

Magnitude of the clinical problem of abdomino-pelvic adhesions/pain – the evidence base

Professor Cindy Farquhar

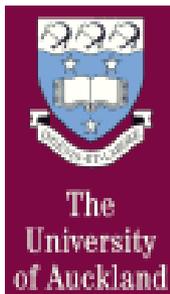
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National Women's and University of Auckland

ESHRE Spring Workshop

Edinburgh

February 2013



The official start of spring in 2013 is.....

- 20th March



Today is the 6th February in New Zealand

- Waitangi Day



Declaration

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

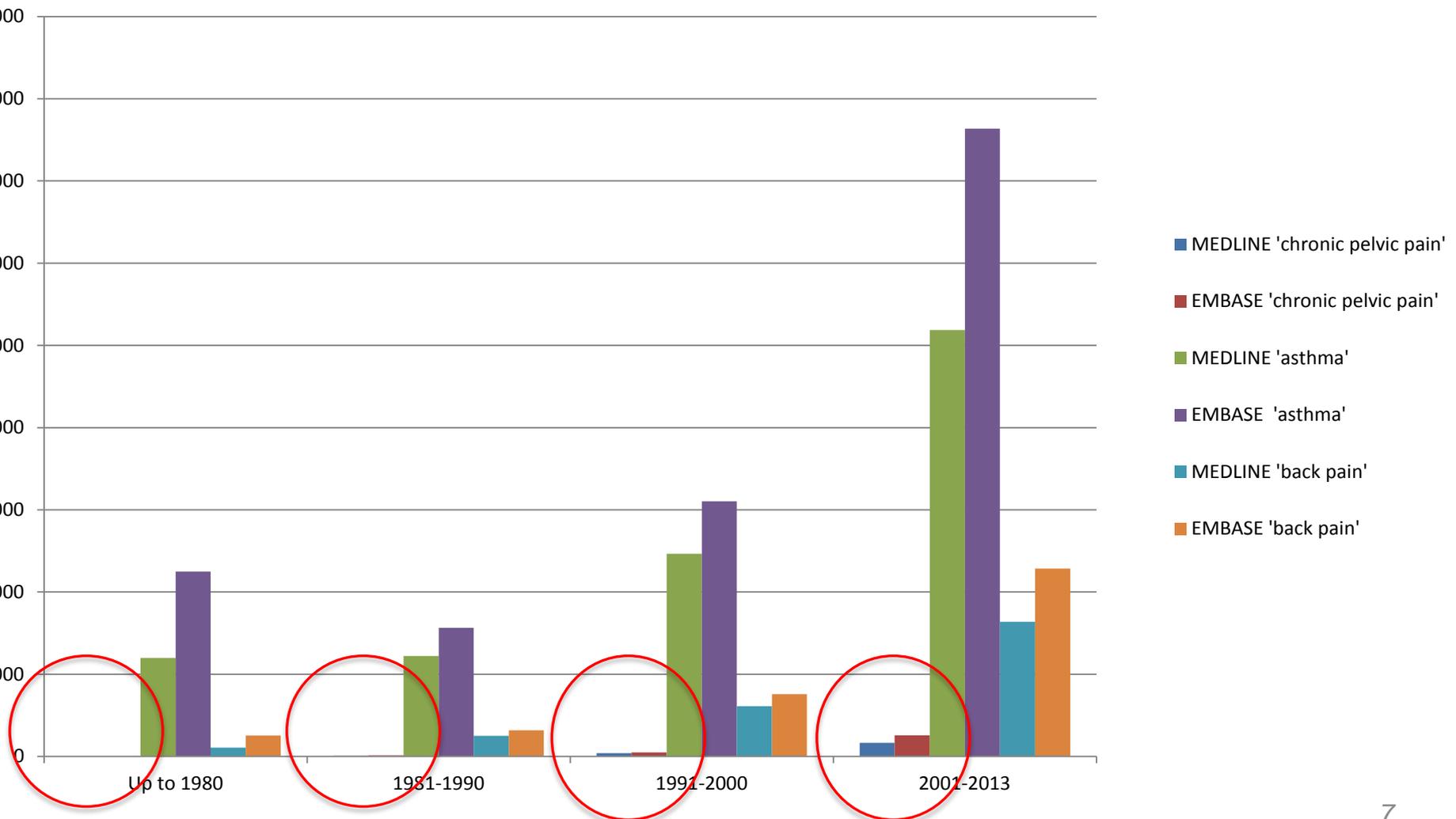
Outline

- Abdomino-pelvic pain and adhesions – size of the problem
- Association between adhesions and chronic pelvic pain
- Clinical perspective

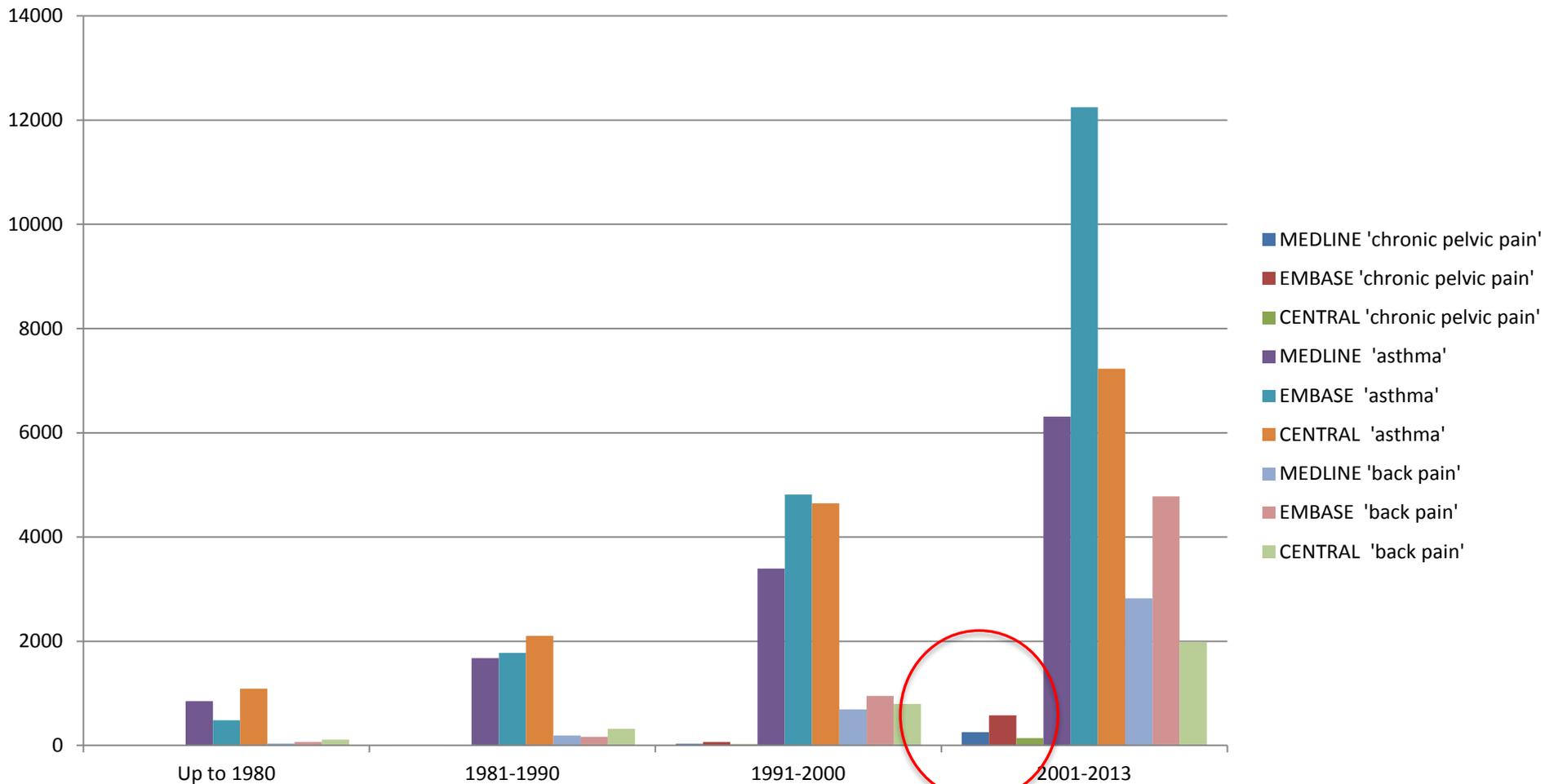
The evidence base.....

- Electronic searches of Medline and Embase and the Cochrane Library
- Google Scholar
- Dates – up to December 2012

Publications for chronic pelvic pain, asthma and back pain....



Individual MEDLINE, EMBASE and CENTRAL searches for randomised controlled trials



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



endorsed by:

painaustralia[™]
working to prevent and manage pain



- 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 Theiry 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

Some pertinent remarks 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”

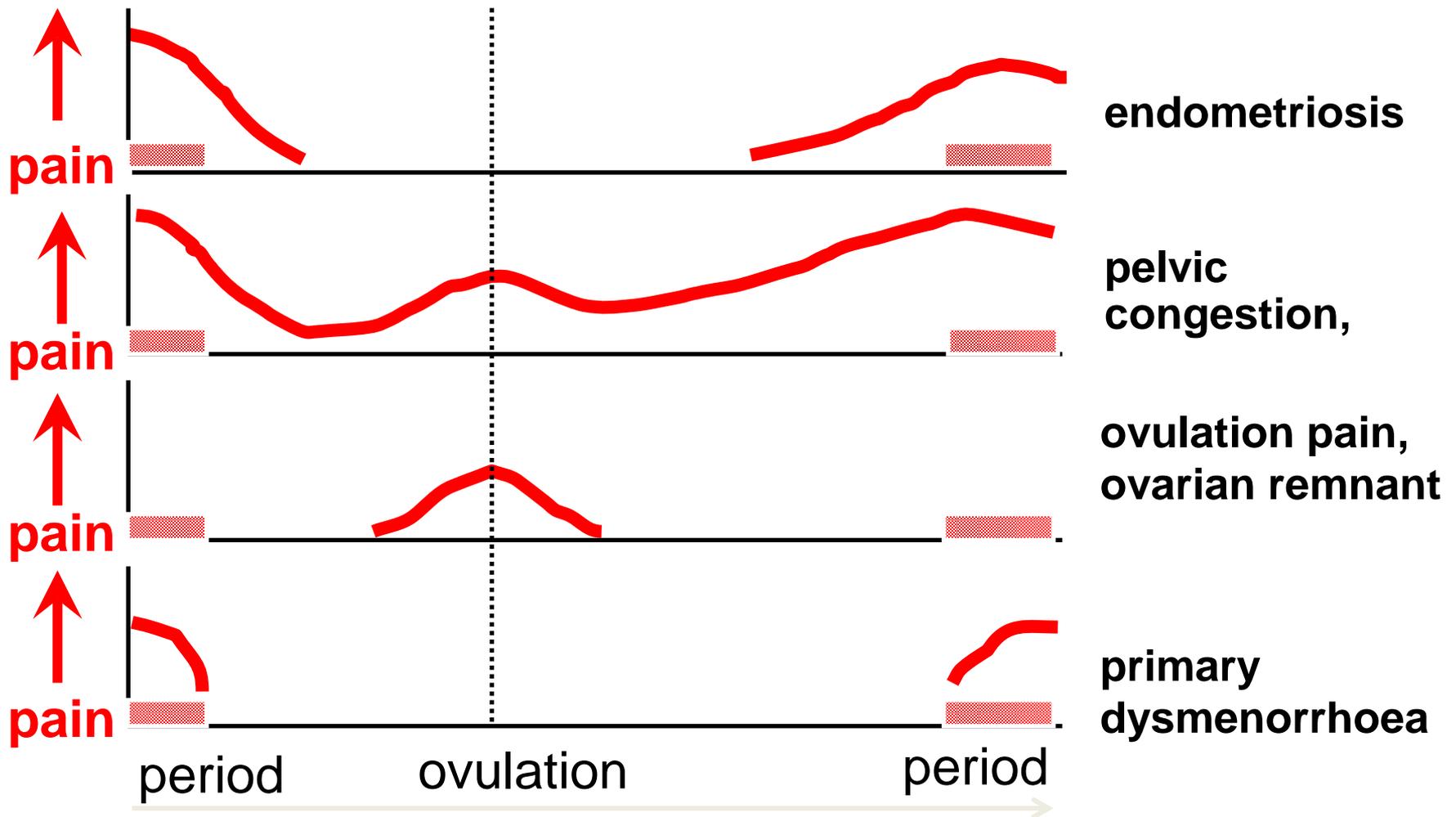
International Association for the Study of Pain

- 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*
 - No obvious pathologies
 - Pelvic congestion*
 - Primary dysmenorrhoea *
 - Midcycle pain*
 - Irritable bowel syndrome
 - Entrapped nerve syndrome
 - Neuropathic pain
 - Painful bladder syndrome
- * *Cyclical pattern*

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”

BMC Public Health



Research article

Open Access

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

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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)

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

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

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



endorsed by:



World Endometriosis Research Foundation - report 2011

TABLE 2

Work productivity in symptomatic women with and without endometriosis.

Work and productivity loss variables	Endometriosis (n = 745)	Symptomatic control (n = 587)	Unadjusted P value	Adjusted P value ^a
General				
Weekly hours paid to work, mean (SD)	39.2 (14.0)	38.6 (12.1)	.44	.047
Weekly hours actually worked, mean (SD)	24.9 (16.1)	28.5 (25.0)	.01	.32
Work Productivity and Activity Impairment dimensions				
Absenteeism^b				
%, mean (SD)	11.2 (21.6)	8.5 (20.0)	.069	.58
h/wk, mean (SD)	4.4 (8.0)	3.3 (8.4)	.24	.82
Presenteeism^c				
%, mean (SD)	25.8 (26.8)	17.9 (22.1)	<.001	.26
h/wk, mean (SD)	6.4 (7.9)	5.1 (6.7)	.001	.36
Overall work productivity loss^d				
%, mean (SD)	32.3 (29.8)	22.0 (25.1)	<.001	.045
h/wk, mean (SD)	10.8 (12.2)	8.4 (10.2)	<.001	.032
Activity impairment^e				
%, mean (SD)	28.5 (26.9)	19.6 (23.4)	<.001	.48

^a Variables adjusted for included educational attainment, marital status, type and number of symptoms, severity of pelvic pain, and comorbidity.

^b Time absent from work owing to symptoms.

^c Reduced effectiveness while on the job owing to symptoms.

^d Combination of absenteeism and presenteeism.

^e Reduced effectiveness while doing non-work-related activities, e.g., child care, exercise, housekeeping, etc.

Evidence report published in 2012



Effective Health Care Program

Comparative Effectiveness Review
Number 41

**Noncyclic Chronic Pelvic
Pain Therapies for Women:
Comparative Effectiveness**



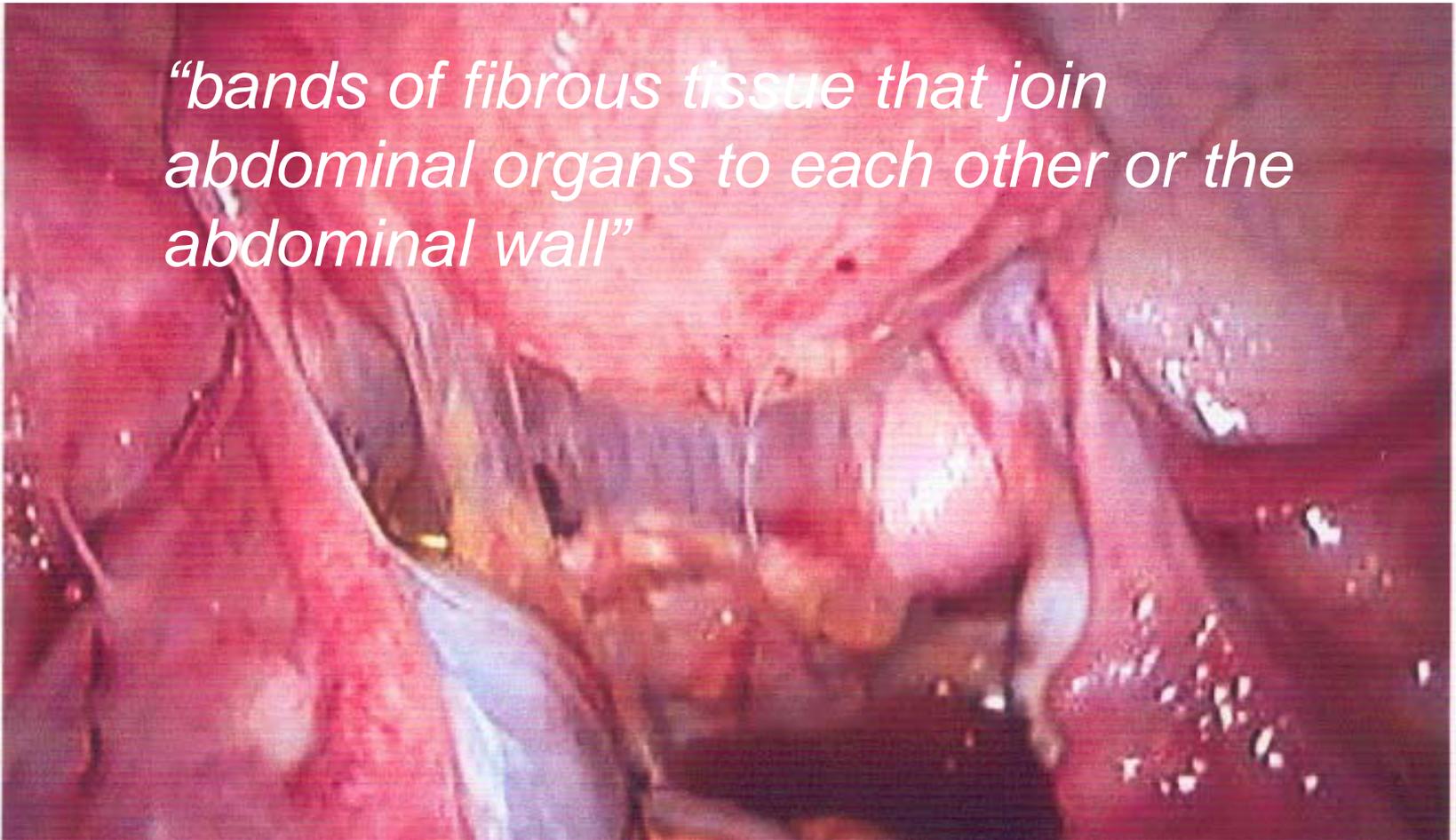
AHRQ

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

- 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

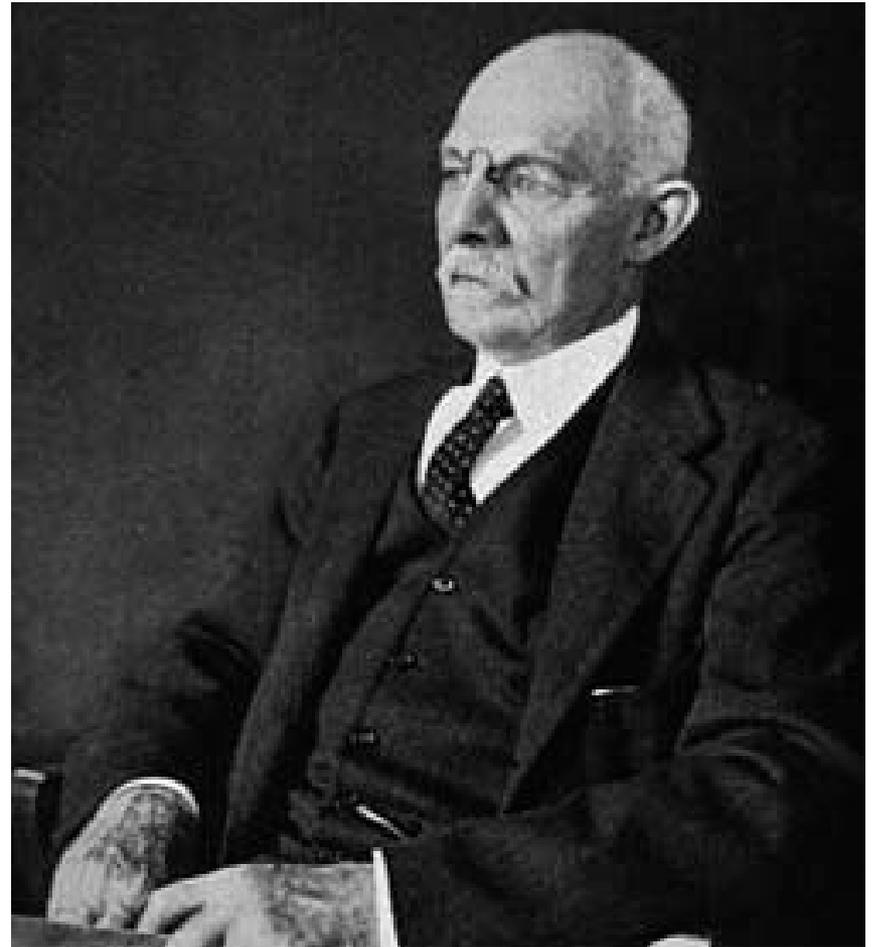
Now to adhesions.....

“bands of fibrous tissue that join abdominal organs to each other or the abdominal wall”



A brief history of adhesions

- William Halsted introduced gloves in 1889 when his scrub nurse had an allergy to antiseptic
- Latex gloves with powder soon became the norm, followed by corn starch – both of which resulted in granulomata
- Many staff found to be allergic to latex which has now been phased out



Professor Harold Ellis

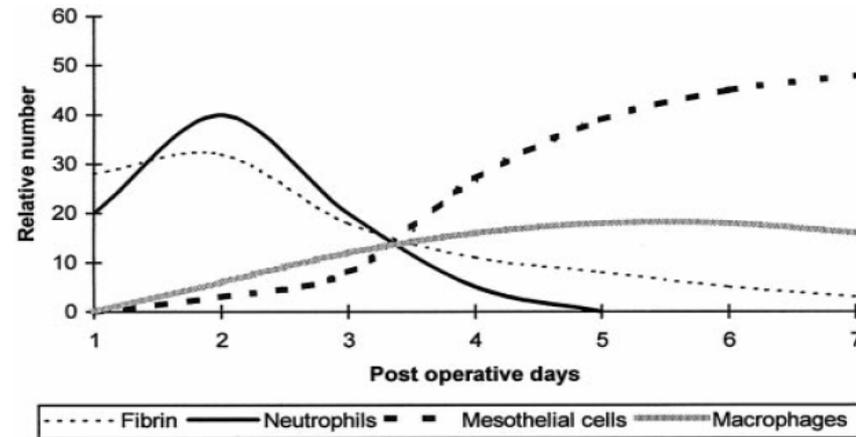
- Described post-op adhesions as almost inevitable
- Decried the common practice of oversewing the peritoneum
- Advocated reducing all foreign bodies – talc, gauze threads, suture material
- Described a minor epidemic of adhesions in the 1970s with change in glove sterilisation



When an injury to the serosa occurs....

The area is invaded by inflammatory cells:

- Day 1-2 neutrophils
- 24 hours to 5-6 days macrophages bind to the area
- Day 3 mesothelial cells begin to cover the bound macrophages which in turn embed deeper
- If all goes well, then the area is restored to a continuous sheet of MT cells within 7 to 10 days

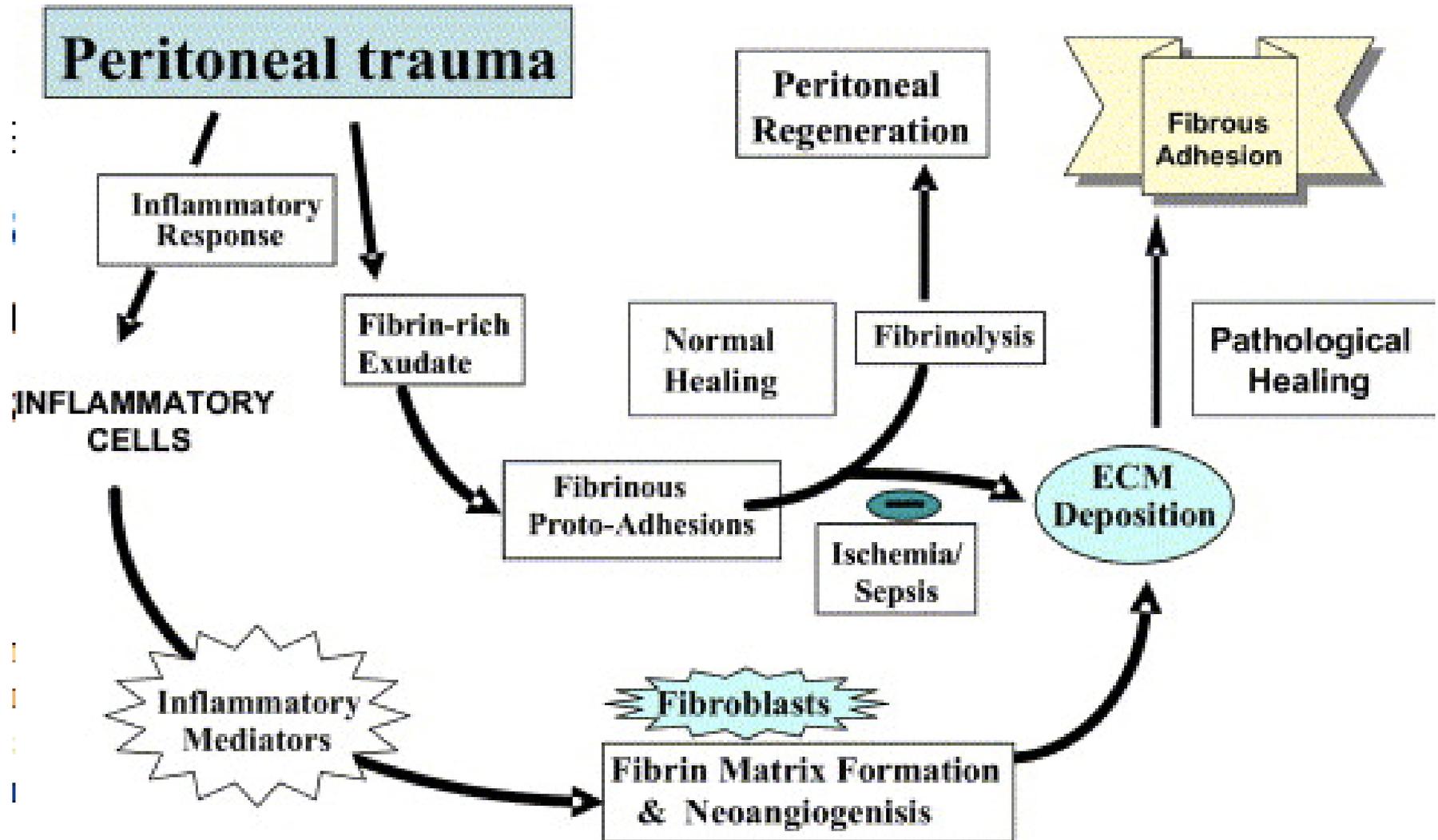


Adhesions occur when...

- There is excessive amounts of EC matrix secreted by fibroblasts and myofibroblasts
 - Results in weak fibrous bridges developing which may become firm if they become vascularised and if collagen is deposited

Why does normal healing fail and become adhesion forming

- Unclear what shifts the mechanism
- BUT there is a long list of potential initiators
 - ischaemia, trauma, inflammation, haemorrhage, chemical and thermal injury, tissue dessication, genetic prediposition, reaction to foreign body, endometriosis
- Adhesions form as a result of an complex interplay between the inflammatory system, abnormal fibrinolysis and aberrant ECM remodelling



Post surgical adhesions are very common

- Incidence of adhesions forming after surgery varies from 55-100%

(Diamond 1991)

Adhesions are very common even when we try really hard to avoid them....

Pelvic Adhesions following Reconstructive Surgery			
	Time from Initial Proced.	Total No. Patients	% with Adhesions
Diamond et al	1 wk - 12 wk	106	86
DeCherney	4 wk - 16 wk	20	41
	1 y - 3 y		75
Surrey	6 wk - 8 wk	31	71
	> 6 mo	6	83
Pittaway et al	4 wk - 6 wk	23	100
Trimbos-Kempor	8 days	188	55
Daniell	4 wk - 6 wk	25	96

Adhesions are less frequent with laparoscopic surgery than with open surgery

- Diamond 1987
 - 51% had new adhesions following laparoscopic surgery
- Lundorff 1991
 - Ectopic pregnancy: more than 50% adhesions after open surgery compared to 15% in the laparoscopic group

Burden of disease for adhesions

- Difficult to report
- How common are complications following adhesion formation?
 - Pain? Present in 25-50% of women with CPP
 - Infertility – 15-20% of infertility is tubal adhesion related
 - Intestinal obstruction – mostly related to surgery and endometriosis

Categories of infertility



Percentage of couples referred

Tubal adhesions and fertility

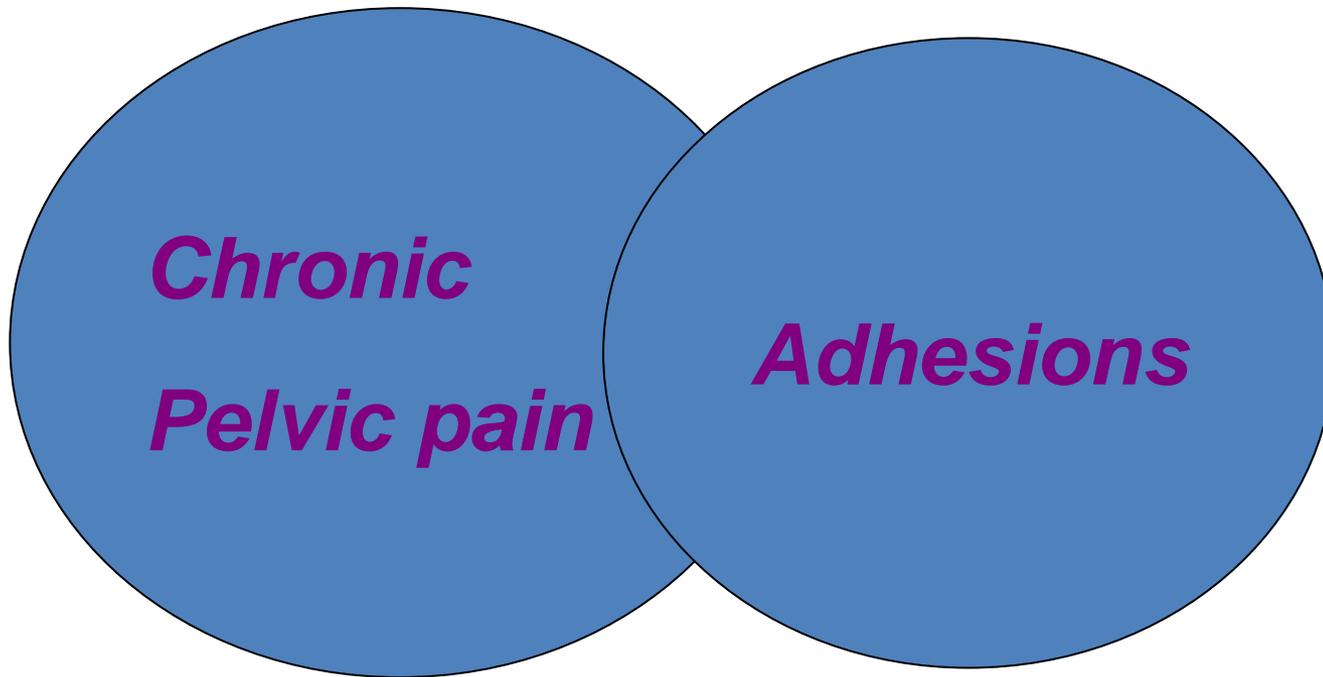
- The incidence of tubal infertility following pelvic inflammatory disease
 - after 1 episode of pelvic infection is 12%
 - 23% after 2 episodes
 - 54% after 3 episodes of pelvic infection

(Westrom et al 1980)
- Surgical treatment to restore patency is often successful
- Adhesions may interfere with assisted reproduction
 - Distortion makes monitoring and ovum pick up more difficult

The cost of adhesiolysis

- In 1994 – 1% of all hospitalisations in the US were for adhesiolysis, rising slightly in 2004
- Nearly 60% of surgery for bowel obstruction in the US were secondary to adhesions, and more than 2/3rds of small bowel obstruction
 - High morbidity and potential for mortality
 - Litigation prone condition
- Infertility and pain is not often costed.....

What is the relationship between adhesions and pain



What is the relationship between adhesions and pain

- Challenges
 - Paucity of well designed studies in the field of adhesions and in chronic pelvic pain
 - Many studies cite endometriosis in association with adhesions
 - Of the published studies there is little difference in the prevalence of adhesions found in women with and without CPP

How might the pain arise from adhesions?

- Restricting organ mobility – stimulating stretch receptors in the smooth muscle of adjacent organs or abdominal wall
- Laparoscopic studies showed that 80% of patients with significant pelvic adhesions had pain when the adhesions were probed
 - Nerve endings have been identified in adhesions in both women with and without pain (Kligman)

Sulaiman 2001

How to establish if adhesions cause pelvic pain...

Bradford Hill 1897-1991

- Epidemiologist
- Criteria for causality
 - Experimental studies
 - Strong and consistent association
 - Temporal relationship
 - Biological and epidemiological plausibility
 - Dose response
 - Specific association
 - Analogous to similar relationship



Is there experimental evidence from human studies ?

- Studies with an experimental design that would suggest a relationship are required:
 - That is, if pain is caused by adhesions, then removing the adhesions should relieve the pain
 - Randomised controlled trial of adhesiolysis in women with pelvic pain

RCTs of adhesiolysis

- SR of RCTs by AHRQ in US 2012
 - Concluded no evidence of benefit with lysis of adhesions
 - Two RCTs and one non randomised study

	Surgical approach	No. of women	Improvement	Length of follow up
Peters 1992	Laparotomy	48	No but in the group with more severe adhesions there was some improvement	9-12
Swank 2004	Laparoscopic	100 (some men)	57% vs 42% difference between adhesiolysis and diagnostic group but not s.significant.	12 months
Lamvu 2006	Unclear	85 women in MD clinic	Improvement in pain similar in women who had surgery or not	12 months

Is the association strong ?

- Strength of association
 - There are other explanations for pain but it is on the list....
 - Other explanations – endometriosis, physiological changes, neuropathic pain

Is the association consistent from study to study ?

- Consistency of association:
 - There are not a lot of studies
 - Quite a lot of inconsistency in the medical literature

Is there a temporal relationship?

- Do adhesions precede the onset of pain
 - Impossible to know as it is uncommon to undertake diagnostic laparoscopy except when pain already present

Is there a dose-response relationship?

Adhesions that are dense and vascular are more likely to cause pain (Peters et al 1991)

Is the association biologically plausible?

- Yes
 - Microlaparoscopic studies suggest pain when the adhesions are stretched
 - Adhesions have been shown to have nerve endings...
 - But they are also present in women with adhesions and with no pain

Is the association specific?

- Adhesions are frequently reported in women with no pain
- Saravelos and Cooke 1995
 - 15% of controls with no adhesions had pain and 36% of women with adhesions had pain

Summary of causality criteria - do adhesions cause pain?

NOT VERY CONVINCING

Question	Explanation of question	Role of adhesions in causing pain	
Is there experimental evidence from human studies?	Are there studies of adhesiolysis that show relief of pain?	RCTs have not shown this but not enough studies	X/?
Is the association strong?	Any other explanation possible?	Women may have pain without adhesions	X
Is the association consistent between studies	Consistent results ?	No, a moderate variation	X /?
Is the temporal relationship correct?	Do the adhesions precede the pain?	Difficult to establish	X
Is there a dose-response relationship?	The worse the adhesions the worse the pain?	Possibly but difficult to establish	?
Does the association make biological sense?	Is there a scientific explanation for the pain?	Yes, nerve endings and stretching	√
Is the association specific?	How much overlap between pain and adhesions?	Some overlap	X/? 50

Bringing the topic into focus.....



One of my patients.....Carol

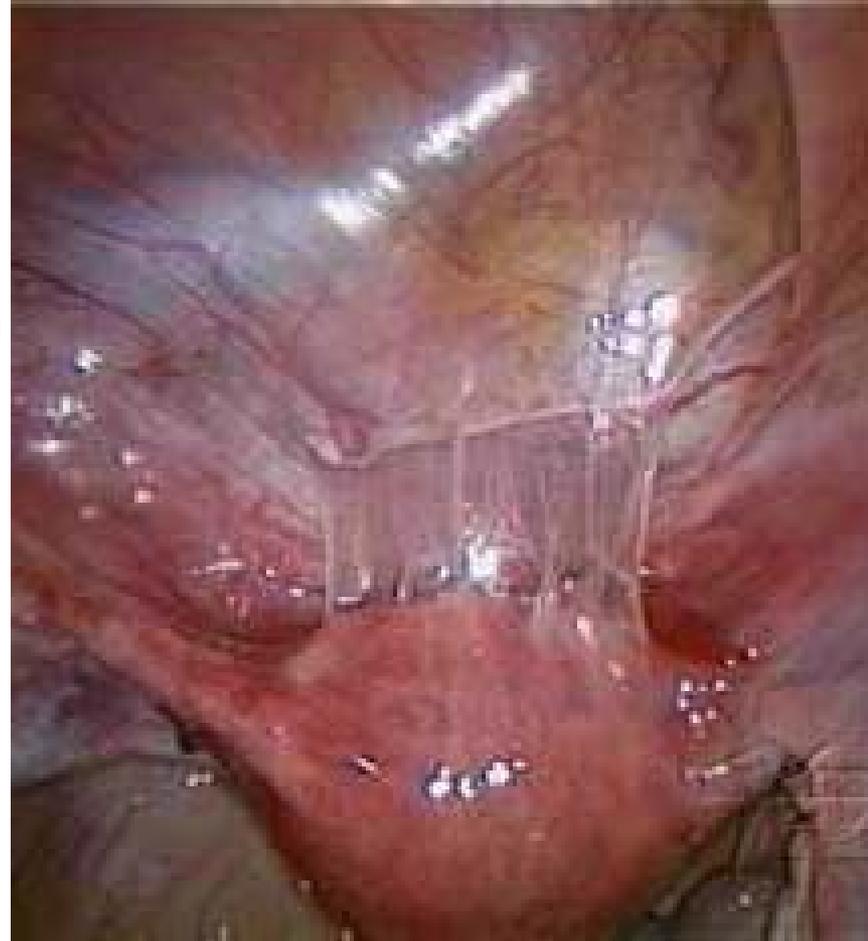
- Referred in April 2011 with a semi-acute onset of pain over 3 months
- 38 year old secondary school teacher
- Previous myomectomy (prior to conceiving)
- P2G3
 - two children both born by c-section (now aged 8 and 5), midtrimester loss at 17/40 (abruption)
- One year following delivery had mirena insertion

Past History

- 2009 - symptoms of rectal prolapse and had a De Lorme Procedure
- Nov 2010 – recurrent symptoms and had laparoscopic ventral mesh rectopexy
 - Left with symptoms of tightness and discomfort in the vagina, pain radiating to the back, pain with fullness in the bowel
- March 2011 Ultrasound suggested Mirena embedded in the c-section scar – removed and given one week antibiotics– no improvement

May 2011.....

- Laparoscopy
 - The pelvis was injected and evidence of inflammatory process with adhesions between the bladder and uterus and also fine adhesions around the tubes
 - Treated for infection
 - Started amitryptiline at night
 - Pain diary
 - Lengthy explanation about neuropathic pain and need for long term treatment
 - Jadelle



Over 2011

- Gradual improvement in pain scores (diary)
- Able to return to work
- Bleeding on and off
- End of 2011 – overall better and discharged...

September 2012

- Return of symptoms
 - Pain in vagina present all the time
 - Worse at end of the day
 - Exacerbated by standing
 - Searing or burning nature to the pain
 - Avoiding sex
 - Pain when bowel is full

Examination

- Normal findings except for roughness in the upper vagina 2 cm below the posterior fornix which was not tender
- Unable to move the cervix without pain
- Rectal examination normal
- Reviewed by colorectal surgeon
- MRI – not helpful

Summary

- 40 year old women
- Chronic pelvic pain
- Multiple insults – surgeries, mesh, infections
- Questions
 - Should the mesh be removed?
 - Would a hysterectomy help relieve pain?

More questions than answers....

- When to investigate?
- Just treat symptoms?
- What is the best approach?

My view

- All women with cyclical pelvic pain should generally be offered an ultrasound and laparoscopy **once**
 - Endometriosis or adhesions is unable to be diagnosed reliably any other way
- The decision to repeat laparoscopies when previous laparoscopies were negative should be made cautiously
 - Chronic Pelvic Pain: How many surgeries are enough? C Butrick 2007

Avoid seeking diagnosis at all costs

- A diagnosis may never be made
- Patients often want a diagnosis
 - Continuing to seek a diagnosis may not be helpful
 - Assisting your patient to understanding this may be helpful

Principles of care

- Multidisciplinary approach
- Avoid multiple diagnostic tests
- Avoid fertility destroying surgery
- Focus on return to normal daily activities/QOL
- Evidence based: balance harms and benefits of all approaches

Negative spiral of pain

- Chronic pain may lead to
 - ongoing distress
 - uncertainty about the future
 - anxiety
 - loss of sleep
 - negativity
 - low mood
 - fatigue



Our role?

- To break that negative spiral –
 - by being as factual and honest as possible
 - to seek to provide effective interventions without doing harm....

There is long way to go yet....

