

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



SCIENCE MOVING  
PEOPLE  
MOVING SCIENCE





# **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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# 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



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## Declaration

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

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## 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?

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## Scene setting slide

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## The evidence base.....

- Electronic searches of Medline and Embase and the Cochrane Library
- Google Scholar
- Dates – up to February 2013

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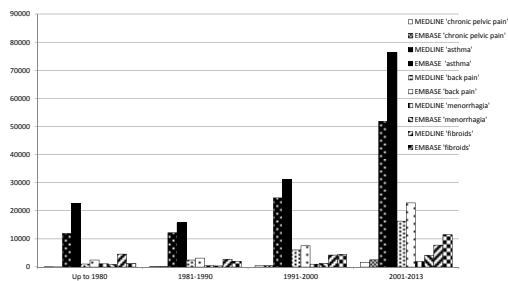
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## Publications for chronic pelvic pain, asthma, back pain, menorrhagia and fibroids



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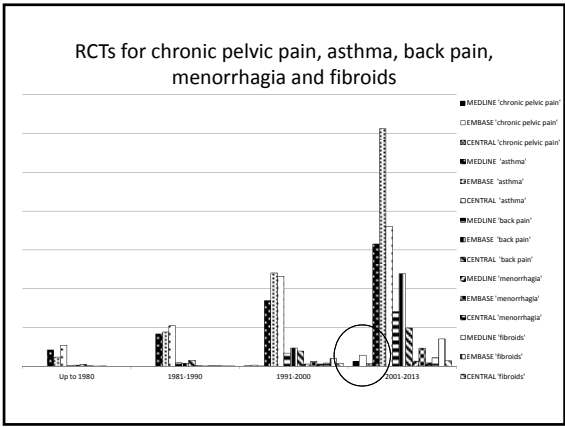
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The \$6 Billion Woman  
and the  
\$600 Million Girl

Edited by:

- 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 Thierry Vancaille

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**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

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### 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

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### 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*)

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### Chronic pelvic pain

- |   |   |
|---|---|
| <ul style="list-style-type: none"><li>• Recognised pathologies<ul style="list-style-type: none"><li>– Endometriosis/adenomyosis*</li><li>– Adhesions</li><li>– Ovarian remnant*</li><li>– Residual ovary*</li></ul></li></ul> | <ul style="list-style-type: none"><li>• No obvious pathologies<ul style="list-style-type: none"><li>– Pelvic congestion*</li><li>– Primary dysmenorrhoea *</li><li>– Midcycle pain*</li><li>– Irritable bowel syndrome</li><li>– Entrapped nerve syndrome</li><li>– Neuropathic pain</li><li>– Painful bladder syndrome</li></ul></li></ul> |
|---|---|
- \* Cyclical pattern

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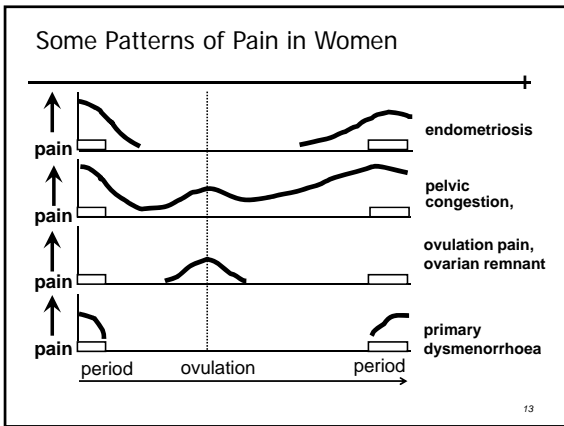
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### Abdomino-pelvic pain

- 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

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### WHO systematic review 2006: “a neglected reproductive health morbidity”

**BMC Public Health**

Research article [Open Access](#)

**WHO systematic review of prevalence of chronic pelvic pain: a neglected reproductive health morbidity**

Fallavi Latthe<sup>1\*</sup>, Manish Latthe<sup>2</sup>, Lale Say<sup>3</sup>, Metin Gülmezoglu<sup>3</sup> and Khalid S Khan<sup>4</sup>

Address: <sup>1</sup>Birmingham Women's Healthcare NHS Trust, Birmingham, UK; <sup>2</sup>Queen's Medical Centre, Central Birmingham, UK; <sup>3</sup>WHO/UNEP/WHO World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland and <sup>4</sup>Academy Department of Obstetrics & Gynaecology, University of Birmingham, Birmingham, UK

\*Corresponding author

Published: 06 July 2006  
BMC Public Health 2006, 6:177 doi:10.1186/1471-2108-6-177

Received: 12 September 2005  
Accepted: 04 July 2006

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## 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)

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## 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

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## 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

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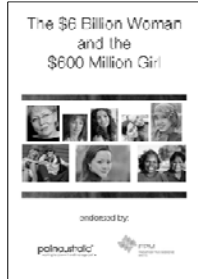
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## Back to this....

- 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



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## World Endometriosis Research Foundation - report 2011

**TABLE 2**  
Work productivity in symptomatic women with and without endometriosis.

Work and productivity loss variables	Endometriosis (n = 245)	Symptomatic control (n = 387)	Unadjusted P value	Adjusted P value*
<b>General</b>				
Weekly hours paid to work, mean (SD)	39.2 (14.8)	38.6 (17.1)	.44	.147
Weekly hours actually worked, mean (SD)	24.9 (16.1)	28.2 (25.8)	.01	.32
<b>Work / productivity and Activity impairment dimensions</b>				
<b>Absenteeism<sup>†</sup></b>				
% mean (SD)	11.2 (21.8)	8.5 (20.3)	.060	.55
h/wk, mean (SD)	4.4 (8.0)	3.3 (8.4)	.24	.52
<b>Presenteeism<sup>‡</sup></b>				
% mean (SD)	25.8 (26.8)	17.9 (22.1)	<.001	.26
h/wk, mean (SD)	6.4 (7.5)	5.1 (6.7)	.001	.56
<b>Overall work productivity loss<sup>§</sup></b>				
% mean (SD)	33.2 (29.8)	22.9 (26.1)	<.001	.045
h/wk, mean (SD)	10.0 (12.2)	8.4 (10.2)	<.001	.002
<b>Activity impairment<sup>¶</sup></b>				
% mean (SD)	28.5 (26.9)	19.6 (23.4)	<.001	.48

\* Variables adjusted for included educational attainment, marital status, type and number of symptoms, severity of pelvic pain, and comorbidity.  
<sup>†</sup> Time absent from work owing to symptoms.  
<sup>‡</sup> Reduced effectiveness while on the job owing to symptoms.  
<sup>§</sup> Combination of absenteeism and presenteeism.  
<sup>¶</sup> Reduced effectiveness while doing nonwork-related activities, e.g., child care, exercise, housework, etc.  
 Abbreviations: h/wk, hours per week; SD, standard deviation.

Nnoaham et al 20

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## 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

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## 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

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## The impact of heavy periods...

	LNG – IUS		Thermal balloon ablation	
	N = 42		N = 41	
Days of bleeding (mean (SD))	7.4	3.3	7.0	2.6
Number of days of heavy bleeding (mean (SD))	3.8	2.0	3.4	1.3
Number of days of painful bleeding (mean (SD))	3.8	1.8	4.1	2.6
Unable to leave house on heaviest days	27	66%	31	76%
Number of days housebound*	1.6	1.4	1.8	1.4
Sleep disturbed	39	95%	39	95%
Number of nights disturbed* (mean (SD))	2.9	1.7	2.3	1.1

\*Only includes women who were housebound or had nights disturbed

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## Quality of Life

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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

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“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

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### 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

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**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?

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**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?

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**Does the instrument assess what  
it purports to assess?**

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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

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### 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



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### 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)

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## 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

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## 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

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## Generic Instruments

### Disadvantages

- Sacrifices some level of detail
- Questionnaire items less relevant
- Less sensitive to change

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### 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

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### SF 36

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

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### EQ5D

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

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## 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

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## 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)

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## Disease or condition specific measures

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

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## Uterine Fibroid Symptom – Quality of Life

- Spies 2004
  - 37 questions on fibroid symptoms
    - 8 symptoms questions
    - 29 health related quality of life
  - Useful 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

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## UFS-QOL

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

Spies 2004

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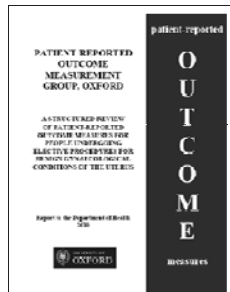
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## Report on PROM by the University of Oxford

- 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



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## Randomized controlled trials and quality of life measures

From the Cochrane Register of Trials

- Chronic pelvic pain: 21 rcts
- Fibroids: 16
- Menorrhagia: 48

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## Studies with heavy menstrual bleeding including fibroids

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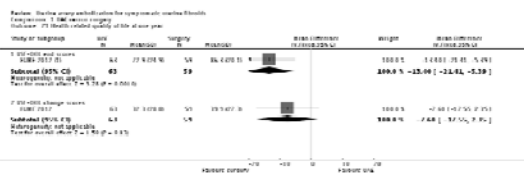
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## Reporting using UFS-QOL for fibroids



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## 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)

SF-36 scores	Overall (n = 79)	TBA (n = 39)	LNG-IUS (n = 40)
Randomisation	63.7 (19.0)	63.7 (14.4)	63.7 (22.7)
3 months	77.9 (13.7)	78.2 (13.7)	77.7 (17.0)
12 months	78.1 (16.8)	76.9 (16.8)	79.3 (16.5)
24 months	76.2 (18.6)	74.9 (18.8)	77.5 (20.1)

TBA, thermal balloon ablation.

TALIS study, Busfield 2004

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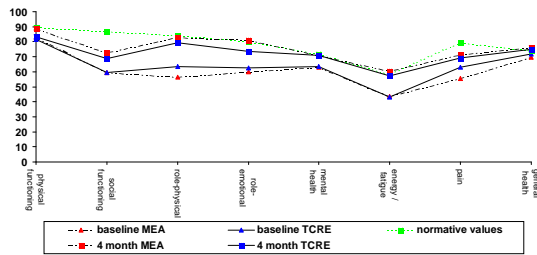
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## MEA versus TCRE

fig. 5.1. Short Form 36 scores




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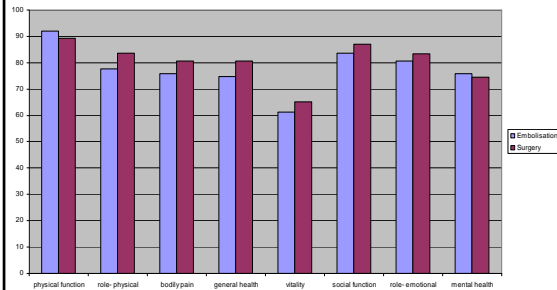
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SF 36 at 12 months



REST Study

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“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

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### What's next?

- RCOG has embarked on PROM development for heavy menstrual bleeding
- No progress in the assessment of women with chronic pain

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**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

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**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

ESHRE 2013

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**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
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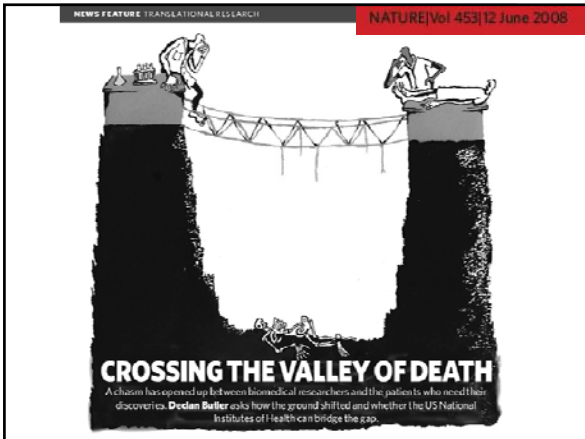
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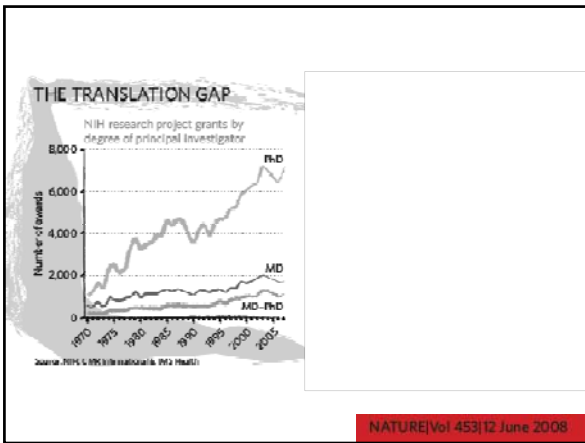
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Grimshaw JM et al, Knowledge translation of research findings. Implement Sci. 2012; 7: 50.

- 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].

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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?

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**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

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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

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Progestin effects on endometrium  
Progesterone and progestins  
Progesterone receptors  
The nuclear receptor superfamily  
PR co-activators & co-repressors

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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

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

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**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

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From basic research to clinical management  
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
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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, PhD<sup>1</sup>, Thomas M. D'Hooghe, MD, PhD<sup>2,3</sup>,  
Asgerally Fazleabas, PhD<sup>4</sup>, Linda C. Giudice, MD, PhD, MSc<sup>5</sup>,  
Grant W. Montgomery, PhD<sup>6</sup>, Felice Petraglia, MD<sup>7</sup>, and  
Robert N. Taylor, MD, PhD<sup>8</sup>

Reproductive Sciences  
00(0) 1-17  
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sagepub.com/journalsPermissions.nav  
DOI: 10.1177/1933719113477495  
rsc.sagepub.com  


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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.

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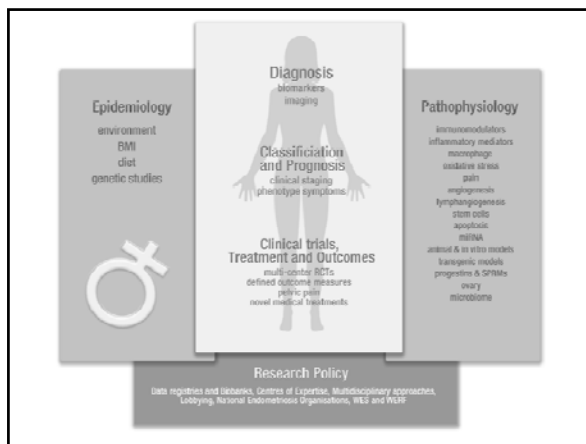
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**nature genetics**

**A genome-wide association study identifies genetic variants in the *CDKN2BAS* locus associated with endometriosis in Japanese**

Satoko Uno<sup>1,2</sup>, Hitoshi Zembutsu<sup>1</sup>, Akira Hirasawa<sup>1</sup>, Atsushi Takahashi<sup>4</sup>, Michiaki Kubo<sup>5</sup>, Tomoko Akahane<sup>3</sup>, Daisuke Aoki<sup>3</sup>, Naoyuki Kamatani<sup>1</sup>, Kotchi Hirata<sup>2</sup> & Yosuke Nakamura<sup>1</sup>

NATURE GENETICS | VOLUME 42 | NUMBER 8 | AUGUST 2010

**Genome-wide association study identifies a locus at 7p15.2 associated with endometriosis**

Jodie N Painter<sup>1,2,3</sup>, Carl A Anderson<sup>2,3,4,5</sup>, Dale R Nyholt<sup>6,7</sup>, Stuart Macgregor<sup>8</sup>, Jinghui Liu<sup>9</sup>, Sang Hong Lee<sup>1</sup>, Ann Lambert<sup>9</sup>, Zhen Z Zhao<sup>1</sup>, Fenella Roseman<sup>2</sup>, Qun Cao<sup>2</sup>, Scott D Gordon<sup>9</sup>, Leanne Wallace<sup>2</sup>, Anjali K Henders<sup>1</sup>, Peter M Visscher<sup>1</sup>, Peter Kraft<sup>10,11</sup>, Nikolaj G Martin<sup>12</sup>, Andrew P Morris<sup>13</sup>, Susan A Treloar<sup>13,14</sup>, Stephen H Kennedy<sup>15,16</sup>, Stacey A Missmer<sup>17,18,19</sup>, Grant W Montgomery<sup>20,21</sup> & Krista T Zondervan<sup>16,14</sup>

NATURE GENETICS | VOLUME 43 | NUMBER 1 | JANUARY 2011

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**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>).

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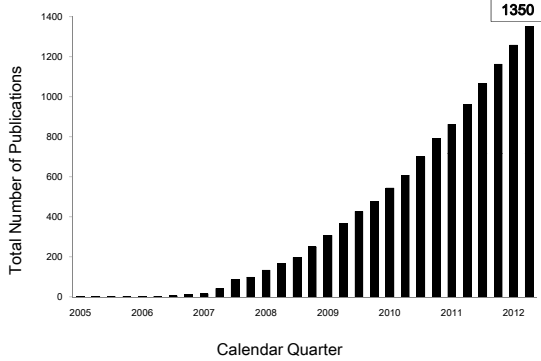
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**Published GWA Reports, 2005 – 6/2012**




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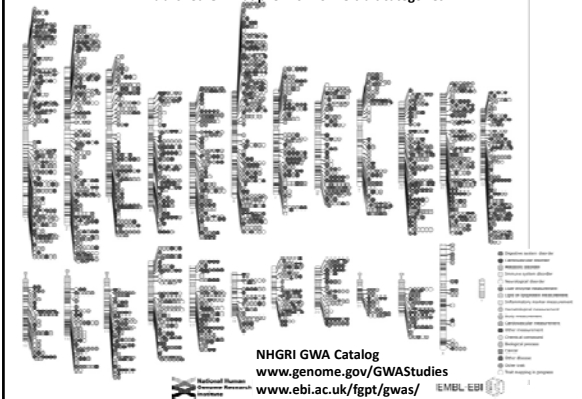
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**Published Genome-Wide Associations through 07/2012**  
Published GWA at  $p \leq 5 \times 10^{-8}$  for 18 trait categories




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## 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

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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.

le: 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

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

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- Clinical conditions of endometriosis, fibroids, and HMB
- How to prioritise basic research that can be translated into patient benefit?

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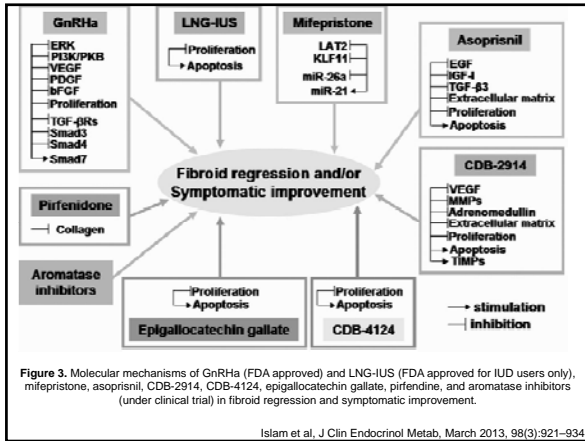
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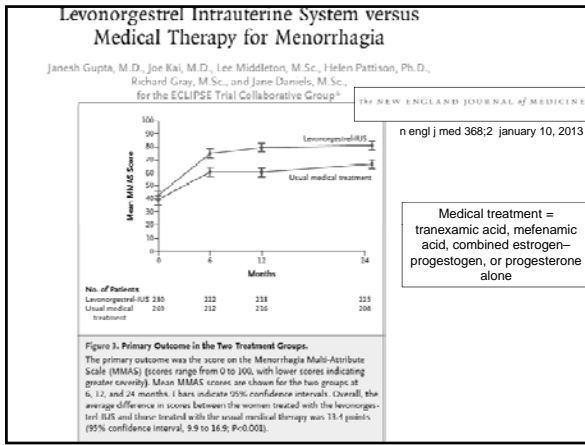
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**CONCLUSIONS**  
 In women with menorrhagia who presented to primary care providers, the levonorgestrel-IUS was more effective than usual medical treatment in reducing the effect of heavy menstrual bleeding on quality of life.

Mirena: IUD with LNG, a progestin from the 1960's, still better than any of the more recent medical approaches for treating HMB.

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

**Conclusions:**

- 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

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	<h3>References</h3> <ol style="list-style-type: none"><li>1. Butler D. Translational research: crossing the valley of death. <i>Nature</i>. 2008 Jun 12;453(7197):840-2.</li><li>2. Grimshaw JM, Eccles MP, Lavis JN, Hill SJ, Squires JE. Knowledge translation of research findings. <i>Implement Sci</i>. 2012;7:50.</li><li>3. McGlynn EA, Asch SM, Adams J, Keesey J, Hicks J, DeCristofaro A, et al. The quality of health care delivered to adults in the United States. <i>N Engl J Med</i>. 2003 Jun 26;348(26):2635-45.</li><li>4. Grol R. Successes and failures in the implementation of evidence-based guidelines for clinical practice. <i>Med Care</i>. 2001 Aug;39(8 Suppl 2):I46-54.</li><li>5. Rogers PA, D'Hooghe TM, Fazleabas A, Giudice LC, Montgomery GW, Petraglia F, et al. Defining Future Directions for Endometriosis Research: Workshop Report From the 2011 World Congress of Endometriosis in Montpellier, France. <i>Reprod Sci</i>. 2013 Feb 20.</li><li>6. Uno S, Zembutsu H, Hirasawa A, Takahashi A, Kubo M, Akahane T, et al. A genome-wide association study identifies genetic variants in the CDKN2BAS locus associated with endometriosis in Japanese. <i>Nat Genet</i>. 2010 Aug;42(8):707-10.</li><li>7. Painter JN, Anderson CA, Nyholt DR, Macgregor S, Lin J, Lee SH, et al. Genome-wide association study identifies a locus at 7p15.2 associated with endometriosis. <i>Nat Genet</i>. 2011 Jan;43(1):51-4.</li><li>8. Nyholt DR, Low SK, Anderson CA, Painter JN, Uno S, Morris AP, et al. Genome-wide association meta-analysis identifies new endometriosis risk loci. <i>Nat Genet</i>. 2012 Oct 28;44(12):1355-9.</li><li>9. Manolio TA. Genomewide association studies and assessment of the risk of disease. <i>N Engl J Med</i>. 2010 Jul 8;363(2):166-76.</li><li>10. Freedman ML, Monteiro AN, Gayther SA, Coetzee GA, Risch A, Plass C, et al. Principles for the post-GWAS functional characterization of cancer risk loci. <i>Nat Genet</i>. 2011 Jun;43(6):513-8.</li><li>11. Sansseau P, Agarwal P, Barnes MR, Pastinen T, Richards JB, Cardon LR, et al. Use of genome-wide association studies for drug repositioning. <i>Nat Biotechnol</i>. 2012 Apr;30(4):317-20.</li><li>12. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. <i>Am J Obstet Gynecol</i>. 2003 Jan;188(1):100-7.</li><li>13. Cha PC, Takahashi A, Hosono N, Low SK, Kamatani N, Kubo M, et al. A genome-wide association study identifies three loci associated with susceptibility to uterine fibroids. <i>Nat Genet</i>. 2011 May;43(5):447-50.</li><li>14. Gupta J, Kaji J, Middleton L, Pattison H, Gray R, Daniels J. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. <i>N Engl J Med</i>. 2013 Jan 10;368(2):128-37.</li></ol>
<b>ESHRE 2013</b>	

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## Endometrialgia: neuronal pathways in the perception of endometriosis-associated pain

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

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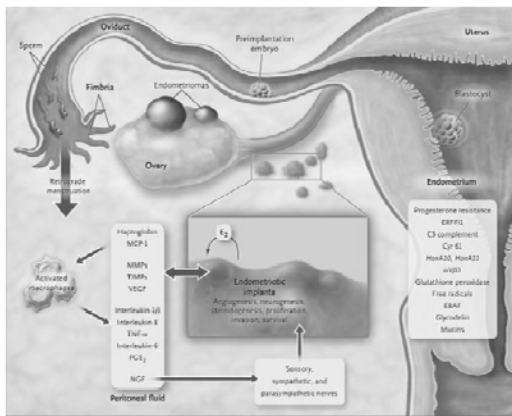
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*N Engl J Med.* 2010 June 24; 362(25): 2389-2398.

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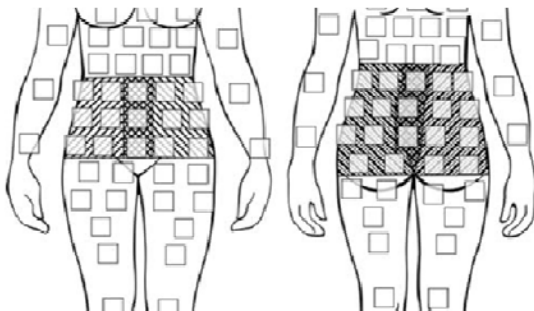
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## Relating Pelvic Pain Location to Surgical Findings of Endometriosis.



*Obstet Gynecol.* 2011 August; 118(2 Pt 1): 223-230.

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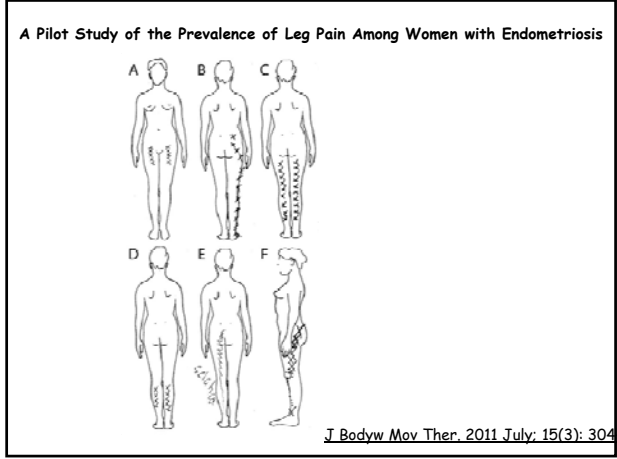
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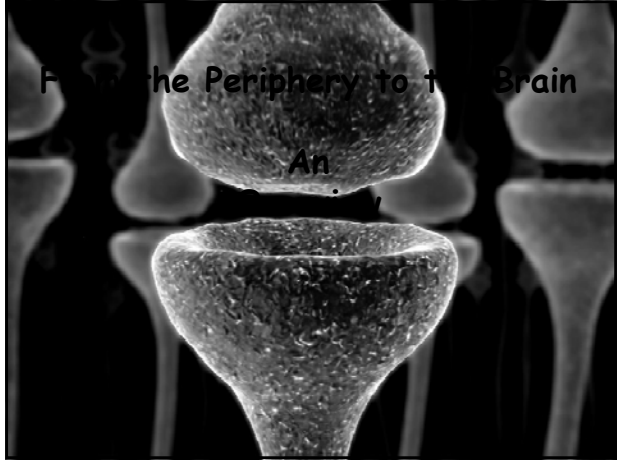
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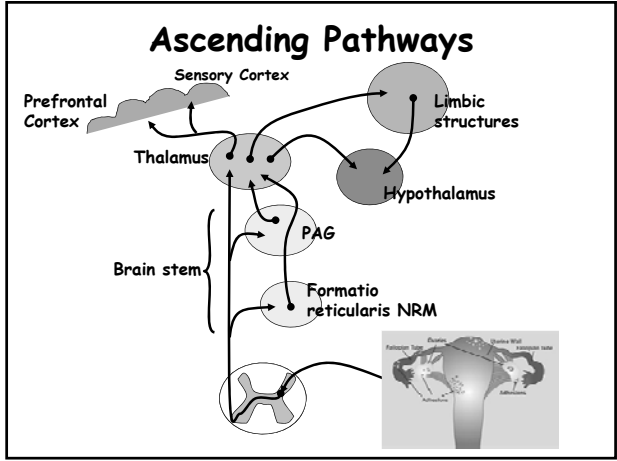
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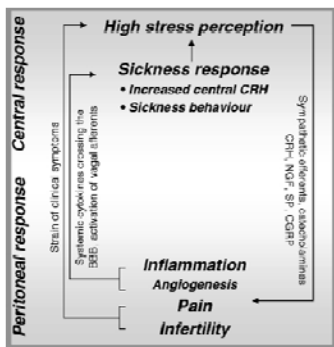
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Hypothetical scenario for endometriosis: the 'brain-body-brain cross talk'.



Semin Immunopathol. 2007 June; 29(2): 193-210.

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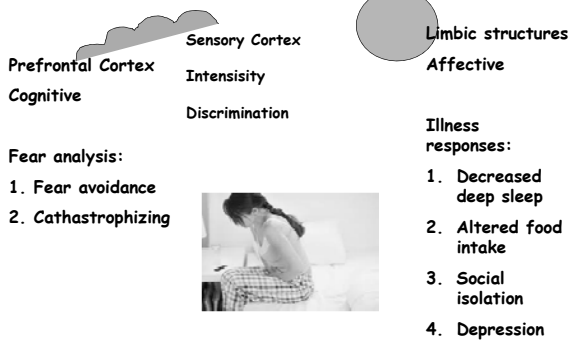
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## Central projections




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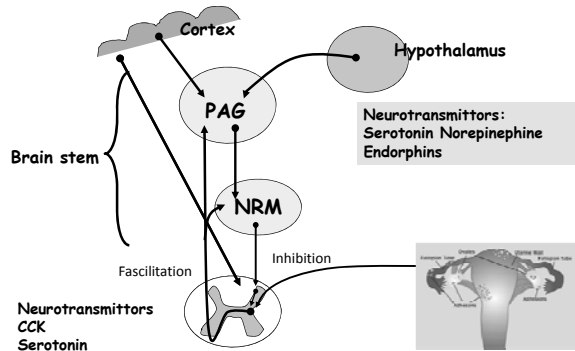
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## Descending Pathways




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## Pain classification - aetiology

### ADAPTIVE

- Nociceptive pain (adhesion)
- Inflammatoric pain (cyst)

### MALADAPTIVE

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

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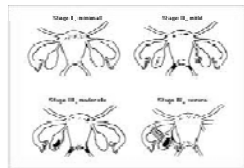
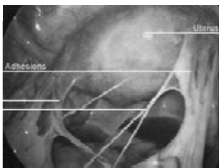
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## Pain classification

### ADAPTIVE - Nociceptive pain

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



EXAMPLES OF THE CLASSIFICATION OF ADHESIONS AS PICTURED FROM THE AMERICAN SURVEY OF THE ABDOMINAL PRACTICE

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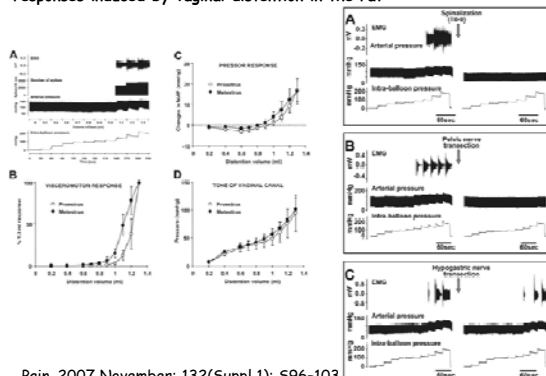
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### Influence of endometriosis on visceromotor and cardiovascular responses induced by vaginal distension in the rat



Pain. 2007 November; 132(Suppl 1): S96-103

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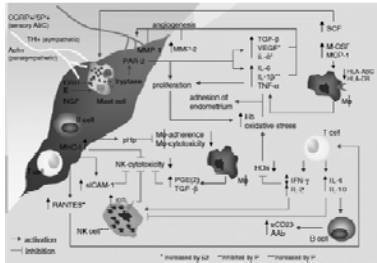
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# Pain classification

ADAPTIVE: Inflammatory pain (cyst)

Neuroendocrine-immune disequilibrium in endometriosis



Semin Immunopathol. 2007 June; 29(2): 193-210.

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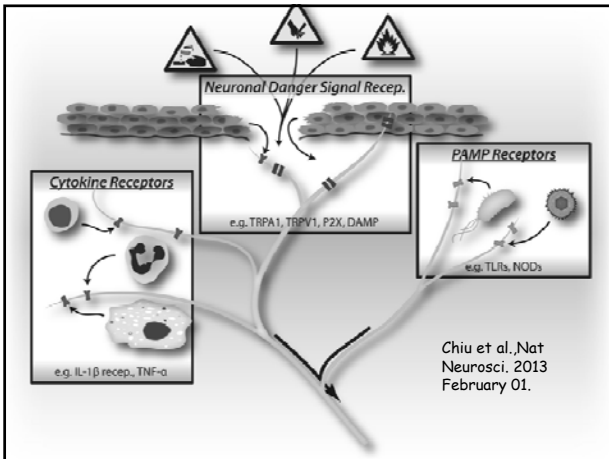
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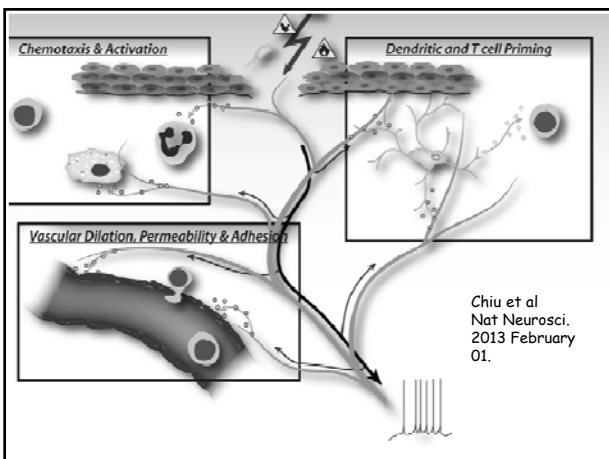
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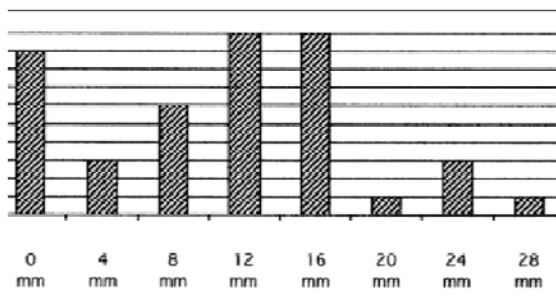
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## Distance of pain from border of lesion.



JSLs. 2000 Jan-Mar; 4(1): 5-9.

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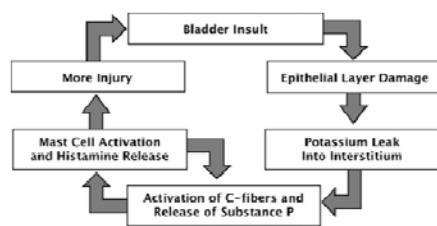
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## Interstitial Cystitis and Endometriosis in Patients With Chronic Pelvic Pain: The "Evil Twins" Syndrome



JSLs. 2005 Jan-Mar; 9(1): 25-29.

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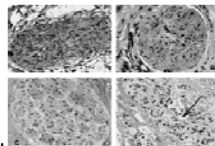
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## Pain classification

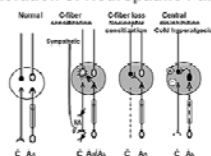


### MALADAPTIVE

- Neuropathic pain (postsurgical nerve lesion)

Medscape www.medscape.com

### Conceptualization of the Generation of Neuropathic Pain



1. Stimulus evoked - Hyperphen. -Allodynia
2. Spontaneous

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## Pain classification

**MALADAPTIVE**

- Idiopathic/Functional pain (central sensitisation, disinhibition, central facilitation)

Nature Reviews | Neurosciences

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## Target sites for pain treatment

**Periphery  
Spinal cord  
Brain stem  
Brain**

Hum Reprod Update. 2011 May-Jun; 17(3): 327-346.

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## Endometrialgia: Holistic treatment

**Polytherapy**

**Function**

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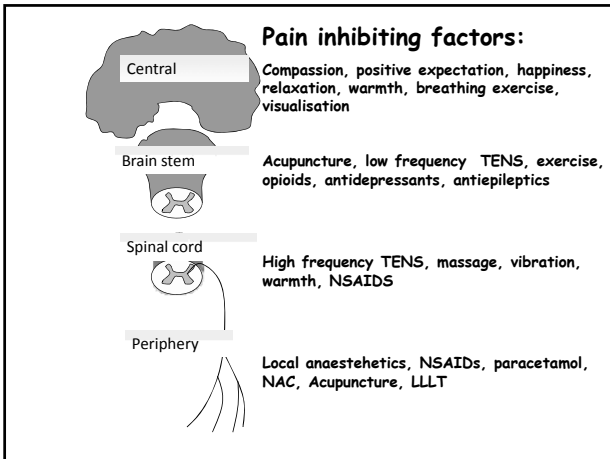
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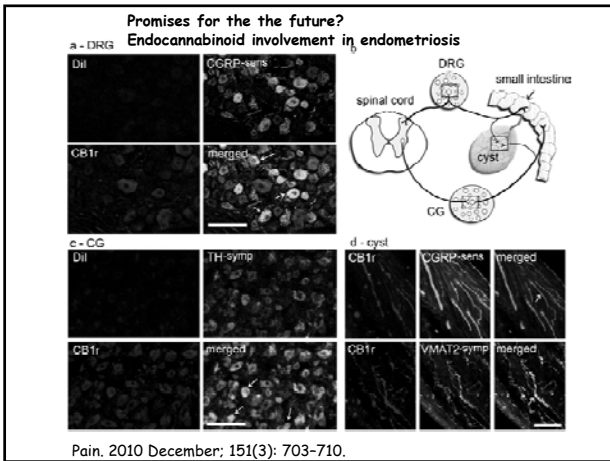
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**Pain as a reward: Changing the meaning of Pain from negative to positive co-activates opioid and cannabinoid systems**

Benedetti et al., Pain. 2013 Mar;154(3):361-7.

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.

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# Pelvic pain and bleeding the impact on female sexuality ?



PD Dr. Brigitte Leeners,  
Division for Reproductive-Endocrinology,  
University Hospital Zurich

- No conflicts of interests -

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## 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

Brigitte Leeners, Division for Reproductive Endocrinology, Zurich

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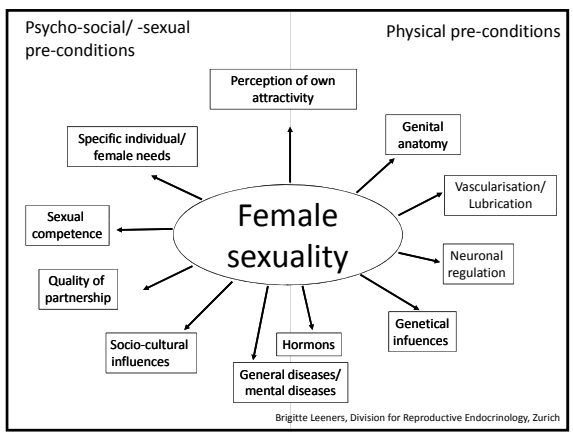
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Brigitte Leeners, Division for Reproductive Endocrinology, Zurich

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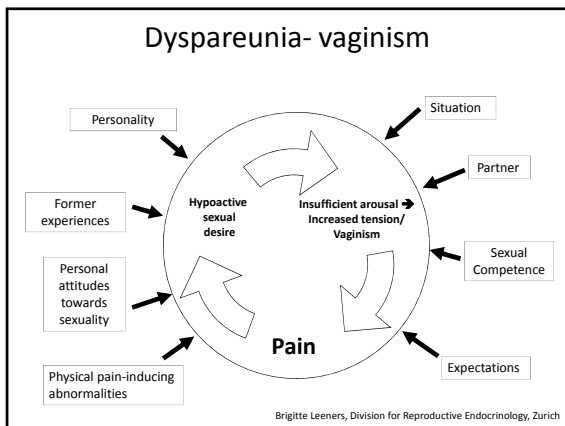
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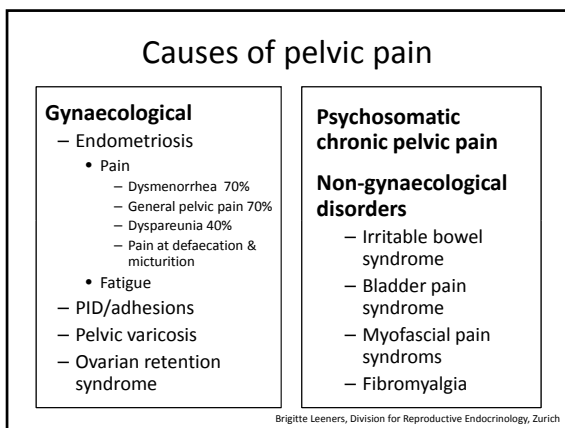
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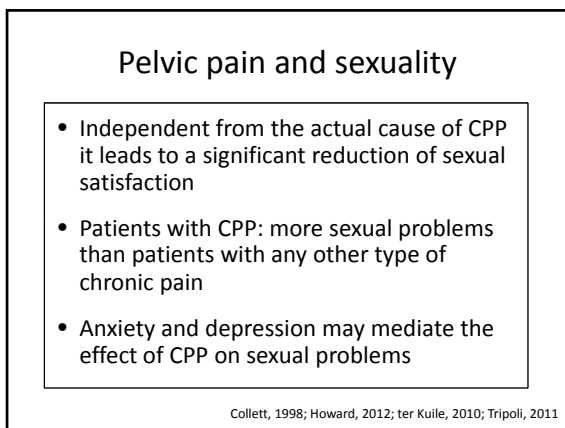
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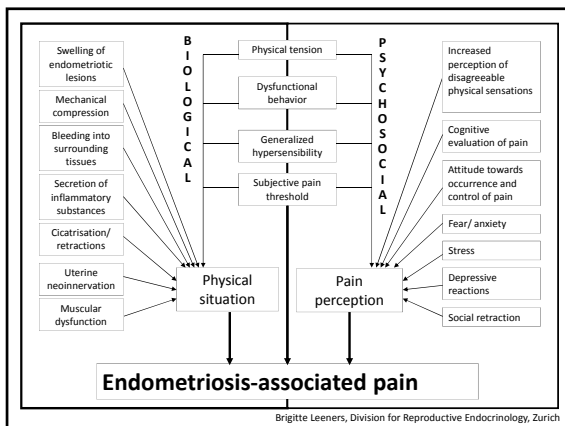
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### Zurich Endometriosis- Quality of life study

- Swiss-German Multicenter Study
- Questionnaire
  - Socio-demographic data
  - Endometriosis
  - Pain (modified version BPI und PDI)
  - Ressources (SOC)
  - Stress perception (PSQ20)
  - Education and profession
  - Satisfaction with medical support
  - Childhood experiences (Modified version CTQ)
  - Lifestyle, Every day life
  - Partnership (PFB)
  - Sexuality (modified version BISF, GSF)
  - Anxiety, Depression (PHQ, GAD)
- Confirmation of Endometriosis/ ASRM Stage according to medical charts

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### First Symptoms

ASRM	< 1 year	1 year	2-5 years	6-10 years	> 10 years
I (N=44)	4/ 9.1	3/ 6.8	15/ 34.1	7/ 15.9	15/ 34.1
II (N=53)	3/ 5.7	8/ 15.1	17/ 32.1	6/ 11.3	19/ 35.8
III (N=74)	2/ 2.7	3/ 4.1	19/ 25.7	15/ 20.3	35/ 47.3
IV (N=106)	5/ 4.7	3/ 2.8	19/ 17.9	23/ 21.7	56/ 52.8
Unknown (N= 89)	4/ 4.5	2/ 2.2	19/ 21.3	19/ 21.3	45/ 50.6
<b>Total (N=366)</b>	<b>18/ 4.9</b>	<b>19/ 5.2</b>	<b>89/ 24.3</b>	<b>70/ 19.1</b>	<b>170/ 46.4</b>

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### Number of operations

ASRM	1	2	3	4	> 4
1 (N=42)	4/ 9.5	18/ 42.9	15/ 35.7	5/ 11.9	3/ 7.1
2 (N=57)	3/ 5.3	26/ 45.6	23/ 40.4	3/ 5.3	2/ 3.5
3 (N=78)	2/ 2.6	42/ 53.8	26/ 33.3	6/ 7.7	2/ 2.6
4 (N=107)	5/ 4.7	35/ 32.7	41/ 38.3	15/ 14.0	11/ 10.3
Unknown (N=93)	1/ 1.1	39/ 41.9	27/ 29.0	25/ 26.9	1/ 1.1
Total (N=380)	15/ 3.9	160/ 42.1	132/ 34.7	54/ 14.2	19/ 5.0

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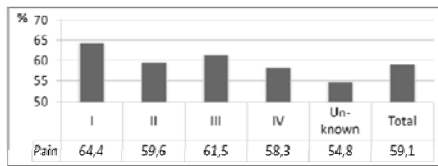
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### Pain & daily duration of pain



ASRM	< 1 h	2-3 h	4-9 h	10-18 h	18-24 h	unknown
I (N=45)	0	7/ 15.6	14/ 31.1	4/ 8.9	5/ 11.1	15/ 33.3
II (N=57)	6/ 10.5	8/ 14.0	10/ 17.5	4/ 7.0	7/ 12.3	22/ 38.6
III (N=78)	3/ 3.8	10/ 12.8	21/ 26.9	6/ 7.7	9/ 11.5	29/ 37.2
IV (N=105)	12/ 11.4	16/ 15.2	17/ 16.2	4/ 3.8	15/ 14.3	41/ 39.0
Unknown (N=92)	6/ 6.5	14/ 15.2	12/ 13.0	4/ 4.3	14/ 15.2	42/ 45.7
Total (N=380)	27/ 7.1	55/ 14.5	74/ 19.5	25/ 6.6	50/ 13.2	149/ 39.2

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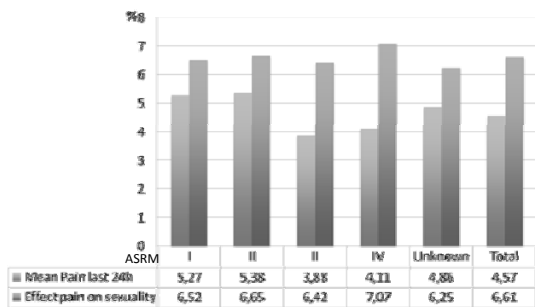
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### Intensity of pain and estimated effect on sexuality



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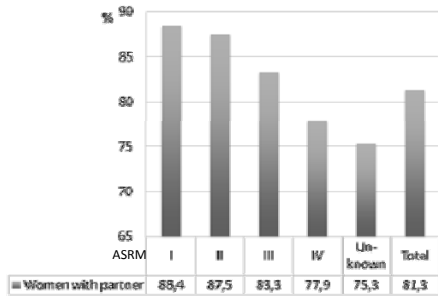
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### Actual sexual partner



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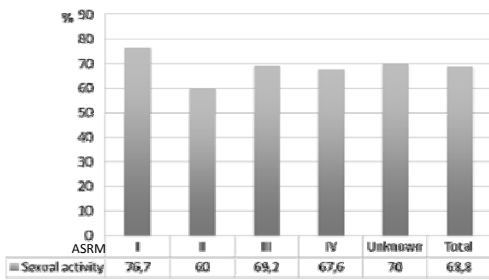
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### Sexual activity last month



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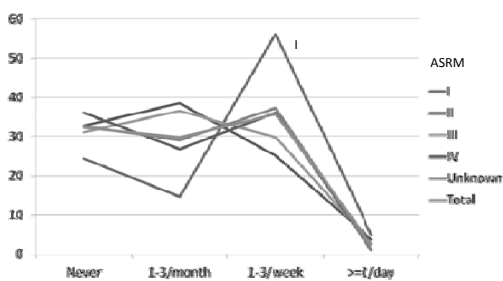
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### Frequency sexual Intercourse



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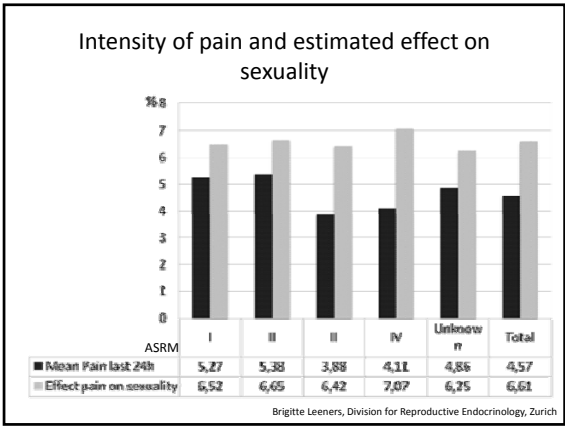
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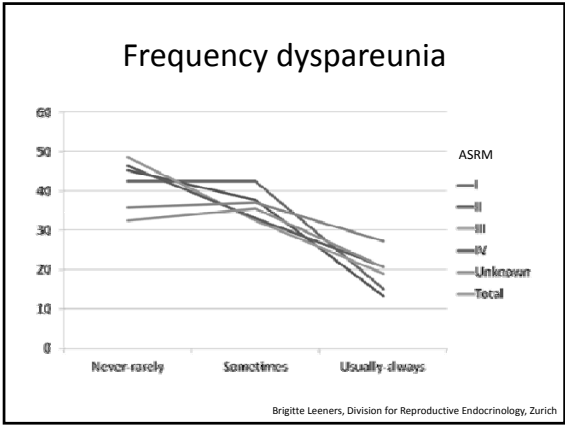
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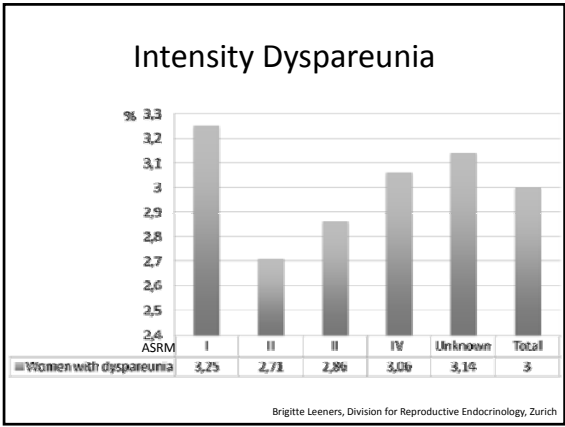
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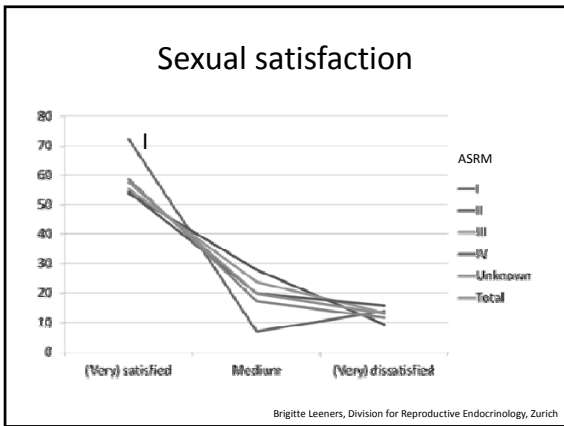
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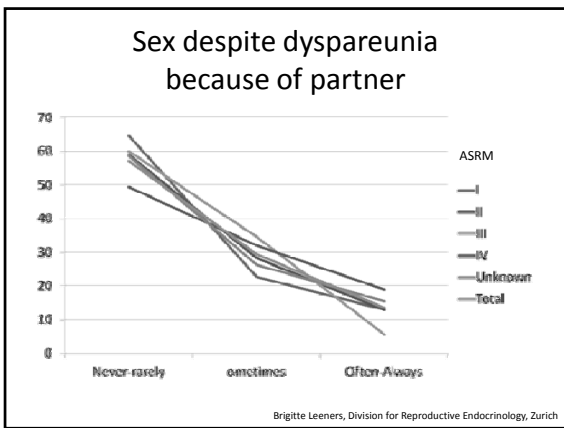
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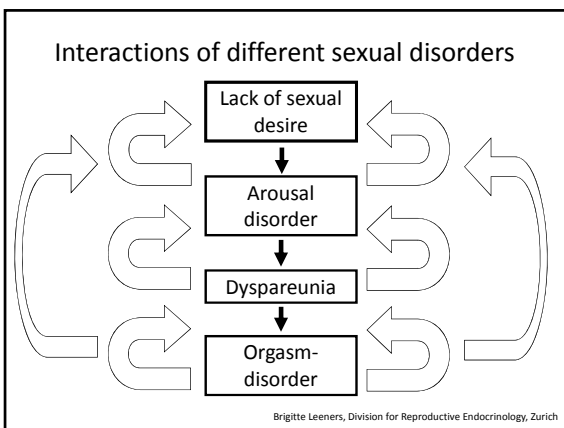
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# CAVE

Solving Chronic pelvic pain does not necessarily solve the sexual problem!

Bergeron, 2001, Goldfinger, 2009

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## Bleeding

- Increased risk for sexually transmitted diseases
- Exacerbation of infectious diseases
- Dysmenorrhea
- Sexual preferences
  - Religious concerns?
  - Estetic aspects?
  - Odour?
  - Staining?

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## 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)

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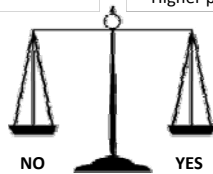
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- Irregular sex partner
- Conservative religious denominations



- 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

Hensel, 2007  
Tanfer, 1996  
Rempel, 2003

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## 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; Alexander, 1990

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## 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)
- Kardiovascular events (↑ during menstruation)

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## Counselling

- Investigate circumstances of onset of symptoms
- Active offer to discuss sexuality/ Integrate sexual counselling into health care
- Information on pathophysiological background of dyspareunia/dysmenorrhea
  - 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“

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## 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

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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.**

Gruppo Italo Belga  
[www.gynsurgery.org](http://www.gynsurgery.org)

Philippe R. Koninckx  
Anastasia Ussia

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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 organise surgery
- The claimed benefits
- Pitfalls to avoid

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## Pelvic pain : the decision to do surgery

- The decision to do surgery
  - Symptoms and exams
  - Absolute and relative indications to do surgery
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**Gynaecological Pain : Where ?**

- Below the umbilicus eventually radiating to the back

The diagram consists of two parts. On the left, a simple outline of the lower abdomen is shown with a vertical line extending downwards from the umbilicus. On the right, a more detailed outline of the lower abdomen and back is shown. A vertical line extends from the umbilicus down to the pelvic region, and two diagonal lines extend from the pelvic region up to the lower back, indicating the path of pain radiation.

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**Gynaecological Pain : Where ?**

- Below the umbilicus eventually radiating to the back

**Isolated back pain is not gynaecological**

The diagram is identical to the one in the first block, showing the lower abdomen and back with lines indicating pain radiation from the umbilicus to the back. A text box is overlaid on the diagram, stating "Isolated back pain is not gynaecological".

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**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

**Below the knee is not gynaecological**

The diagram is identical to the one in the first block, showing the lower abdomen and back with lines indicating pain radiation from the umbilicus to the back. A text box is overlaid on the diagram, stating "Below the knee is not gynaecological".

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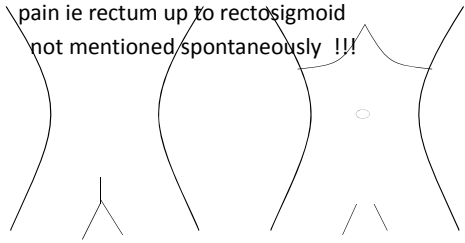
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### Gynaecological Pain : Radiation

- Perineal radiation is pathognomonic for bowel pain ie rectum up to rectosigmoid not mentioned spontaneously !!!



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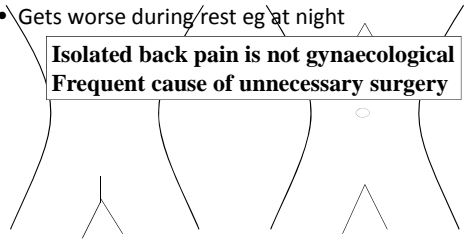
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### Sacro ileac joint : Radiation

- Back pain and ipsilateral fossa pain
- Gets worse during rest eg at night

**Isolated back pain is not gynaecological  
Frequent cause of unnecessary surgery**



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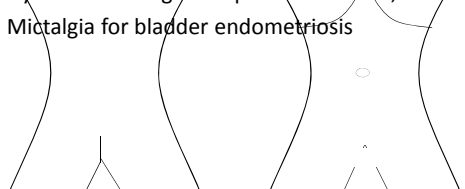
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### Gynaecological Pain : Cyclicity

- Endometriosis pain typically increases during menstruation
- Dyschesia in larger deep endometriosis, evt + blood
- Mictalgia for bladder endometriosis



**But all pain increases during menses.....  
increase thus is not pathognomonic for endo**

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### Causes of chronic pelvic pain

*We only recognise what we know*

- Where when type ?
- Clinical exam
  - Abnormalities ?
  - Painful ?
- 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 organical
- Interstitial cystitis
- Referred pain from sacro ileac joint
- Nerve entrapment in the wall

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### 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

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### Symptoms vary with lesion

	Prevalence	Pain	Infertility
• Subtle :	80%	no	no
• Typical :	25%	in 50% +	?
• Cystic :	10%	in 80% +++	++++
• Deep :	2-3%	in 95% ++++	???

- Adenomyosis
- Peritoneal pockets – Müllerianosis - Choristoma

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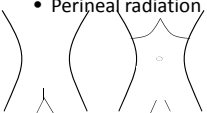
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### How to suspect Deep endo ?

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



- Pelvic pathology
  - Deep Endometriosis
  - Adhesions
  - Ovarian cysts.....
  - Oviduct : hydrosalpinx, eup
  - Uterus : adenomyosis , myoma
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### Endosalpingiosis

□ Atypical endometriosis




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### Adenomyosis



adenomyosis

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

<b>Definition = Pathology</b> = postmortem	No animal model No pathophysiology
<b>Strongly associated</b> with age with endometriosis with pain & infertility with interstitial cystitis	<b>Diagnosis by imaging</b>
	<b>Treatment</b> when ? How ??

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

- The decision to do surgery
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  - Absolute and relative indications to do surgery
  - Background knowledge
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  - Therapeutic
    - What can be done <-> should be done
    - How do we organise surgery
- The claimed benefits
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**Pelvic pain : the decision to do surgery**

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## 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, eup
  - Uterus : adenomyosis , myoma
  - Pelvic floor and retroversion
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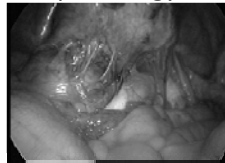
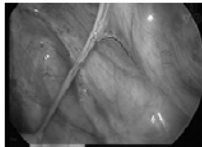
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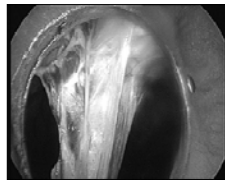
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## In the absence of other pathology

### • Adhesiolysis



- High recurrence rate
- Unproven benefits
- common sense



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## In the absence of other pathology

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



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



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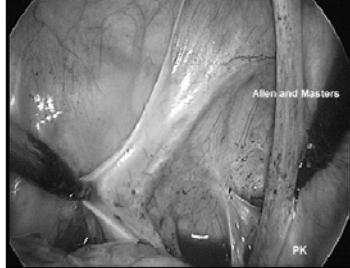
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### In the absence of other pathology

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



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

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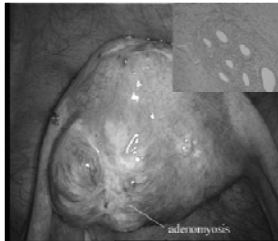
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### In the absence of other pathology

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



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

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### 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
  - > 4cm
  - intrinsic ureteral
  - personal cases : HMV CA

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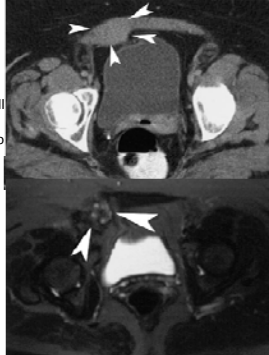
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## Abdominal wall endometriosis

- 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



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## Endometriosis of the Lung

### Case report:

Young girl of 16 years old

Recurrent shortness of the 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

21 | 20 Title of presentation | Author of presentation | 05/01/2019

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## Liver Endometriosis

- [J Radiol Case Rep, 2010;4\(11\):26-31. doi: 10.3941/jrcr.v4i11.589. Epub 2010 Nov 1. Hepatic endometriosis mimicking metastatic disease: a case report and review of the literature. Asran M, Rashid A, Szklaruk J.](#)

- 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 atypical imaging features of hepatic endometriosis in a 61 year-old female that mimic 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.

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## Cyclic haemorrhagic Ascites

- **Ussia, A.,** Betsas, G., Corona, R., De, Cicco C., and Koninck, P. R. Pathophysiology of cyclic hemorrhagic ascites and endometriosis. *J Minim Invasive Gynecol* 15(6), 677-681. 2008.
- 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 recurrences, whereas after unilateral ovariectomy or cystectomy 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



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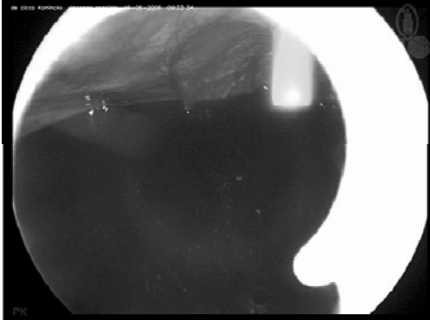
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## Endometriosis with ascites

- 6 liters



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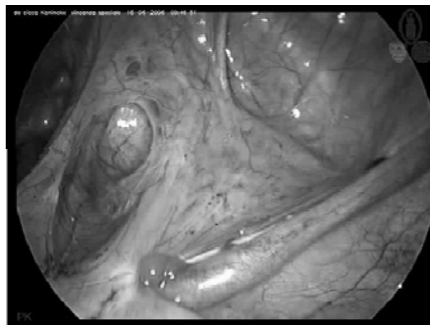
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## Endometriosis with ascites

- 6 liters



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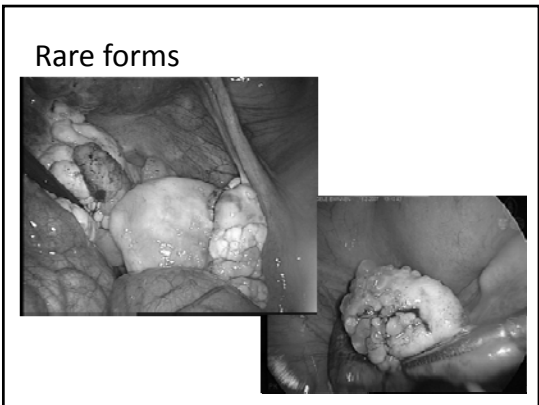
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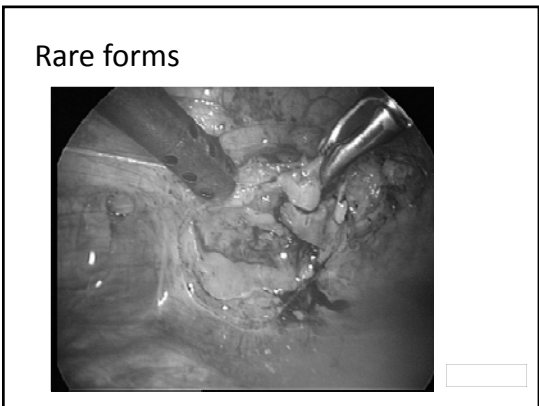
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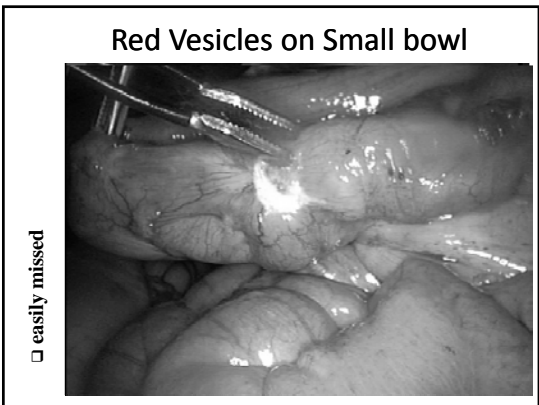
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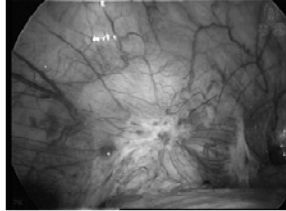
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### Typical endometriosis : excision

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



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### Cystic ovarian endometriosis : excision

- Pain relief
- Recurrence rates
- Ovarian damage

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### Deep endometriosis : excision

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



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### 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.

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### 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

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### The Elephant in the Room: Quality Control of Endometriosis Data

Philippe R. Koninckx, MD, PhD\*, Ronald E. Batt, MD, PhD, Lone Hummelshoj, Enda McVeigh, MD, Anastasia Ussia, MD, and John Yeh, MD, PhD



*"I'm right there in the room, and no one even acknowledges me."*  
The New Yorker, 9/18/06

THE JOURNAL OF  
MINIMALLY INVASIVE  
GYNECOLOGY

- Congresses needed
- Critical reading
- Hidden agenda
- !! EBM
- Overinterpretation
- Of results
- speculation

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## 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.

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## 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)

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## 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

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### *Conflict of interest*

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

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### *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

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*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.

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*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*

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*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.**

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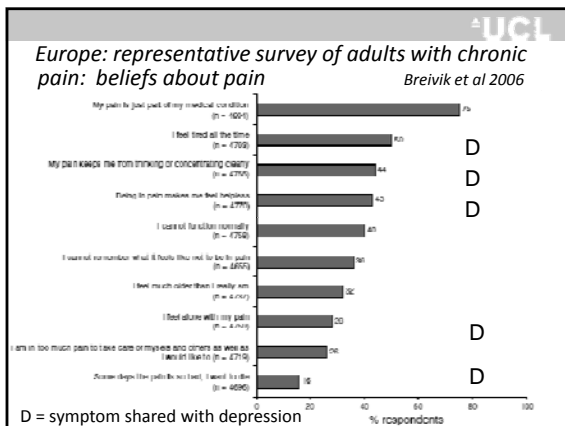
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*Psychological models*

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.

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*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 *Denny & Mann 2008*
- 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*

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*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 gynae consultation: *Price et al. 2006*

- explanation important – cancer anxiety; understanding pain.
- explanations lacking, inadequate, or conflicted with previous ones.

200 women surveyed in gynae 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.

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*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 2005*).

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

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*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.**

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**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 predicating 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**

authors	date	RCTs	N	pain site	improved
Turner	1996	4	>200	low back	multiple
<b>Morley et al</b>	1999	25	>1600	<b>mixed</b>	multiple
Van Tulder et al	2000	7	>300	low back	pain, function
Guzmán et al	2001	10	>1900	low back	pain, function
Ostelo et al	2005	21	>1400	low back	function
Hoffman et al	2007	22	>1700	low back	multiple
Nestoriuc et al	2008	21	>3000	tension headache	headache freq.
<b>Williams et al</b>	<b>2012</b>	<b>42</b>	<b>&gt;4800</b>	<b>mixed</b>	multiple
Glombiewski et al	2010	23	>1300	fibromyalgia	multiple

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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.

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*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.



**The Pain Toolkit**  
...is for people who live with persistent pain

A persistent pain problem can be difficult to understand and manage on an everyday basis.

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*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.

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*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.

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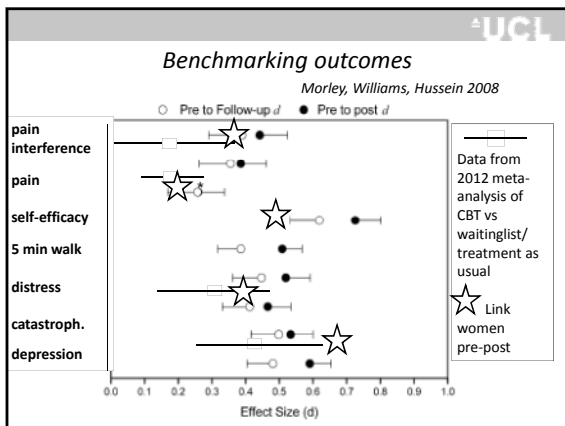
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**Research priorities**

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.

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**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!*

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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
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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
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