td>170/46.4</td>
</tr>
</tbody>
</table>
**Number of operations**

<table>
<thead>
<tr>
<th>ASRM</th>
<th>1 (N=42)</th>
<th>2 (N=57)</th>
<th>3 (N=78)</th>
<th>4 (N=107)</th>
<th>Unknown (N=92)</th>
<th>Total (N=380)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/5.5</td>
<td>3/5.3</td>
<td>3/2.6</td>
<td>5/4.7</td>
<td>1/1.1</td>
<td>15/3.9</td>
</tr>
<tr>
<td></td>
<td>18/42.9</td>
<td>26/45.6</td>
<td>42/53.8</td>
<td>31/37.5</td>
<td>39/41.9</td>
<td>160/41.1</td>
</tr>
<tr>
<td></td>
<td>3/15.7</td>
<td>2/40.4</td>
<td>3/10.1</td>
<td>3/14.0</td>
<td>3/20.0</td>
<td>56/14.2</td>
</tr>
<tr>
<td></td>
<td>5/11.9</td>
<td>2/3.5</td>
<td>6/7.7</td>
<td>12/14.0</td>
<td>25/26.9</td>
<td>54/14.2</td>
</tr>
<tr>
<td></td>
<td>3/7.1</td>
<td></td>
<td>2/2.6</td>
<td>12/14.3</td>
<td>7/11.5</td>
<td>19/5.0</td>
</tr>
</tbody>
</table>

**Pain & daily duration of pain**

<table>
<thead>
<tr>
<th>ASRM</th>
<th>&lt;1 h</th>
<th>1-2 h</th>
<th>3-9 h</th>
<th>10-24 h</th>
<th>unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>77/15.6</td>
<td>14/31.5</td>
<td>6/16.7</td>
<td>52/13.1</td>
<td>52/13.1</td>
<td>105/21.9</td>
</tr>
<tr>
<td></td>
<td>8/11.4</td>
<td>13/26.9</td>
<td>6/12.3</td>
<td>77/13.3</td>
<td>32/18.0</td>
<td>161/31.6</td>
</tr>
<tr>
<td></td>
<td>1/2.1</td>
<td>3/6.5</td>
<td>1/2.1</td>
<td>3/6.3</td>
<td>1/2.1</td>
<td>1/2.1</td>
</tr>
<tr>
<td></td>
<td>3/6.5</td>
<td>1/2.1</td>
<td>3/6.3</td>
<td>1/2.1</td>
<td>1/2.1</td>
<td>1/2.1</td>
</tr>
<tr>
<td></td>
<td>27/5.5</td>
<td>57/11.5</td>
<td>25/4.8</td>
<td>50/10.2</td>
<td>50/10.2</td>
<td>149/30.2</td>
</tr>
</tbody>
</table>

**Intensity of pain and estimated effect on sexuality**
Sexual satisfaction

Sex despite dyspareunia because of partner

Interactions of different sexual disorders
CAVE
Solving Chronic pelvic pain does not necessarily solve the sexual problem!

Berceron, 2001; Goldfinger, 2009

Bleeding

- Increased risk for sexually transmitted diseases
- Exacerbation of infectious diseases
- Dysmenorrhea
- Sexual preferences
  - Religious concerns?
  - Esthetic aspects?
  - Odour?
  - Staining?
Sexual activity during menses:
Epidemiology

- 3-30% of sexually active women
  (Lurie, 2010)
  - Adolescent women: 2.4-4%
    (Hensel, 2007; Hensel, 2004)
  - Adult women: 25-30%, 16% last menstrual period
    (Barnhart, 1995; Tanfer, 1996; Kalichman, 2005)

- Feeling comfortable with menses
  - Sexual activity during menstruation
    (Hensel, 2007; Tanfer, 1996; Rempel, 2003)

Brigitte Leeners, Division for Reproductive Endocrinology, Zurich

- Higher arousal with romantic and unconventional sexual activities
  - Reduced sensitivity to disgust
  - Higher partner support

- Higher sexual interest
  - Greater reported frequency of intercourse
  - Larger number lifetime partners

- Use of marijuana before intercourse
  - Better education, high income, white

Intercourse during menses and STDs

- Enhanced ascension of bacteria - loss of endocervical barrier
- Reflux of potentially contaminated blood (chlamydia trachomatis, mycoplasma hominis) into fallopian tubes
- Iron (from menstrual flow) promotes gonococcal growth
- Sloughing of endometrium enhances bacterial penetration into bloodstream
- Alteration immune system
- Female to male transmission of infected blood (HIV, Hep B + C)

Ehrhardt 1991; James, 1978; Aleksander, 1996
Sexual intercourse during menses: STDs

<table>
<thead>
<tr>
<th>Behavior</th>
<th>% Ever STD</th>
<th>Odds Ratio</th>
<th>Adjusted Odds Ratio</th>
<th>Unweighted Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercourse during last menstrual period</td>
<td>No</td>
<td>32.38</td>
<td>2.083</td>
<td>202</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>14.13</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Usually intercourse during menstrual cycle</td>
<td>No</td>
<td>27.78</td>
<td>2.629</td>
<td>540</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>13.7</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Women who have ever had vaginal intercourse

HIV, Chlamydia, Genital herpes, Condyloma, Gonorrhea, Syphilis, Trichomonas, Gardnerella vaginalis, Hepatitis B, Chancroid

Tanfer, 1996

Dysmenorrhea and SFQ-Scores

<table>
<thead>
<tr>
<th>Sexual Function Questionnaire Scores in Patients With and Without Lifelong Dysmenorrhea</th>
<th>LD - Average Domain Score</th>
<th>No LD - Average Domain Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desires</td>
<td>4.87 ± 2.39</td>
<td>4.52 ± 1.73</td>
</tr>
<tr>
<td>Arousal (Sensation)</td>
<td>2.33 ± 1.50</td>
<td>1.83 ± 1.63</td>
</tr>
<tr>
<td>Arousal (Lubrication)</td>
<td>5.35 ± 3.16</td>
<td>4.87 ± 2.37</td>
</tr>
<tr>
<td>Arousal (Cognitive)</td>
<td>5.17 ± 3.37</td>
<td>4.83 ± 2.44</td>
</tr>
<tr>
<td>Orgasm</td>
<td>3.04 ± 1.65</td>
<td>2.82 ± 1.31</td>
</tr>
<tr>
<td>Pain</td>
<td>6.80 ± 4.66</td>
<td>5.92 ± 7.08</td>
</tr>
<tr>
<td>Deployment</td>
<td>5.0 ± 7.07</td>
<td>4.5 ± 1.98</td>
</tr>
<tr>
<td>Parity</td>
<td>2.67 ± 1.71</td>
<td>3.5 ± 1.24</td>
</tr>
</tbody>
</table>

LD - Lifelong Dysmenorrhea; p – NS (all tests).

Meik, 2010

Dysmenorrhea

- Is more frequent in women with sexual dysfunctions
- Is particularly frequent in the age range 26-31 years

Sarracino, 2008
Diseases & menstrual cycle

- Asthma (↑ premenstrual/during menstruation)
- Arthritis (↑ premenstrual/during menstruation)
- Diabetes (↑ premenstrual/during menstruation)
- Depressionen, suicide (↑ premenstrual/during menstruation)
- Epilepsia (↑ premenstrual/during menstruation)
- Hospitalization in psychiatric hospital (↑ during menstruation)
- Cardiovascular events (↑ during menstruation)

Counselling

- Investigate circumstances of onset of symptoms
- Active offer to discuss sexuality/integrate sexual counselling into health care
- Information on pathophysiological background of dyspareunia/dysmenorrhoea
  - Physical + psychosomatic/ aspects i.e. direct and indirect mechanisms
- Question on sexual abuse experiences
- Information on strategies to solve the problem
  - Exploration, communication and realization of individual sexual needs
  - Adequate foreplay
  - Different positions and sexual „techniques”

Transferal to a specialist in Sexual medicine

- When feeling inadequately trained for/unwell with sexual counselling
- In case of specific sexual problems for example vaginism, hypoactive sexual desire disorder
- When no amelioration occurs after 2-3 consultations
References

Medical management and patient benefit – *Khalid Khan (United Kingdom)*

Contribution not submitted by the speaker
**Pelvic Surgery and Patient Benefit**

*Knowledge has to be sucked into the brain, not pushed into it.*

Victor F. Weisskopf, in *The Privilege of Being a Physicist*

*Surgery is Intellectual, not technical.*

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**Pelvic Surgery : Teaching aims**

- The decision to do surgery
  - Symptoms and exams
  - Absolute and relative indications to do surgery
  - Background knowledge
- The surgical intervention
  - Diagnostic
  - Therapeutic
    - What can be done ↔ should be done
    - How do we organize surgery
- The claimed benefits
- Pitfalls to avoid

---

**Pelvic pain : the decision to do surgery**

- The decision to do surgery
  - Symptoms and exams
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  - Background knowledge
- The surgical intervention
  - Diagnostic
  - Therapeutic
    - What can be done ↔ should be done
    - How do we organize surgery
- The claimed benefits
- Pitfalls to avoid
Gynaecological Pain: Where?

- Below the umbilicus eventually radiating to the back

Gynaecological Pain: Radiation

- Below the umbilicus eventually radiating to the back
- Ovarian pain can be lateralised and radiates up to the knee, anterior medial side

Isolated back pain is not gynaecological

Below the knee is not gynaecological
### Gynaecological Pain: Radiation

- Perineal radiation is pathognomonic for bowel pain, i.e., rectum up to rectosigmoid not mentioned spontaneously.

### Sacroiliac Joint: Radiation

- Back pain and ipsilateral fossa pain
- Gets worse during rest, e.g., at night

**Isolated back pain is not gynaecological**

**Frequent cause of unnecessary surgery**

### Gynaecological Pain: Cyclicity

- Endometriosis pain typically increases during menstruation
- Dyschesia in larger deep endometriosis, e.g., blood
- Mictalgia for bladder endometriosis

**But all pain increases during menses...**

**Increase thus is not pathognomonic for endo**
Causes of chronic pelvic pain

We only recognise what we know

• Where when type?
• Clinical exam
  • Abnormalities?
  • Palpation?
• Ultrasound
  • +++ ovaries
  • ++ uterus
  • + deep endometriosis
• Decision
  • dismiss
  • surgery-more exams

Pelvic pathology
  • Endometriosis
  • Adhesions
  • Ovarian cysts....
  • Oviduct: hydrosalpinx, eup
  • Uterus: adenomyosis, myoma
  • Pelvic floor and retroversion
  • Pelvic congestion
  • Chronic PID
  • Chronic EUG

Intestinal pathology
  • Colon, appendix, small bowel
  • Functional and organic
  • Interstitial cystitis
  • Referred pain from sacro iliac joint
  • Nerve entrapment in the wall

Pelvic congestion
• Chronic PID
• Chronic EUG

• Adenomyosis
• Peritoneal pockets – Müllerianosis - Choristoma

Decision

• Additional exams: Never go fishing
• Decision to do surgery is based upon
  • Presumptive diagnosis and severity of pain
  • Alternative treatments
  • Risk to miss the diagnosis
• Once decision is taken
  • Do we need additional exams?
  • Preoperative preparation
  • Anticipated duration and difficulty of surgery

Symptoms vary with lesion

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Pain</th>
<th>Infertility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtle</td>
<td>80%</td>
<td>no</td>
</tr>
<tr>
<td>Typical</td>
<td>25%</td>
<td>in 50% +</td>
</tr>
<tr>
<td>Cystic</td>
<td>10%</td>
<td>in 80% +++</td>
</tr>
<tr>
<td>Deep</td>
<td>2-3%</td>
<td>in 95% ++++</td>
</tr>
</tbody>
</table>

Adenomyosis

Peritoneal pockets – Müllerianosis - Choristoma
How to suspect Deep endo?

- Pain symptoms
- Perineal radiation
- Dysmesis (blood)
- Mictalgia (blood)
- Dy DD CP
- Aided by exams

- Pelvic pathology
- Deep Endometriosis
- Adhesions
- Ovarian cysts...
- Oviduct: hydrosalpinx, eup
- Uterus: adenomyosis, myoma
- Pelvic floor and retroversion
- Pelvic congestion
- Chronic PID
- Chronic EUG
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- Colon, appendix, small bowel
- Functional and organical
- Interstitial cystitis
- Referred pain from sacro ileac joint
- Nerve entrapment in the wall

Endosalpingiosis

Adenomyosis
**Adenomyosis: a hot topic**
(articles = 900; 500, last 10 years)

<table>
<thead>
<tr>
<th>Definition = Pathology</th>
<th>No animal model</th>
</tr>
</thead>
<tbody>
<tr>
<td>= postmortem</td>
<td>No pathophysiology</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis by imaging</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Strongly associated with age</th>
</tr>
</thead>
<tbody>
<tr>
<td>with endometriosis</td>
</tr>
<tr>
<td>with pain &amp; infertility</td>
</tr>
<tr>
<td>with interstitial cystitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>when? How?</td>
</tr>
</tbody>
</table>

---

**Pelvic pain: the decision to do surgery**

- The decision to do surgery
  - Symptoms and exams
  - Absolute and relative indications to do surgery
  - Background knowledge
- The surgical intervention
  - Diagnostic
  - Therapeutic
    - What can be done ↔ should be done
    - How do we organise surgery
- The claimed benefits
- Pitfalls to avoid
Diagnosis of chronic pelvic pain

- Complete inspection
  - + Liver and diaphragm
  - + appendix
  - With little Trendelenburg

- Do we have a plausible explanation
- Probability of cure by surgery

- Decision
  - Intervention to do
  - Intervention not to do
  - When to do – when to refer

- Pelvic pathology
  - Endometriosis
  - Adhesions
  - Ovarian cysts...
  - Oviduct: hydrosalpinx, e.g.
  - Uterus: adenomyosis, myoma
  - Pelvic floor and retroversion
  - Pelvic congestion
  - Chronic PID
  - Chronic EUG
  - Intestinal pathology
    - Colon, appendix, small bowel
    - Functional and organical
    - Interstitial cystitis

In the absence of other pathology

- Adhesiolysis
  - High recurrence rate
  - Unproven benefits
  - Common sense

- Pelvic congestion syndrome
  - Unclear cause of pain
  - Decision...

http://www.gynsurgery.org/topics/pelvic-pain/
In the absence of other pathology

- Allen and Master
  - Spider
  - Up to the pudendal nerve

http://www.gynsurgery.org/topics/pelvic-pain/

In the absence of other pathology

- Fibroma – adenomyosis
  - Spider
  - Up to the pudendal nerve

http://www.gynsurgery.org/topics/pelvic-pain/

Rare cases of endometriosis

"well known but rare"

- Rare localisations
  - Abdominal wall
  - Lymph nodes
  - Lungs
  - Liver
  - Occasional: brain, bone, small bowel……

- Rare presentations
  - Hemorrhagic ascites
  - Bowel perforation/occlusion
  - Cancer: Is endometriosis "protective"?

- Surgically rare endometriosis
  - > 4 cm
  - Intrinsic ureteral
  - Personal cases: HMV CA
Abdominal wall endometriosis

- Giant abdominal wall tumor
- 32 years old women, after c-section, started abdominal pain, and progressively increasing mass in the wall with irradiation to the leg. Diagnosis of desmoid tumor by surgeon. Impossible to remove -> biopsy and diagnosis of endometriosis
- We performed excision after which the plastic surgeon reconstructed the fascia
- Mass 6*8 cm
- Laparoscopy: no endometriosis
- Today, after 3 years the patient is

Endometriosis of the Lung

Case report:
- Young girl of 16 years old
- Recurrent shortness of breath; emoptysis, and chest pain.
- Investigation: x-ray of the chest was negative, blood exam negative, CAT scan neg; bronchoscopy negative
- Consulted for dysmenorrhea and I suspected lung endometriosis
- MRI and CAT-scan during menstruation showed bilateral focal intrapulmonary endometriosis;
- Laparoscopy: no evidence of pelvic endometriosis
- Treatment GNRH analogues + O/C continuously solved the symptoms

Liver Endometriosis

- Endometriosis of the liver is an uncommon disease characterized by the presence of endometrial tissue in the liver. There are no pathognomonic radiological features for hepatic endometriosis and preoperative diagnosis is difficult by imaging. Most cases are diagnosed after surgery. We report typical imaging features of hepatic endometriosis in a 61 year-old female that mimics metastatic disease to the liver. She was referred to our institution with a presumed diagnosis of metastatic neuroendocrine tumors to the liver. After imaging guided core biopsy and histologic and immunohistochemical analysis, the diagnosis of hepatic endometrial stromal proliferation was made. We review the literature and provide imaging features that may help in reaching the correct diagnosis of hepatic endometriosis.
Cyclic haemorrhagic Ascites

- Abstract: Massive hemorrhagic ascites (4470 mL, range 1-10 L) in women with endometriosis is a rare condition occurring predominantly in black women. Of the 43 case reports published, 42 are compatible with the hypothesis that the hemorrhagic ascites is predominantly a consequence of excessive ovarian transudation similar to a Meigs syndrome. Indeed, bilateral ovariectomy cures the condition without recurrence, whereas after unilateral ovariectomy or oophorectomy recurrence rate is more than 50%; during ovarian suppression by luteinizing hormone-releasing hormone agonist ascites disappears, but reappears after treatment. Superficial pelvic endometriosis also contributes to the ascites because after superficial endometriosis destruction the recurrence rate is only 4 in 14. Based on these data, it is suggested, to scrutinize the ovaries for tumors given the analogy with Meigs syndrome. In women desiring fertility, conservative treatment with destruction of endometriosis only can be attempted given the cure rate of some 20%. It is unknown what the effect of ovulation induction would be.

Endometriosis with ascites

- 6 liters
Rare forms

Red Vesicles on Small bowl

- Easily missed
Typical endometriosis: excision

- Pain relief
  - RCT Sutton
  - Huge placebo effect
- Solid evidence for pain relief is scarce
- Non dangerous surgery: so why not

Cystic ovarian endometriosis: excision

- Pain relief
- Recurrence rates
- Ovarian damage

Deep endometriosis: excision

- Pain relief
- Recurrence rates
- Why bowel resection for low lesions should be avoided
- With appendectomy?
Pelvic Surgery: Benefits

- Absence of RCT's
  - Blinding
  - Evaluation of surgeon not of the technique

- Necessary for diagnosis

- Surgery is often therapeutic although the impact of a strong placebo effect cannot be ruled out

- Therefore surgery is intellectual rather than technical.

Pitfalls to avoid

- Medical therapy for many years without a diagnosis

- The first surgery should be the last surgery

- If too difficult: refer

- Hysterectomy cures it all

- You only recognise what you know
Quality control of surgery

Abstract
Quality control of surgical treatments is close to nonexistent for individual surgical procedures and, therefore, rare adverse events cannot be detected by the sheer number of interventions analyzed. An ethical review board is rarely consulted before a new procedure is attempted or introduced. Although the outcome of surgery is surgeon and environment dependent, the only estimation of quality is results and complication rates. These, however, reflect publications by dedicated groups or data from surveys that do not necessarily reflect reality accurately.

Conclusions: Chronic pelvic pain

- Avoid therapy without a diagnosis
- Without a laparoscopy the diagnosis is rarely made
- Adequate preoperative counseling and information
- During laparoscopy, surgery should be done carefully with the actual knowledge
- Prevention of postoperative adhesions (and pain)
Psychologically-informed pain management and pain self-management

Amanda C de C Williams
Research Dept of Clinical, Educational & Health Psychology
University College London, UK
& Pain Management Centre, UCLH

Conflict of interest
I have carried out paid teaching or consultation for Pfizer, Astellas, & Janssen

Psychologically-informed pain management and pain self-management: learning objectives

Understand the role of beliefs and emotions in pain presentation
Recognise the mediating role of appraisal of symptoms in determining impact on quality of life
Appreciate the implications of current evidence for developing psychological treatments
Identify the main elements of longer-term self-management of pain and symptoms
Psychology is an integral part of pain

Pain is an emotional experience, full of personal meaning and a threat to wellbeing. Pain has impact on all areas of life: high rates of disability, work loss, dependency, withdrawal from life anxiety, depression, social isolation, frustration economic problems for individual, family; medical system burden. These are not inevitable, and can be reversible. Pain is not ‘just psychological’, nor ‘psychosomatic’, nor an expression of psychological problems or needs. Such ideas have no scientific basis, and patients find them perplexing and undermining.

Chronic pain as a disease in its own right?

Pain is an emergent experience, modulated by interaction between spinal cord and brain.

“Thus it is possible for central nervous system activities subserving attention, emotion and memories of prior experience to exert control over the sensory input.” Melzack & Wall 1965

Changes in activation patterns are seen in people with disease-related pain (e.g. rheumatoid arthritis), with central sensitisation, and with ‘functional’ pain problems. Descending modulatory system is dysfunctional:
- inhibitory system is underactive,
- and/or descending facilitatory system is overactive.

Opioidergic and dopaminergic systems function abnormally.

Tracey & Bushnell 2010

Cognitive behavioural models

Behaviour which constitutes disability
avoiding activities associated with pain guarded and restricted movement

Unhelpful beliefs & mis/understanding of pain
fears about meaning of pain, and prognosis catastrophic misinterpretation of internal / external information beliefs about helplessness in face of pain

Associated emotions
fears, anxieties, low confidence; frustration, hopelessness ...

Weakly held unhelpful beliefs & behaviour may be corrected by information & advice from an authoritative source - a doctor.

Strongly held unhelpful beliefs & behaviour need more unravelling, and/or direct disconfirmation by experience - psychology.
Europe: representative survey of adults with chronic pain: beliefs about pain

Breivik et al 2006

<table>
<thead>
<tr>
<th>Item</th>
<th>D = symptom shared with depression</th>
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Psychological models

Behavioural models: understanding effects of learning and contingencies on behaviour.

Cognitive models, theoretically and empirically supported, now becoming integrated with identifiable brain processes.

Integrated biopsychosocial models: take more account of emotion as well as behavioural and cognitive aspects. Hard to achieve.

Psychodynamic models & psychosomatic models, invoke unconscious processes; weak theory, largely untested.

Personality models, much tested but showing little support.

But these last two psychological models of pain inform lay (patients' and professionals') mis/beliefs about pain.

Studies of women with pelvic pain: 1

Women with pelvic pain had high levels of distress about what was wrong compared with women with no pain, but similar levels of distress to other women with chronic pain.

Savidge & Slade 1997

In depth study of women with endometriosis about primary care:

- Delay (mean 5 ½ years) to diagnosis
- Doctors' lack of knowledge ("pregnancy will cure it")
- Not taken seriously ("just period pain", "psychological")

Search for 'validation & recognition'. McGowan et al. 2007

Lack of findings made women feel they were seen as neurotic. Being told nothing was wrong was heard as denying pain, and usually broke the therapeutic relationship.

Stigma of heavy bleeding; need to conceal bleeding, supplies and disposal of towels & tampons. Particularly hard at work. Seear 2009
Studies of women with pelvic pain: 2

Women with endometriosis: higher pain assoc with lower quality of life, but not with diagnosis. *Souza et al. 2011*

Women in pelvic pain tertiary clinic followed up over year of treatment. Catastrophic thinking at baseline predicted pain at baseline and less pain relief with treatment. *Martin et al. 2011*

Women with chronic pelvic pain interviewed before initial gynaec consultation:
- explanation important – cancer anxiety; understanding pain.
- explanations lacking, inadequate, or conflicted with previous ones.
200 women surveyed in gynaec outpatient clinics: high levels of distress associated with symptoms and treatment. *Glover et al., 2003*
- nearly 30% getting adequate help from friends & family, and others said would like help but ambivalent about psychology.
- need to recognise distress not universal, and integrate psychology.

Sexual abuse: systematic review, prospective study, empirical study

Women with pelvic pain report high levels of childhood sexual abuse – as do those with back pain, eating disorders, etc. ... 

Systematic review (*Latthe et al., 2006*): abuse was a predisposing factor alongside social, medical, and psychological ones – but mainly in poorer quality studies.

Prospective study (*Raphael et al., 2001*): those with childhood physical or sexual abuse or neglect had no more pain than matched controls. Pain is associated with retrospective report of abuse or neglect.

Healthy subjects with history of sexual abuse are less sensitive to pain stimuli and rate it less unpleasant than controls, but have more pain complaints. (*Fillingim & Edwards 2003*).

All conclude: it’s more complex than we thought.

Aims of (any) pain treatment

Improve control of pain.
Help build realistic model of problem
Reduce disabling effects of pain by work towards short and long term goals by graded steps
Reduce distress associated with pain and projected future
Reduce effects of pain on family and friends
Reduce unhelpful encounters with health system

*Focus on pain alone may leave patient inactive and anxious.*

*But focus on activity without efforts to relieve pain makes patient feel disbelieved and uncared for.*
**Cognitive content of CBT for pelvic pain**

Establishing new understanding of pain and of treatment options. “Rewriting” personal treatment history in that light

Understanding relationship between beliefs and self-statements, emotions, and behaviour.

Identifying and modifying unhelpful beliefs and imagery which adversely affect behaviour and/or mood.

Challenging catastrophic thinking.

Focus on living with pain, not predating all on pain relief.

Promoting acceptance, mindfulness, emotional distance from pain and its implications.

By various means, activating descending pain modulatory system.

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**Systematic reviews & meta-analyses**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Date</th>
<th>RCTs</th>
<th>Pain site</th>
<th>Improved</th>
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<tr>
<td>Turner et al.</td>
<td>1996</td>
<td>4</td>
<td>low back multiple</td>
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<td>Morley et al.</td>
<td>1999</td>
<td>25</td>
<td>&gt;1600 mixed multiple</td>
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<td>Van Tulder et al.</td>
<td>2000</td>
<td>7</td>
<td>low back pain, function</td>
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<tr>
<td>Guzmán et al.</td>
<td>2001</td>
<td>10</td>
<td>&gt;1900 low back pain, function</td>
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<tr>
<td>Ostelo et al.</td>
<td>2005</td>
<td>21</td>
<td>&gt;1400 low back function</td>
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<tr>
<td>Hoffman et al.</td>
<td>2007</td>
<td>22</td>
<td>&gt;1700 low back multiple</td>
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<tr>
<td>Nestoriuc et al.</td>
<td>2008</td>
<td>21</td>
<td>&gt;3000 tension headache freq.</td>
<td></td>
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<tr>
<td>Williams et al.</td>
<td>2012</td>
<td>42</td>
<td>&gt;4800 mixed multiple</td>
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<tr>
<td>Głowbiowski et al.</td>
<td>2010</td>
<td>23</td>
<td>&gt;1300 fibromyalgia multiple</td>
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**Cochrane reviews**

“Small to moderate benefits, more for disability, mood and catastrophic thinking than for pain, were found in trials which compared CBT with no treatment. Some of these were still positive six months later. Behaviour therapy showed few and only brief benefits.”

Williams et al., 2012

Groups were mixed: mostly musculoskeletal, but some pelvic pain. By contrast

- non-surgical treatments for pelvic pain in women (Stones et al., 2007) showed small benefits for pain and function, but did not assess mood, and rarely quality of life.
- systematic review and meta-analysis (Proctor et al., 2007) of behavioural treatment for dysmenorrhea, but not clear that any of 5 trials included 2ary dysmenorrhea, and conclusions were that weak intervention and poor methodology.
Self-help, mutual help & internet resources

Advantages of internet
- easily accessible as needed
- more informal than treatment
- translated into multiple languages

Shortcomings
- rarely tested for efficacy
- lack interpersonal relationship = much of placebo effect
- require motivation: hard for those with depressed mood
- may include unhelpful / harmful content
- require good analytic and observational skills

Systematic review of internet pain management programmes (Bender et al 2011) showed gains in pain and function but not distress from CBT, and high withdrawal rate.

Best for supporting pain management, not substituting.

Dedicated pain management for pelvic pain

Pain management programme helps identify patients’ models & understandings of their pain.
By patients’ request, groups are male only or female only.

We work on beliefs & behaviour, including physiotherapy.
- Focus on relaxation (rather than strengthening) & stretch
- Promote bladder control
- Promote sexual function
- Reduce fear of movement, touch, pressure
- Use graded exposure – progressing towards feared target activity by small increments, according to reduction in anxiety at each step.

Results from pain management programme for chronic pelvic/urogenital pain (Link)

Adapted from an effective CBT programme for chronic musculoskeletal and other pain.
7 day programme over several weeks
88 women in 10 programmes (and 30 men in 3 programmes).
Mean age 45 and just over half living with partner
Median duration of pain 6 years.
Half the women had previous surgery.
Benchmarked against published mixed chronic pain outcomes: pre-
post data from UK pain management of mixed chronic pain (Morley et al., 2008), and 2012 meta-analysis of CBT against
waiting list/treatment as usual.
**Benchmarking outcomes**

Morley, Williams, Hussein 2008

Data from 2012 meta-analysis of CBT vs waiting list/treatment as usual
Link women pre-post

**Research priorities**

Outcome evaluation and process studies of application of best of psychological treatments to women with pelvic pain.

Developing the use of portable technology to support and extend pain management methods.

How to improve primary care recognition of problems needing investigation from normal menstruation?

Testing of current available explanations of disorders on healthy and affected women; development of better explanations as necessary; dissemination.

**Take-home messages**

Helping your patients understand pain is an investment in their health and in treatment adherence and success.

It is common, particularly in women, for chronic pain to be associated with significant distress. Treating pain usually reduces this distress.

Psychological interventions drawn from the evidence base in other areas of chronic pain should be used in chronic pelvic pain, alone or in combination with medical and physical therapies.

Thank you!
Quality of life outcomes and trial regulation: influence on future clinical study design - Stephen Kennedy (United Kingdom)

Contribution not submitted by the speaker
You can now register for these upcoming ESHRE Campus events:

- Application and challenges of emerging technologies in preimplantation and prenatal diagnosis
  12-13 September 2013 - Prague, Czech Republic

- Female genital tract congenital malformations: new insights in an old problem
  27-28 September 2013 - Thessaloniki, Greece

- Introducing new techniques into the lab
  4-5 October 2013 - Barcelona, Spain

- Polycystic ovary syndrome: A new look at an old subject
  25-26 October 2013 - Rome, Italy

- Infections from conception to birth: role of ART
  7-8 November 2013 - Berlin, Germany

- Endoscopy in reproductive medicine
  20-22 November 2013 - Leuven, Belgium

- From early implantation to later in life
  28-29 November 2013 - Brussels, Belgium

Mark your calendar for:

- Premature ovarian insufficiency
  6-7 December 2013 - Utrecht, The Netherlands

www.eshre.eu
(see "Calendar")

Contact us at info@eshre.eu