Chronic Pain Conditions in Women

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The Plan

- Defining chronic pain
- Chronic pain burden of disease
- Sex differences in pain perception, expression and prevalence
- Biopsychosocial aspects of chronic pain in women using fibromyalgia and chronic pelvic pain as examples
- Chronic pain in pregnancy
Pain

- IASP definition: Unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage

- Acknowledges the emotional dimension of pain

- Understanding of pain in the absence of tissue damage

- Highlights the role of mental health professionals in the assessment and management of chronic pain conditions
Acute Pain

- Functional role
- Sudden onset
- Limited duration
- Associated with tissue damage and inflammation
- Resolves with tissue recovery
- Intact neural pathways
- Effectively modulated by analgesics, opioids
Chronic Pain

- No longer serves a functional role
- Does not resolve with tissue recovery
- Can result from damage to tissue or nerve damage
- Complex nervous system changes including central sensitization
- Requires a multidisciplinary approach to biopsychosocial assessment and management
- Typical acute pain treatments can be ineffective or unsafe
- Psychiatric comorbidity
Chronic Pain
Burden of Disease

By 2030 the WHO predicts that the 4 leading contributions of global burden of disease will be:
- Unipolar depression
- Coronary artery disease
- Cerebrovascular disease
- Road traffic accidents

Chronic pain is an associated comorbidity of all of these

AND chronic pain is a condition in its own right

(Mathers. WHO The global burden of disease. 2004 Update.)
Chronic Pain Burden of Disease

- USA: Up to 64% report a chronic pain condition over their lifetime (Johannes et al. 2010), nearly 50 million American adults have significant chronic pain or severe pain (NIH 2015)

- Europe: 29% general population report pain as a significant problem (Konig et al. 2009)

- WHO: 22% primary care patients had pain present for most of the time for at least 6 months (Gureje et al. 1998)

- RSA: 41% patients attending primary healthcare clinics experience chronic pain (Waqar-un-Nisa et al. 2012)

- RSA: 43% adults living in a rural community reported suffering from chronic pain (Igumbor et al. 2011)
Chronic Pain Risk Factors

- Sociodemographic
- Clinical
- Psychological
- Biological
Yellow Flags
Highlight Risk for Chronicity

- Attitudes- towards the current problem
- Beliefs- unhelpful, catastrophising
- Compensation- injury at work, road accident fund
- Bad diagnostic communication- e.g. your spine is crumbling
- Emotional stressors- depression, anxiety
- Family issues- overly supportive or dismissive
- Work dissatisfaction
Sociodemographic Risk Factors

- Female gender
- Older age
- Lower socioeconomic status
- Employment status and occupational factors
- History of abuse or interpersonal violence

Gender versus Sex

Sex - biological differences (anatomy, chromosomes reproductive organs, secondary sexual characteristics)

Gender - broader, more complex psychological, sociocultural and political construct, refers to social roles, personal identification and internal awareness

Gender is a continuous variable

The Sex, Gender and Pain Special Interest Group of the IASP suggest that both constructs should be examined (Racine et al. Pain. 2012)
Pain research should be directed towards:

- What conditions lead to the expression of sex and gender differences in pain and reactivity
- What mechanisms underlie these differences
- How these differences can inform clinical management of pain

(Greenspan et al. Pain. 2007)
Sex Differences in Pain Perception

In experimental studies, women have:

- Lower pain thresholds
- Lower pain tolerance
- Greater intensity with pain
- Different analgesic sensitivity

Sex Differences in Pain Perception

- Observed differences are not always consistent
- Multiple confounding factors

Review of 10 years of studies concluded: (Racine et al. Pain. 2012)
- Women and men have comparable thresholds for cold and ischaemic pain
- Women tolerate less thermal and pressure pain
- Experimental evidence that genetic, hormonal, physiological factors contribute to sex differences in pain sensitivity in healthy subjects is small and inconsistent
- Cognitive and social factors may explain sex-related differences
- Challenge the validity of conducting research in healthy subjects
Sex Differences in Pain Expression

In epidemiologic studies women report:

- More severe pain
- At higher frequency
- Greater number body regions
- More negative responses

Sex Differences in the Prevalence of Chronic Pain Conditions

A number of pain conditions are more prevalent in women:

- Migraine
- Temporomandibular joint disorder
- Carpal tunnel syndrome
- Raynaud disease
- Fibromyalgia
- Arthritis
- IBS
- Pain related to autoimmune disorders e.g. RA
- Interstitial cystitis (Craft. Pain. 2007)
Table 2
Sex prevalence of various painful disorders

<table>
<thead>
<tr>
<th>Female prevalence</th>
<th>Male prevalence</th>
<th>No sex prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine headache with aura</td>
<td>Migraine without aura</td>
<td>Acute tension headache</td>
</tr>
<tr>
<td>Chronic tension headache</td>
<td>Cluster headache</td>
<td>Cluster-tic syndrome</td>
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<tr>
<td>Post-dural puncture headache</td>
<td>Post-traumatic headache</td>
<td>“Jabs” and “jolts” syndrome</td>
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<tr>
<td>Hemicrania continua</td>
<td>SUNCT syndrome</td>
<td>Secondary trigeminal neuralgia</td>
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<tr>
<td>Cervicogenic headache</td>
<td>Raeder’s paratrigeminal syndrome</td>
<td>Neuralgia of nervus intermedium</td>
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<tr>
<td>Tic douloureux</td>
<td>Pancoast tumor</td>
<td>Painful ophthalmoplegia</td>
</tr>
<tr>
<td>Temporomandibular joint disorder</td>
<td>Thromboangiitis obliterans</td>
<td>Maxillary sinusitis</td>
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<tr>
<td>Occipital neuralgia</td>
<td>Brachial plexus avulsion</td>
<td>Toothache due to dentinoenamel defects</td>
</tr>
<tr>
<td>Periapical periodontitis &amp; abscess</td>
<td>Pancreatic disease</td>
<td>Toothache due to pulpitis</td>
</tr>
<tr>
<td>Atypical odontalgia</td>
<td>Duodenal ulcer</td>
<td>Cracked tooth syndrome</td>
</tr>
<tr>
<td>Burning tongue</td>
<td>Abdominal migraine</td>
<td>Dry socket</td>
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<tr>
<td>Carotidynia</td>
<td>Lateral femoral cutaneous neuropathy</td>
<td>Vagus nerve neuralgia</td>
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<tr>
<td>Chronic paroxysmal hemicrania</td>
<td>Post-herpetic neuralgia</td>
<td>Stylohyoid process syndrome</td>
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<tr>
<td>Temporal arteritis</td>
<td>Hemophilic arthropathy</td>
<td>Thoracic outlet syndrome</td>
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<tr>
<td>Carpal tunnel syndrome</td>
<td>Ankylosing spondylitis</td>
<td>Brachial plexus tumors</td>
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<tr>
<td>Raynaud’s disease</td>
<td></td>
<td>Esophageal motility disorders</td>
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<tr>
<td>Chilblains</td>
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<td>Chronic gastric ulcer</td>
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<tr>
<td>Causalgia</td>
<td></td>
<td>Chron’s disease</td>
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<tr>
<td>Reflex sympathetic dystrophy</td>
<td></td>
<td>Diverticular disease of colon</td>
</tr>
<tr>
<td>Hemicrania continua</td>
<td></td>
<td>Carcinoma of the colon</td>
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<tr>
<td>Chronic venous insufficiency</td>
<td></td>
<td>Familial Mediterranean fever</td>
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<tr>
<td>Fibromyalgia syndrome</td>
<td></td>
<td>Hereditary coproporphyia</td>
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<td>Esophagitis</td>
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<td>Acute herpes zoster</td>
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<td>Reflux esophagitis with peptic ulcer</td>
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<td>Burns</td>
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<tr>
<td>Slipping rib syndrome</td>
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<td>Twelfth rib syndrome</td>
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<tr>
<td>Gallbladder disease</td>
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<tr>
<td>Post-cholecystectomy syndrome</td>
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<tr>
<td>Irritable bowel syndrome</td>
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<tr>
<td>Interstitial cystitis</td>
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<tr>
<td>Acute intermittent porphyria</td>
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<tr>
<td>Proctalgia fugax</td>
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<tr>
<td>Chronic constipation</td>
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<tr>
<td>Pyriformis syndrome</td>
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<tr>
<td>Peroneal muscular atrophy</td>
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<tr>
<td>Multiple sclerosis</td>
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<tr>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Pain of psychological origin</td>
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</tbody>
</table>
Sex Differences in the Prevalence of Chronic Pain Conditions

- Many clinical pain conditions show no sex difference before puberty but show increased prevalence in one sex (usually women) after puberty e.g. migraine, TMD (Greenspan et al. Pain. 2007)

- Severity of symptoms for several pain conditions vary across the menstrual cycle e.g. headaches, fibromyalgia, IBS (Manson. Metabolism. 2010)

- Impact of pregnancy and the postpartum state on several pain conditions e.g. migraine, TMD
Biological Underpinnings of Sex Differences in Pain

- Sexual differentiation of pain appears to occur similarly to sexual differentiation of other phenomena.

- Organizational and activational effects of gonadal steroid hormones: estrogen, progesterone, testosterone.

- Considerable evidence for estrogenic involvement in migraine, temporomandibular disorder and arthritis.

Biological Underpinnings of Sex Differences in Pain


- Sexual differentiation and behaviour
- Cardiovascular function
- Bone formation
- Haemostasis
- Water and salt balance
- Metabolic rate
- Inflammation
- Impact on many brain systems including the nociceptive system

- Estrogenic modulation of pain is complex with estrogen having both pro- and antinociceptive effects and widespread distribution of ER in pain-relevant areas of the body
Sex–Specific Brain Alterations in Chronic Pain

- More prominent primary sensory motor structural and functional alterations in female chronic pain patients compared to males
- Greater insula reactivity in male patients
- Differences in the degree of anterior cingulate structural alterations
- Differences in emotional-arousal activity

(Gupta et al. Neuroscience Research. 2016)
Psychological and Social Factors that may Impact on Sex Differences in Pain Experience, Expression and Prevalence

- Depression
- Anxiety
- Coping styles
- Pain catastrophizing
- Coping strategies
- Gender/sex specific beliefs and expectations
- Perceived self efficacy
- Culture
- History of abuse
- Disability
- Social role

(Racine. Pain. 2012.)
Men and women experience and express pain in different ways.

There are differences in the prevalence of certain pain conditions between men and women.

Most explanations focus on biological mechanisms.

Different pain mechanisms may operate in men versus women.

Growing understanding of the importance of psychological and social factors.
Fibromyalgia in Women

- Prevalence 2-8% of population (Clauw. JAMA. 2014)
- 1990 diagnostic criteria emphasized chronic widespread pain with tender points
- Almost all patients were women because they have more tender points than men
- Newer 2011 diagnostic criteria are symptom based and do not require counting tender points
- Now male:female ratio of 2:1
Figure. Example of a Patient Self-report Survey for the Assessment of Fibromyalgia Based on Criteria in the 2011 Modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia

**Widespread Pain Index**
(1 point per check box; score range: 0-19 points)

1. Please indicate if you have had pain or tenderness *during the past 7 days* in the areas shown below.
   Check the boxes in the diagram for each area in which you have had pain or tenderness.

   ![Diagram showing widespread pain areas](image)

**Symptom Severity**
(score range: 0-12 points)

2. For each symptom listed below, use the following scale to indicate the severity of the symptom *during the past 7 days*.
   - No problem
   - Slight or mild problem: generally mild or intermittent
   - Moderate problem: considerable problems; often present and/or at a moderate level
   - Severe problem: continuous, life-disturbing problems

<table>
<thead>
<tr>
<th>Points</th>
<th>No problem</th>
<th>Slight or mild problem</th>
<th>Moderate problem</th>
<th>Severe problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Fatigue</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>B. Trouble thinking or remembering</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>C. Waking up tired (unrefreshed)</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

3. During the *past 6 months* have you had any of the following symptoms?

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Pain or cramps in lower abdomen</td>
<td>□ No</td>
<td>□ Yes</td>
</tr>
<tr>
<td>B. Depression</td>
<td>□ No</td>
<td>□ Yes</td>
</tr>
<tr>
<td>C. Headache</td>
<td>□ No</td>
<td>□ Yes</td>
</tr>
</tbody>
</table>

**Additional criteria (no score)**

4. Have the symptoms in questions 2 and 3 and widespread pain been present at a similar level for at least 3 months?
   □ No | □ Yes

5. Do you have a disorder that would otherwise explain the pain?
   □ No | □ Yes

ACR indicates American College of Rheumatology. Scoring information is shown in blue. The possible score ranges from 0 to 31 points; a score ≥13 points is consistent with a diagnosis of fibromyalgia. Additional scoring information and a printer-ready version of this survey that patients can complete are available online (eFigure 1 and eFigure 2 in the Supplement).
Fibromyalgia in Women

- Complex heterogenous condition with abnormal peripheral and central pain processing

- Fatigue, impaired cognition (short and long term memory, concentration, attention), non restorative sleep (Sumpton et al. Handb Clin Neurl. 2014.)

- Women presenting with fibromyalgia require detailed history, physical examination, completion of the Patient Self Report Survey, basic investigations (FBC, TSH, Vit D, ESR, CRP), exclusion of other pain disorders, assessment of psychosocial context
Fibromyalgia in Women

Psychosocial Factors

- Fibromyalgia is associated with other pain syndromes: headache, dysmenorrhea, TMD, chronic fatigue, IBS, interstitial cystitis, endometriosis, chronic back pain

- Familial and genetic factors

- Environmental triggers and risk factors: acute pain, infection, trauma, psychological distress, poor sleep, obesity, physical inactivity, job dissatisfaction, lack of support

- Psychiatric comorbidity: depression, anxiety, OCD, PTSD

- Psychological factors: catastrophizing and fear of movement
Fibromyalgia in Women
Management

- Biopsychosocial interdisciplinary approach aimed at improving health-related QOL
- Patient education
- Aerobic and strengthening exercise, acupuncture, hydrotherapy, meditative movement
- Psychological- CBT, mindfulness based stress reduction
- Biological: low dose amitriptylline, duloxetine, tramadol, pregabalin

(Macfarlane et al. Ann Rheum Dis. 2017.)
Chronic Pelvic Pain in Women

- Persistent, noncyclic pain perceived to be in structures related to the pelvis that lasts more than 6 months (Engler et al. European Association of Urology Guidelines. 2015.)

- Prevalence rates of 6-27% (Ahangari. Pain Physician. 2014.)

- In half of cases there are associated entities such as IBS, interstitial cystitis, endometriosis or pelvic adhesions (Speer et al. Am Fam Physician. 2016.)

- A significant number of patients have no aetiology for their pain on investigation
Chronic Pelvic Pain in Women

- Complex neuromuscular-psychosocial disorder consistent with a complex regional pain syndrome or functional somatic pain syndrome (Speer et al. Am Fam Physician. 2016.)

- Multiple systems:
  - Gastrointestinal
  - Urological
  - Gynaecological
  - Oncological
  - Musculoskeletal
  - Neurological
  - Psychosocial
Chronic Pelvic Pain in Women

- Women presenting with CPP require detailed history, physical examination, basic testing (FBC, ESR, urinalysis, STD testing, pelvic ultrasonography)

- When pain is severe patients should be referred for laparoscopy; endometriosis 33%, adhesions 24%, absence of pathological conditions 35% (Stein. Gastroenterol Clin N Am. 2013.)

- Red flags: post coital bleeding, postmenopausal bleeding, post menopausal onset of pain, unexplained weight loss, pelvic mass, haematuria
Chronic Pelvic Pain in Women
Psychosocial factors

- Nearly half of women with chronic pelvic pain report a history of sexual, physical or emotional trauma
- Adult sexual assault is associated with greater severity of CPP (Yosef et al Am J Obstet Gynaecol. 2016.)
Chronic Pelvic Pain in Women Management

- Interdisciplinary biopsychosocial approach with the aim of improving QOL and functioning

- Biological: Treat obvious disease processes, depot medroxyprogesterone, gonadotrophin-releasing hormone agonists with add-back hormone therapy, gabapentin, TCAs, SNRIs, NSAIDS, neuroablative techniques, botox

- Pelvic floor physiotherapy

- Up to 10% of hysterectomies are performed for CPP, up to 40% of patients will have recurrent pelvic pain (Stein.2013)

- Psychological: Education, biofeedback, Behaviour therapy, CBT
Chronic Pain in Pregnancy

- Most women will experience some pain in pregnancy
- Pre-existing condition e.g. fibromyalgia, low back pain, headache
- Direct consequences of pregnancy: weight gain, postural changes, pelvic floor dysfunction, hormonal factors, fluid retention, joint laxity
- New onset pain- must exclude obstetrics cause e.g. APH, miscarriage as well as medical or surgical cause e.g. appendicitis, kidney stones
- Women are at risk of under treatment of pain in pregnancy because of concerns of using drugs in pregnancy
- Few analgesic drugs are absolutely contraindicated in pregnancy but studies in pregnant women are not available for most pain medications
The use of analgesics in early pregnancy is associated with no or low risks for the embryo but if possible synthetic opioids and NSAIDs should be avoided, if exposure has occurred there is no reason to consider interruption of pregnancy.

Continued use of analgesics may increase the risk of preeclampsia and preterm birth, especially opioids.

NSAID or high doses of acetylsalicylic acid should not be used during late pregnancy to avoid excessive bleeding and premature closure of ductus arteriosus.

Use of opioids towards the end of pregnancy can cause neonatal symptoms (NAS) and long–lasting effects on child development can possibly occur.

Acetaminophen is acceptable throughout pregnancy.

Triptans can be used for migraine in pregnancy, sumatriptan is preferable, ergots should be avoided.
Chronic Pain in Pregnancy
Gabapentin & Pregabalin

- Few studies

- Fujii: Prospective study 223 women on gabapentin vs 223 unexposed pregnancies, 43% sample using for pain (Fujii. Neurology. 2013.)

- Gabapentin group higher rates of preterm birth, low birth weight and admission to neonatal intensive care but no differences in malformations

- Winterfeld: prospective study, 164 pregabalin exposed pregnancies vs 656 controls (Winterfeld. Neurology. 2016.)

- Increased risk of birth defects in exposed group but also increased rates of smoking in the pregabalin group, pregabalin exposed pregnancies that resulted in malformations were exposed to more medications and had more complicated medical conditions than the comparison group
TCAs and SNRIs:

- Modest increased risk of:
  - Spontaneous abortion
  - Preterm birth
  - Low birth weight

- Conflicting evidence for small absolute increased risk of PPH with 3rd trimester exposure

- Poor neonatal adaption syndrome with 3rd trimester exposure

- No confirmed risk of birth defects (Chisolm. BMJ. 2016.)
Consequences of Untreated Chronic Pain

- Sleep
- Cognition - memory, attention
- Mood, anxiety, suicide
- Cardiovascular health - hypertension, morbidity
- Sexual function
- Quality of life and functionality

(Fine. Pain Medicine. 2011.)
Chronic Pain in Pregnancy

- Risk benefit decision
- Involve the parents in decision making
- Use lowest effective dose
- Use agents with the lowest risk to the mother and fetus
- Be prepared to adjust doses as pregnancy advances
- Ensure adequate fetal screening
- Refer to specialist services
- Monitor neonate for withdrawal
Summary

- There are sex and gender differences in the experience, expression and prevalence of pain.
- Psychological and social variables powerfully influence the experience and expression of pain.
- More research is needed on sex and gender differences in pain experience and management.
- As in all chronic pain patients, women with chronic pain need a biopsychosocial approach to assessment and management.
- Chronic pain must be managed in pregnancy giving consideration to the risks of prescribing medications versus the risks of untreated pain.
Selected References


