Differences in Pain between Women and Men

Sex differences in pain: the evidence
- Women generally report experiencing more recurrent pain, more severe pain and longer lasting pain than men
- Evidence for sex differences in pain is wide ranging, and includes basic science, epidemiology and clinical research
- For example, experimental studies show that women have lower pain thresholds and tolerance to a range of pain stimuli when compared to men

Prevalence of painful conditions in men and women
- There are sex differences in the prevalence rates for some painful conditions
- There are more painful conditions where there is greater female prevalence than male prevalence
- Examples of painful conditions where there is greater female prevalence include fibromyalgia, irritable bowel syndrome, temporomandibular disorder, rheumatoid arthritis and osteoarthritis, migraine headache with aura
- Examples of painful conditions where there is greater male prevalence include cluster headache, coronary heart disease, gout, ankylosing spondylitis, duodenal ulcer, pancreatic disease

Other factors impact on sex differences in pain experience
- Pain experiences vary considerably within the sexes as well
- Changes in sex hormones have been found to moderate pain (e.g., menstrual cycle, pregnancy)
- Sex differences in pain can vary across the lifespan. Many of the observed gender differences in pain prevalence (i.e. headache, abdominal and visceral pain) appear to reduce beyond the reproductive years.
- Sex differences in pain can vary across different cultures as well

Sex differences in pain treatment
- Sex differences in analgesia exist
- There are sex differences in the side effects associated with drugs, including analgesics
- Sex differences in non-pharmacological chronic pain treatments have also been found

Reasons why men and women differ in pain and analgesia
- Biological mechanisms include sex hormones, genetics, and anatomical differences. Some of these biological factors (i.e. gonadal hormones) become less apparent in the post-menopausal years.
- Psychosocial influences include emotion (e.g., anxiety, depression), coping strategies, gender roles, health behaviors and use of health care services

What needs to be done?
- Sex differences should be considered in the investigation of pain
- Raise awareness of the similarities and differences between the sexes when considering pain and analgesia
- Greater understanding of the different health needs of men and women

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Epidemiology of Pain in Women

Gender Differences in Rates of Common Pain Conditions in the General Population\(^1,2\)

- Age and sex-specific prevalence patterns differ for different pain conditions. However, prevalence rates of most common chronic pain conditions are higher among women than among men. For example, in population-based studies of adults, the female: male ratios for headache, neck, shoulder, knee and back pain average around 1.5:1; for orofacial pain conditions the ratios are about 2:1; for migraine headache the ratio is 2.5:1; and for fibromyalgia (a less prevalent but often disabling condition) the gender ratio is over 4:1.

- It is not yet clear whether we find higher rates of pain in women in prevalence surveys because women are more likely to get these conditions in the first place (i.e., higher incidence rates) or if the conditions have a longer duration in women.

- Women are more likely than men to experience multiple pains simultaneously. Having multiple pain conditions is associated with higher levels of disability and psychological distress than having a single pain condition, and having multiple pains is a risk factor for onset of new pain conditions.

Sex and Gender-Related Risk Factors for Pain\(^3-5\)

- The female reproductive hormone estrogen clearly plays a role in some pain conditions (e.g., migraine headache, temporomandibular disorder pain). For other pain conditions, the evidence of hormonal involvement is less clear. However, rates of many common pain conditions increase for girls as they pass through puberty, whereas rates for adolescent boys are stable or rise less steeply than for girls.

- Men and women respond differently to various classes of opioid medications, suggesting that endogenous opioid system may differ in the two sexes, possibly influencing rates of pain.

- Women are more likely to experience depression than are men, and depression appears to be a risk factor for common pain conditions; similarly, women experience more physical conditions than do men, and the presence of such co-morbidities is hypothesized to be a risk factor for pain.

Epidemiology of Female-Specific Pain Conditions\(^6-9\)

- Dysmenorrhea (painful menstrual periods) is extremely common, affecting 40-90% of women. About 15% of women describe their menstrual pain as excruciating. The prevalence and severity of primary dysmenorrhea are highest in late adolescence and the young adult years.

- Chronic (non-menstrual) pelvic pain can be caused by gynecological conditions (e.g., endometriosis, infection) or non-gynecological conditions (including irritable bowel syndrome or bladder-related pain). A large US study found that the prevalence of chronic pelvic pain from all causes was approximately 15% among women of reproductive age.

- Vulvodynia is chronic pain in the vulvar area in the absence of known infectious, dermatological, metabolic, autoimmune or neoplastic causes. In one community study, pain in the vulvar region was reported by over 18% of women, with 12% reporting knife-like pain or pain on contact, and over 6% reporting persistent itching or burning sensations; however, it is not known the extent to which these conditions were attributable to the medical causes mentioned above.

- Approximately 45% of women experience pain in the lower back/pelvic girdle during pregnancy. One-quarter of all women have pain of sufficient severity to require medical attention. Post-partum, about 25% of women experience lower back/pelvic girdle pain, with about 5% of all women experiencing severe pain.

- Labor pain is almost universal, experienced in over 95% of labors.

Pain-Related Health Care Use and Disability\(^3,6\)

- Women are more likely to seek health care for pain than men are, resulting in a high proportion of women in many pain treatment settings. The higher rate of treatment seeking among women may be due to the fact that pain is often more severe for women than for men.

- It is unclear whether women or men are more likely to experience employment disability associated with pain conditions; numerous factors such as type of work and family responsibilities influence employment disability rates. However, when disability is defined in terms of limitations in activities of daily living as well as work absence, women have higher rates of pain-related disability.

- Although rates vary across populations, a median of about 20% of girls report missing school days due to dysmenorrhea.

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Sex Differences in Pain – Basic Science Findings

Why is it important to study sex differences in laboratory animals (rats and mice)?
1. Using laboratory animals allows much more powerful experimental techniques to be brought to bear on the problem (e.g., genetic manipulation, electrophysiological recording, experimental drug administration), leading to discovery of underlying mechanisms.
2. Non-human animals are unlikely to have gender-related stereotyped roles, and thus differences seen would likely be “biological” rather than “sociocultural” in origin.

Are laboratory animals of both sexes commonly studied?
NO. A recent survey of papers published in Pain revealed that 79% of all studies employed male subjects only, 8% female subjects only, and only 4% explicitly designed to test for sex differences should they be there. Note that this is in contrast to the situation in humans, where both sexes are now commonly studied.

What findings in this field have achieved consensus?
1. Male rodents are usually more sensitive than females to opioid-mediated analgesia, both from opiate drugs and endogenous release (i.e., stress-induced analgesia); these effects are bigger when using lower-efficacy opiates (e.g., morphine).
2. Steroid hormones clearly and often robustly affect pain sensitivity in rodents (estrogen, progesterone, and testosterone), although the direction of effect is variable.
3. Sex differences in pain/analgesia are likely to be found within the descending pain modulatory pathway (periaqueductal gray→rostroventral medulla→spinal cord).
4. There appears to be sex-specific analgesic mechanisms, involving at least partially divergent genetic and neurochemical factors. These may relate to the phenomenon of pregnancy-induced analgesia.
5. Sex differences interact importantly with genetic background.

What findings are still controversial?
1. Whether male and female rodents differ significantly in their sensitivity to noxious stimuli. The answer appears to depend importantly on the test used and the genetic background of the tested population.
2. Whether pain/analgesic sensitivity differs across the estrous cycle (the rodent equivalent of menstrual cycle). Any number of studies have reported such differences, but the directions of effect are contradictory.

What genes/proteins have been implicated in sex differences in pain/analgesia?
1. Estrogen Receptor
2. Mu- / Kappa- / Delta-Opioid (MOR, KOR, DOR) Receptors
3. GABA-A Receptors
4. N-methyl-D-aspartate (NMDA) Receptor
5. Melanocortin-1 Receptor (MC1R)
6. Orphanin FQ/Nociceptin (OFQ/N) Receptor
7. Protein Kinase A/C
8. G-protein-coupled Inwardly Rectifying Potassium Channel (GIRK2)
9. Acid-Sensing Ion Channel (ASIC)
10. Alpha2-Adrenergic Receptor

What exciting new developments have occurred recently?
1. Interaction of sex and social context in mice.
2. Sex differences might be produced directly by sex chromosome (X&Y) genes, rather than by gonadal hormones.
3. There are sex differences in itch as well as pain.
4. Sex differences in pain/analgesia are already present on the day of birth.
5. There are sex differences in morphine tolerance and dependence.
6. There are sex differences in mechanisms of inflammation.
What differences are there between sex differences in rodents versus humans?

1. It is not clear that opioids are more effective in men compared to women. There are reports supporting both points of view. The animal literature, by contrast, strongly supports greater opioid efficacy in males.

2. Differences between women and different species of rodents in timing and hormonal variations during their fetal development, their puberty, their ovarian cycle and their progression through reproductive senescence are important considerations in translating research findings between female rodents and women.

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**Sex Hormones and Pain**

- Pain, and in particular chronic pain, shows important sex differences. There could be several reasons for the higher reactivity of females than males to a similar painful stimulation, from genes to hormonal and cultural influences. The difference between the two sexes is multifaceted, involving the occurrence of chronic pain, the kind of pain syndromes experienced, the characteristics of the complications that develop, etc.
- Pain perception varies according to the menstrual cycle phases in women with chronic pain (1). For example, temporomandibular pain is highest in the pre-menstrual period and during menses (2).
- Androgens and estrogens are vital for the proper development and maintenance of the male and female reproductive systems. They also play an important physiological role in the activity and well-being of males and females.

**Estrogens are able to affect nociception and pain**

Estrogen administration in women and in men can increase the incidence of chronic pain conditions (3, 4). These effects can be due to actions induced at peripheral as well as central levels. For instance estrogens:

1. Increase nerve growth factor (NGF) in the dorsal root ganglia (5),
2. Induce c-Fos expression (one of the first signs of neuronal plasticity) in the hippocampus (6),
3. Activate MAP-kinase (a growth factor) by a mechanism that appears not to use estrogen receptors (7),
4. Increase the numbers of dendrite spines and excitatory synapses in hippocampal neurons (8),
5. Rapidly excite neurons in the cerebral cortex, cerebellum and hippocampus by a non-genomic mechanism (9),
6. Potentiate glutamate binding to N-methyl-D-aspartate (NMDA) receptors (8, 10),
7. Increase postsynaptic potentials in the hippocampus by increasing currents mediated by kainate receptors (9).

All these effects can increase nociception and pain.

In addition to their hyperalgesic role, estrogens also seem to play an important role in inducing anti-nociception. For instance, simulation of pregnancy in ovariectomized rats, with high plasma levels of estrogens and progesterone, results in an increased pain threshold (11). These analgesic effects can be related to the fact that estrogens regulate the transcriptional control of opioid synthesis and of delta and kappa-opioid receptors in lamina II of the spinal cord (12). Administration of estrogen in women increases pain-induced mu-opioid receptor binding in the brain, suggesting that exogenous estrogen enhances functioning of the endogenous opioid system (13).

**Androgens are able to affect nociception and pain**

An inverse relationship was found between plasma testosterone and work-related neck and shoulder disorders in female workers (14). Low-dose transdermal testosterone therapy was found to improve angina threshold in men with chronic stable angina (15). In male rats, testosterone has a protective role in adjuvant-induced arthritis (16) and testosterone, administered to both male and female rats, change formalin-induced responses (17, 18) and analgesia (19).
Gender and the Brain in Pain

Several reviews have demonstrated that women respond to noxious and potentially noxious stimuli with greater pain experience than men (1, 2). In particular, women tend to have reduced pain threshold compared to men - women respond with pain to lower intensity stimuli than men. In addition, there are numerous pain conditions that show a bias towards women: Berkley listed 38 clinical pain disorders as having a female prevalence but only 15 having a male prevalence and 24 having no sex prevalence. It is tempting, therefore, to suggest that women have a biological profile that predisposes them to experience pain at lower stimulus intensities and thus also suffer a disproportionate amount of clinical pain.

This general hypothesis is supported by animal studies that have shown, for example, greater opioid mediated stress induced analgesia in male rats compared with female rats (3, 4). Stress induced analgesia may be suppressed by estrogen raising the possibility that hormonal differences between men and women contribute to differences in pain perception (5). In contrast, more recent evidence, using positron emission tomography to directly assess opioid binding in vivo, has demonstrated greater opioid receptor availability and activation of endogenous opioid activation during delivery of a noxious stimulus in a high versus low estrogen state (6). The different role of various opioid mediated mechanisms under various conditions remains open for investigation.

Advances in brain imaging technology mean that further brain differences between genders can be directly assessed in human populations. There are, for example, gender related structural differences including the size and morphology of the corpus callosum, preoptic hypothalamic area, planum temporale, the percent of gray matter in the human brain, and the density of neurons. Furthermore, it is well established that men and women have different spatial and verbal skills and these differences correlate with gender differences in brain function (7). The observed behavioral and clinical differences in pain response might also relate to structural and functional differences between men and women.

In 1998, Paulson et al demonstrated greater responses in the anterior insula and thalamus in female subjects and showed prefrontal activation in the right hemisphere in the male subjects and in the left hemisphere in the female subjects using noxious heat (8). In 2002, Derbyshire reported greater activation of the perigenual and ventral cingulate cortex in the female subjects and greater activation of the parietal, secondary sensory, prefrontal and insula cortices in the male subjects using noxious laser stimuli (9). Also in 2002, Berman et al reported greater insula activity in male subjects receiving an aversive rectal distension, opposite to the greater female insula activity seen in an earlier rectal distension study by Kern et al (2001). More recently, Moulton et al (2006) demonstrated reduced activation in primary sensory, anterior cingulate and prefrontal cortices during noxious heat in females compared to males – a result that differs both from Derbyshire et al (2002) and Paulson et al (1998). These brain imaging findings are intriguing but the considerable variation across studies remains open to interpretation. Variations in activity pattern provide good reason to be cautious before speculating too far regarding the influence of gender on brain imaging differences during delivery of noxious stimuli.

One possible reason for the variability is the fact that pain is complex and a myriad of factors might influence findings in relatively small samples. Criterion effects, differences in body size, skin thickness, or systolic blood pressure, social expectations, cognitive variation, method of stimulation, and differences in psychological traits such as anxiety and depression have all been suggested to account for observed gender differences in pain response. Biological fluctuation because of the menstrual cycle has also recently begun to receive greater attention.

Brain imaging studies on the issue are escalating, with the exciting potential for cutting through these potential sources of variation to provide a clearer understanding of the mechanisms underlying pain in general, as well as how sex and gender factors contribute to these variations.

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Pain During Pregnancy

Pain within the pregnant population is a neglected condition of substantial public health impact (1). Acute and chronic pain syndromes in pregnant women are difficult to manage, not least because there is a need to balance the best interests of the mother and the neonate.

When pain is poorly controlled there can be adverse psychological effects (2), which may cause antenatal, as well as postnatal, depression. Many cases of post-partum depression begin before delivery (3).

Poorly controlled pain may increase the mother's risk of prolonged time in bed resulting in immobility. This can lead to problems such as deep vein thrombosis and pulmonary embolism. The longer women and babies are in hospital, their risk of getting hospital-acquired infections increases (4).

Severe uncontrolled maternal pain may result in a premature fetal delivery; either precipitated spontaneously or induced medically (5). Early delivery of the baby (less than 36 weeks) requires admission to neonatal intensive care, which is one of the most expensive admissions to a public hospital (6). Separation at birth makes this an emotional and stressful time for both the mother and the baby and may increase maternal and neonatal morbidity.

Epidemiology
Pain is common in pregnancy. Approximately 25-56% of pregnant women suffer some lumbopelvic or peripartum pelvic pain. Approximately 8% of these pregnant women become severely disabled with this condition, which may require admission into hospital (7). In one third of pregnant women, pain is a severe problem compromising normal everyday life, work and sleep (7, 8, 9, 10, 11).

There is a lack of any standard definitions. Terms used include: pregnancy related pelvic girdle pain and pregnancy related low back pain. Symphysis pubis dysfunction is a term also used, but some consider that such dysfunction is more often a secondary problem coexisting with lumbar or sacroiliac pain.

In a study of 870 women referred to physical therapy for pain during pregnancy, over 76% of their women complained of pain over the sacroiliac joints and 57% complained of pubic symphysis pain (11). A correlation was found in those women with previous low back pain and pelvic pain, higher pre and end pregnancy weight/body mass index (BMI), increasing parity, a history of hypermobility and pain syndromes in pregnancy (8).

Proposed mechanisms
The main factors are probably mechanical, due to the alteration in posture required to carry the increasing mass in the abdomen, and hormonal, through changes in the pelvic ligaments. The hormone responsible is unclear. Although relaxin acts on human uterine tissue by regulating the expression of metalloproteinases in the matrix, it does not seem to generate musculoskeletal pain problems. Ultrasonography shows an association between the width of the symphysis pubis and pain at that site, irrespective of serum relaxin concentrations. Pregnancy may compromise the inherent stability of bones and ligaments in both the spine and the pelvis, requiring muscular activity to maintain stability of associated joints.

Other pain problems
Other categories of pain syndrome that resulted in hospital admissions for pregnant women were found in a retrospective audit (12). These included pain syndromes such as: nerve entrapment, thoracic pain, degenerating fibroid, post herpetic neuralgia, carpal tunnel syndrome and lumbar disc prolapse.
**Treatment**

Prevention of admission to hospital is the ultimate goal. Once pain has become such that it compromises a woman’s daily living activities, admission to hospital becomes necessary.

Goals of treatment would be firstly to use non-pharmacological techniques, as it is important to understand that the fetus is a passive recipient of any medications that may be administered.

Non-pharmacological techniques include education, advice and exercise prescribed by a physiotherapist. In addition transcutaneous electrical nerve stimulation (TENS), heat or cold packs, local infiltration with local anaesthetic and steroid and physiotherapy can be used with good success (5, 13, 14).

Stabilizing exercises, stretching exercises of specific muscles and massage can all contribute to the reduction of pain in pregnancy by breaking the cycle of pain due to poor posture, increasing lordosis, muscle spasm and increasing immobility (5, 9, 13, 15, 16). The use of aids such as crutches, walking frames, supportive pillows with positioning while sitting and lying, pelvic belts and the use of sacroiliac support belts can increase mobilization and reduce the risks associated with prolonged bed rest and inactivity such as clot formation and muscular deconditioning (16, 17).

Two systematic reviews should also guide practice for pregnant women with non-specific pain in the pelvis or lower back. A Cochrane review found water gymnastics, acupuncture and use of a specifically shaped pillow for sleeping to be beneficial (9). The second systematic review could not extend the conclusions of the Cochrane review because of the heterogeneity of the trials. There does appear to be evidence that individualised physiotherapy and acupuncture treatment provides some relief for these problems (15). Some concern has been expressed about the use of acupuncture and subsequent miscarriage. However, a literature review has failed to identify that such a link exists (18, 19).

The addition of psychological therapies such as self-hypnosis and counseling may be beneficial.

The efficacy of analgesics has not yet been established fully (20, 21) and one of the major times of concern for the use of medications in pregnancy is during the vulnerable period of organogenesis, (weeks 4 – 10). It is important to restrict the use of medications to those that have evidence of safety in order to minimise harm to the developing fetus (22). Medications, such as paracetamol and codeine are safe in pregnancy, although NSAIDs should be avoided. Ensuring there is multidisciplinary team support and involvement is vital to the success of treatment (5, 13).

Obstetric Pain

What is obstetric pain?
Pain related to childbirth may present during pregnancy, during labor when more than 95% of women report pain, occasionally during Caesarean section (CS) if there is a poor quality nerve block or prolonged surgery and after delivery when more than 70% of mothers report acute or chronic pain.

Labor pain as a model of acute pain
The pain of labor has been described as a clinical tool, or model, for studying acute pain (1). The majority of women report pain during labor but pain intensity is of variable severity. Major determinants of pain intensity are:

- Parity
  For example, when pain intensity during labor was measured using a unidimensional score (i.e. mild, moderate and severe), 60% of nulliparous and 45% of multiparous women described pain as severe.
- Back pain in pregnancy
- Antenatal preparation
- Upright posture during labor

When pain severity in labor was compared with that measured during other pain conditions using the multidimensional McGill Pain Questionnaire score (MPQ) (1), the highest score was recorded from nulliparous women during labor followed by (in ranked order):

- Labor pain in nulliparous women who had antenatal classes to prepare for labor pain
- Labor pain in multiparous women
- Chronic back pain
- Cancer pain
- Toothache
- Pain from a fracture

Pain after delivery
Abdominal pain is a frequent symptom in women after vaginal delivery (2). A pain intensity of ‘moderate’ and ‘severe’ is twice as frequent in multiparous (58%) than nulliparous (30%) women. It is exacerbated by breast feeding in most women (96% nulliparous and 81% multiparous). However, pain relief is obtained from standard therapies in only half of these women. The abdominal pain has a temporal relation with uterine contractions and significantly increases in severity with parity and with the duration of the uterine contraction (3). These studies have thus identified women who experience pain at a time where adequate analgesia is lacking.

Psychosocial influences
Childbirth elicits a wide range of emotions, expectations and experiences (4), suggesting that psychosocial factors play an important role. For example, one contributing factor to the increase in CS rates is thought to be mother’s fear of childbirth (5). Fear and anxiety are significant influences on pain experiences, which is one reason why mother’s are accompanied by a ‘significant’ other person during childbirth. Psychosocial factors are also important during CS. For example, one study in the context of elective CS found that mother’s fears were maximal at time of her nerve block, and that psychosocial factors, including negative expectations, perceived lack of control over analgesics, fear during CS and her partner’s fear, predicted postnatal pain intensity (6). Obstetric pain is therefore not only related to the physical process of childbirth but also to psychosocial factors that are operating at the time.

The evidence basis for pain management during labor
The COCHRANE evidence based reports have researched factors that may influence pain in labor:

(a) Continuous support from a partner or caregiver can reduce the frequency of use of epidural analgesia and the amount of other analgesia administered to a mother (7)
(b) Water immersion during labor reduces pain intensity and analgesic use (8)
(c) Complementary and alternative therapies such as self-hypnosis and acupuncture decrease the amount of pain relief required during labor (9).

(d) Epidural analgesia compared with no epidural analgesia or no pain relief provides better pain relief and maternal satisfaction with no increased risk for CS, fetal depression or long term backache. The studies reported do not include the low dose drug mixtures used in practice today so the findings of an increased instrumental delivery are yet to be confirmed (10).

(e) Adoption of the upright position in the second stage of labor can reduce the amount of severe pain experienced (11).

(f) Combined spinal epidural analgesia when used in labor induces pain relief about 5 minutes faster than epidural analgesia but it causes more pruritis (12).

(g) Opioids given intramuscularly for pain relief during labor have not been found to be effective (13).

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Dysmenorrhea: Contemporary Perspectives

Classification/definition:
- Dysmenorrhea (painful periods) is traditionally classified as either primary dysmenorrhea – menstrual pain without pelvic pathology, with onset shortly after menarche, or secondary dysmenorrhea - pain associated with secondary pathology, and the onset may be years after menarche.
- Premenstrual syndrome (PMS) is defined as cyclical mood and behavioral changes occurring during 5 days prior to menses
- Premenstrual dysphoric disorder (PMDD) is the presence of severe affective symptoms during the luteal phase of the menstrual cycle, which may encompass depression, anxiety, concentration difficulties, appetite changes, and sleep changes that interfere with functioning in work, family, and social settings.

Epidemiology:
- Dysmenorrhea affects 40-90% of women.
- Primary dysmenorrhea is most common between the ages of 15-19 years, declining thereafter.
- 5-14% of women have regular school absenteeism as a result of symptoms.
- 13-51% of women have been absent at least once in their lives from school or work due to dysmenorrhea.
- Many cultures, such as some Mediterranean, Muslim, Hindu, and Chinese, still perceive menstruation as taboo and impure, resulting in reluctance of pain report and failure of health care delivery.

Associated risk factors:
- A low BMI is associated with increased risk of primary dysmenorrhea.
- A negative association has been described between consumption of fruit, eggs, and fish and primary dysmenorrhea, perhaps related to intake of omega-3 fatty acids, calcium, and magnesium.
- Psychosocial determinants are also important, as poor mental health, somatoform symptoms, decreased coping ability, depression, and anxiety have been found to be strong determinants of dysmenorrhea.
- Primary dysmenorrhea often co-occurs with nausea and vomiting, diarrhea, tiredness, and feelings of irritability.
  - Many idiopathic pain disorders (IBS, IC/PBS, vulvodynia, dyspareunia, temporomandibular disorder, and migraines) are frequently co-morbid with primary dysmenorrhea,
- Secondary dysmenorrhea presents in association with endometriosis, presence of an IUD, pelvic inflammatory disease, adenomyosis, uterine myomas and adhesions, or cervical obstruction from mullerian anomalies.
- Smoking has been associated with an increased risk of dysmenorrhea, but alcohol is not consistently linked to dysmenorrhea risk.

Presentation:
- Primary dysmenorrhea pain precedes the onset of a menstrual period and typically lasts 2-3 days.
- Secondary dysmenorrhea pain may start 1-2 weeks before menstrual flow and persist beyond the cessation of bleeding.
- The classic labor-like, suprapubic, colicky pain of dysmenorrhea may radiate to the lumbosacral region or anterior thigh.
- Associated visceral symptoms include nausea, vomiting, or diarrhea.
- On examination, prominent uterine tenderness is found during menstruation, which may also extend outside of menses in secondary dysmenorrhea.

Pathophysiology:
- The exact etiology is unclear, but may reflect upregulated cyclooxygenase (COX) enzyme activity and prostanoid synthase activity, which are normally activated in the late luteal phase through release of progesterone inhibition of arachidonic acid production.
- Endometrial prostaglandin production results in increased uterine contractions and relative myometrial ischemia.
- Abnormal uterine contraction patterns and alterations in uterine blood flow are also noted in some dysmenorrhea sufferers.
• Somatization and poor coping are also positively associated with menstrual pain intensity, suggesting that central factors should also be considered.

**Treatments:**
• Conservative measures such as non-steroidal anti-inflammatories (NSAIDs) are used as first-line therapy, ideally initiated prior to the onset of menses by 48 hours to decrease COX substrate.
  o A usual trial of 3-6 months of therapy is conducted before additional evaluation for causes of secondary dysmenorrhea.
• Vitamin and mineral supplementation (i.e. fish oil, thiamine, magnesium, or pyridoxine) may also be effective based on small studies.
• Local nerve stimulation (TENS, hot compresses, acupuncture) has also been shown to be effective in small studies.
• If NSAIDs fail, combined oral contraceptives are often employed to inhibit ovulation and suppress endometrial growth. By maintaining an endocrine state of the early proliferative phase, this approach also decreases prostaglandin levels.
• Continuous progestins (oral, intramuscular or via intrauterine device) may be needed to induce anovulation in recalcitrant cases.
  o While androgen derivatives (danocrine) also induce anovulation, their severe virilizing side effects make them less attractive.
• In more severe cases, short-courses of opioids should be considered for managing breakthrough pain.
• Exirpative surgery (laparoscopic excision of endometriotic lesions, or leiomyoma) should be reserved only if the above fail, while nerve destructive procedures should be used only cautiously.
  o While randomized controlled trials demonstrate that presacral neurectomy is an effective treatment for dysmenorrhea, this procedure does have a risk for causing permanent visceral side effects.

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Chronic Pelvic Pain

Chronic pelvic pain (CPP) is a common, debilitating and complex condition whose etiology remains poorly understood. It can be associated with significant morbidity and loss of physical and sexual functioning.

Patients are distressed by their continuing symptoms, by extensive and repeated investigations and often by the inability of the medical profession to diagnose and treat them effectively. Many patients describe frustration at their inability to get their pain taken seriously or by suggestions that the pain may be due to psychological causes.

Mechanisms and causes of pelvic pain

Chronic pelvic pain can be caused by gynecological conditions, such as endometriosis, adhesions, infection or rarely by tumor, and by non-gynecological causes which can be bowel-related, such as irritable bowel syndrome (IBS), or bladder-related, or musculoskeletal or neuropathic. Often the cause is obscure.

Multiple pelvic organs can be involved. For example, 30-50% women with pelvic pain have urinary frequency. IBS commonly co-exists with pelvic pain.

Three types of visceral hyperalgesia which may be relevant to the clinical presentation of patients with pelvic pain are described (1):

1) Visceral hyperalgesia: hyperalgesia of a viscus from inflammation and / or excess stimulation of the same viscerae.g. irritable bowel syndrome
2) Referred hyperalgesia from viscera: hyperalgesia of somatic tissues in the area of referred pain from viscera, e.g. trigger points in body wall tissues
3) Viscero-visceral hyperalgesia: hyperalgesia of a viscus rendered clinically manifest by a painful condition of another viscerae.g. exacerbation of urinary colic pain in patients with urinary calculus plus dysmenorrhea.

Epidemiology

- The prevalence of CPP in the community is high.
- In the USA, a 3-month period prevalence (excluding mid-cycle pain) of 15% was found in women aged 18-50 (2).
- In the UK, the annual prevalence in primary care was 38 / 1000, a rate similar to that reported for asthma or back pain (3).
- A prevalence of 25.4% was reported in New Zealand (4).
- Women complaining of chronic pelvic pain symptoms contribute to 15-20% of all consultations in the general gynecological clinic and up to 10% of all female attendances in general practice.
- Chronic pelvic pain is the indication for 10-15% of hysterectomies performed in the United States.
- Women with chronic pelvic pain were found to have undergone almost five times more surgeries and to have sought treatment for four times as many somatic conditions unrelated to chronic pelvic pain as compared with pain-free age-matched controls.

Evaluation of women with pelvic pain

- Consultation: Assessment of women with chronic pelvic pain requires a systematic and comprehensive approach. The assessment is a prime opportunity to establish rapport with the patient and initiates the concept that the clinician and the patient are working together to manage symptoms.
- Examination: General observation of the patient, especially of their posture, is important. Scars can be a source of pain. Abdominal wall trigger points can be identified by palpation. Vaginal examination gives the opportunity to assess the gynecological organs and the tone of the pelvic floor musculature.
- Investigation: Trans-vaginal ultrasound scanning, laparoscopy and MRI scanning are the commonest investigations performed. More than 40% of laparoscopies are performed for the diagnosis of chronic pelvic pain. This investigation is not without risk and is expensive.

Psychological factors:

Psychological factors may both contribute to the experience and consequences of pelvic pain. One of the challenges is for the patient to agree that psychological factors may be important in understanding her pain condition and its management.
A therapeutic relationship should be created in which the patient feels heard and understood and is able to ask questions about any concerns and beliefs that she may have.

Women with CPP may have high levels of anxiety and depression and fear serious undiagnosed disease. Sexual dysfunction and relationship distress can result. Specific interventions such as Kegel’s exercises, use of graded dilators, advice on lubrication, advice on intercourse positions and sensate focus exercises can be useful.

A number of controlled studies have shown that women with chronic pelvic pain have a higher incidence of previous sexual and physical abuse (5). Questions should be asked about any previous unwanted or unpleasant sexual experiences in a supportive and open environment. If a history of sexual or physical abuse is affecting current functioning, psychotherapy may be appropriate.

**Treatment**

Treatment has traditionally focused on identifying pathology and utilizing medical, hormonal and surgical interventions to alleviate the pain. Hormonal therapy and surgery can help some patients with pelvic pain, adenomyosis and endometriosis, but unfortunately not all. Core stability exercises and pelvic floor musculature rehabilitation can be beneficial. Drugs used for neuropathic pain have been shown to reduce pelvic pain in a small group of patients unresponsive to weak opioids (6).

As medical understanding of the complexity of CPP has advanced to incorporate the psychosocial aspects of pain, the consensus has shifted to employing a multidisciplinary approach to management acknowledging that pain involves complex interactions between psychological, neurological and physiological mechanisms (7).

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Endometriosis and its Association with Other Painful Conditions

Endometriosis occurs in up to 10% of women of childbearing age (1).

Endometriosis is defined by the abnormal presence of endometrial tissue (tissue with characteristics of the inner lining of the uterus) outside the uterus, usually in the abdominal/pelvic cavity (1). These abnormal tissues are referred to as “ectopic growths,” or sometimes “implants” or “cysts.”

Symptoms associated with this condition include subfertility and pelvic pains (1). The most common of the pains is dysmenorrhea, which is severe pain associated with menstruation (1, 2). Other pains include dyspareunia (pain with coitus or insertion of tampons; i.e., hypersensitivity of the vagina), dyschezia (bowel pain), and chronic pelvic pain (pain generally internally or in muscles of the abdomen, pelvic area and lower back) (1, 2).

For about 20% of women with this disorder, it co-occurs with other chronic pain conditions, such as irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, vulvodynia, temporomandibular joint disorder, migraine, fibromyalgia, and/or with autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, chronic fatigue syndrome, Sjögren’s syndrome (1,6).

Endometriosis is a puzzling disorder due to the uncertain relationship between the defining signs of the condition (ectopic growths) and the varied symptoms (2). Some women have no or minor symptoms, yet when their internal pelvic or abdominal cavity is examined for other reasons, extensive signs are obvious. Other women have very few signs but extremely distressing and painful conditions.

It is poorly understood how the signs (growths) and symptoms (subfertility, pains, co-occurrence with other disorders) develop and become related to each other. What is generally agreed by most clinicians and scientists is that the ectopic growths develop in susceptible women due to “retrograde menstrual flow,” which is when menstrual tissue is pushed backwards through the fallopian tubes into the abdominal/pelvic cavity and then implants and grows there (1). These ectopic growths can then behave in a manner similar to the uterus, shedding their tissues and inflammatory molecules into the abdominal/pelvic cavity. It is also agreed that endometriosis is dependent on estrogens because its signs and symptoms disappear with menopause or removal of the ovaries (1). Recent studies have also shown that the active ectopic growths develop their own blood supply and nerve supply (2). It is possible that the variable relationship between the ectopic growths and symptoms may be due in part to variations in this nerve supply (2).

Treatments for endometriosis are of three main types (1): (a) over-the-counter analgesics, (b) hormonal treatments that stop ovulation in order to reduce levels of estrogens, and (c) surgery (removal of ectopic growths, the uterus, or sometimes cutting certain nerves that supply the pelvic cavity). In some women, complementary/alternative treatments have been useful additions (6). One new possibility, now under study in animal models, are drugs that reduce the blood supply of the ectopic growths (4).

None of these treatments is completely satisfactory or effective (3, 5, 7). Hormonal treatments and removal of the uterus can have unpleasant side-effects and, obviously, prevent conception. Surgery is at best successful 50% of the time, can have unpleasant side-effects, and sometimes symptoms can return (3).

Nevertheless, one can remain optimistic, because considerable basic and clinical research is underway to develop a better understanding of the signs and symptoms and to develop more effective approaches for their treatment (see the following websites: http://www.endometriosisassn.org/; http://www.nlm.nih.gov/medlineplus/endometriosis.html; http://www.endometriosis.org/).

Vulvodynia

What is vulvodynia?
Vulvodynia is a chronic pain syndrome of the vulvar area in the absence of an infectious, dermatological, metabolic, autoimmune or neoplastic process.

Vulvodynia has long been recognized as a common clinical problem and chronic pain of the vulva was already described in American and European gynecological textbooks more than 100 years ago. In 1976 the International Society for the Study of Vulvovaginal Disease (ISSVD) identified idiopathic vulvar pain as a unique entity and subsequently coined the term vulvodynia (1).

In a broader view vulvodynia can be grouped with the chronic non-malignant syndromes of urogenital origin occurring in both men and women (2). These pain syndromes include in addition to vulvodynia: urethral syndrome, coccygodynia, generalized perineal pain, orchialgia, prostatodynia (chronic pelvic pain syndrome in men), chronic penile pain and interstitial cystitis.

What are the symptoms?
Women, who suffer from vulvodynia, typically complain about a hot, burning and stinging sensation and/or a feeling of rawness in the vulvar area. The pain might be localized to a very specific area of the perineum (and the patients can typically identify exactly the painful “spots”), such as the vulvar vestibule, labia or clitoris or it might be affecting the whole perineal area.

These two subtypes of vulvodynia have been termed “localized” and “generalized” vulvodynia.

Vulvar Vestibulitis, one of the subtypes of vulvodynia, refers to localized pain at the vulvar vestibule, the area around the vaginal opening. Women with vulvar vestibulitis typically experience pain when pressure is applied to the vulvar vestibule during sexual intercourse, tampon insertion or a gynecological examination. Clinically two different groups of patients with vulvar vestibulitis have been described: Primary vulvar vestibulitis is defined as dyspareunia from the first attempt of sexual intercourse, whereas in secondary vulvar vestibulitis, the dyspareunia appears after a period of pain-free sexual intercourse.

In women with generalized vulvodynia, the perineal pain is exacerbated by prolonged sitting, and by activities such as bicycle riding and horseback riding.

Who suffers from vulvodynia?
Vulvodynia affects women of all age groups. The incident of symptom onset is highest between the ages 18 and 25 and lowest after age 35 (3). Community studies suggest that vulvar pain is common, and prevalence rates as high as 18% have been reported (4). Vulvar vestibulitis has been described in up to 15% of gynecological outpatients (5). While initial reports postulated that vulvodynia affects primarily Caucasian women, a recent survey of ethnically diverse women showed similar life-time prevalence of chronic vulvar burning pain or pain on contact (3).

How is the diagnosis of vulvodynia made?
Vulvodynia is a diagnosis of exclusion. The differential diagnosis is wide and can include vulvar candidiasis, herpetic infections, lichen planus, Paget's disease, squamous cell carcinoma, postherpetic neuralgia or spinal nerve compression. Thus, a thorough gynecological evaluation, and in selected cases also a neurological and dermatological assessment are necessary.

What causes vulvodynia?
The etiology of vulvodynia is multi-factorial. There is experimental evidence from several psychophysical studies indicating that the pain sensitivity to mechanical and thermal stimuli in the vulvar area is altered in women with vulvodynia (6, 7). In addition to the peripheral sensitization demonstrated in the vulvar area, there is evidence of central sensitization. There is evidence of a possible genetic component in the etiology of vulvodynia (8). A neuromuscular etiology has been considered, resulting in tightness (spasms) of the pelvic floor. Vulvodynia has been shown to be associated with a history of physical and sexual abuse in a subgroup of women (9).
Diagnosis and Treatment:
Current research studies indicate that vulvodynia is a heterogeneous, multi-system and multi-factorial disorder. Therefore, a multidimensional and multidisciplinary treatment approach is recommended. Currently there is no cure for vulvodynia, although some patients experience spontaneous remission.

The first important step is to recognize that the patient is suffering from vulvodynia. Many women with chronic vulvar pain have remained undiagnosed and untreated, because the clinical presentation and treatment approaches are not widely known to health care professionals. A recent study in the USA demonstrated that 60% of women consult at least three doctors in seeking a medical diagnosis. Astoundingly, 40% of those who seek professional help remain undiagnosed after three medical consultations (3).

As a first measure in the treatment of vulvodynia is important to identify and eliminate local irritants and potential allergens. In patients with localized vulvodynia, where a small area is painful, topical treatment regimens might reduce the pain. Oral medications recommended for the treatment of neuropathic pain management have been considered. Surgical procedures have been advocated to remove the hyperalgesic skin area in patients with localized vulvodynia. Vaginal biofeedback and cognitive behavioral therapy have been reported to reduce the pain. As in many other pain conditions of multi-factorial origin, there is usually not one single treatment approach that consistently reduces pain in women with vulvodynia, but a combination of treatments (10).

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Irritable Bowel Syndrome (IBS)

Definition:
Irritable Bowel Syndrome is a chronic episodic medical condition characterized by abdominal pain or discomfort and altered bowel habits in the absence of detectable organic disease. It may present with diarrhea and/or constipation, thus it is often sub-grouped according to stool form: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), IBS-M (mixed diarrhea and constipation), and IBS-A (alternating diarrhea and constipation). It is part of the spectrum of Functional Gastrointestinal (GI) Disorders.

Epidemiology and Economics:
- IBS has worldwide prevalence rates of 9%-23% in the general population and accounts for up to 40% of diagnoses made by gastroenterologists
- It has a net female predominance, i.e., a female-to-male ratio up to 4:1 in clinic setting, with a female predominance also in greater symptom severity
- Its age distribution is unclear; some studies report a higher prevalence in the young and a decrease with age, others find no age influence
- IBS has a large impact on quality of life (QOL) with consequent high direct and indirect healthcare costs (up to 30 billion dollars in the USA).

Pathophysiology:
- The pathophysiology of IBS is still incompletely known, but is probably complex and multifactorial.
- One issue is whether pain is secondary to gut motility abnormalities or to disturbances in sensory processing (visceral hyperalgesia) or both.
- Multiple patterns of abnormal intestinal motility have been described in IBS, but no single motility disturbance is pathognomonic of the syndrome or has a predictable relationship with pain perception.
- In contrast, an increased sensitivity to painful stimuli at gut level is clearly a key feature of IBS, though the anatomic sites, physiologic derangements, cellular mediators and molecular mechanisms* are incompletely understood. It is still debated if the hyperalgesia is primarily arising in the central nervous system or is, at least at the beginning, triggered by a peripheral (infectious) factor [initial peripheral sensitization followed by central sensitization].
- The role of a genetic predisposition is controversial.

* among specific molecules possibly involved in pain pathogenesis of IBS, serotonin (5-HT) has received most attention as it is an important player in the normal peristaltic reflex of the gut and can also sensitize visceral nociceptors and facilitate transient receptor potential family V receptor 1 (TRPV1) function.

Diagnostic Criteria:
- IBS diagnosis is at present performed based on Rome III criteria *, i.e.:
  
  Recurrent abdominal pain or discomfort of at least 3 days/month in the last 3 months associated with 2 or more:
  - Improvement with defecation and
  - Onset associated with a change in frequency of stool and
  - Onset associated with a change of form (appearance of stool)

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

- Alarm symptoms (e.g., weight loss, fever, rectal bleeding, steatorrhea, lactose/gluten intolerance) suggest the possibility of structural disease, such as colon cancer, inflammatory bowel disease, malabsorption disorders (e.g., celiac sprue) but do not necessarily negate a diagnosis of IBS.
Clinical Features and Instrumental Findings:

- The onset of IBS is usually precipitated by disruption of gastrointestinal function secondary to infection, dietary factors, lifestyle changes or psychological stress [IBS patients report a higher prevalence of sexual, physical and emotional abuse compared to healthy individuals].
- The spontaneous pain is described as a cramping, aching abdominal sensation whose severity ranges from mild and intermittent to severe and continuous. It can be precipitated by meals and improved by defecation. In female patients it is influenced by the menstrual cycle, with an increase immediately before and during menses. The abdominal painful areas typically enlarge with the progression of the disease. Abdominal pain is also evoked by intestinal transit (e.g., postprandial colonic contractions, unnoticed by controls) and endoscopic procedures.
- Clinical symptoms associated with abdominal pain are: fatigue, muscle and joint pain, pelvic pain, headache, sleep and sexual disturbance, affective dysfunction, bladder urgency.
- A number of clinical conditions occur more frequently in IBS than in the general population (comorbidities):
  - Psychiatric Disorders (prevalence: 40%-90% in IBS patients)
  - Fibromyalgia Syndrome (prevalence: 31.6% in women with IBS)
  - Recurrent/Chronic Pelvic Pain (prevalence of dysmenorrhea: 50% in women with IBS)
  - Chronic Fatigue Syndrome, Interstitial Cystitis, Back Pain, Temporomandibular Joint Pain, Headache
- IBS patients have abnormal reactivity to noxious stimuli at both visceral\(^1\) and somatic\(^2\) level.
  1. Lower than normal pain thresholds to mechanical and electrical stimuli of the gut in the majority of cases [visceral hyperalgesia]
  2. In somatic abdominal areas of pain referral, lower than normal pain thresholds in skin, subcutis and muscle; In somatic areas outside sites of pain referral, lower than normal pain thresholds in subcutis and muscle; controversial results in skin, with normal, higher than normal or lower than normal pain thresholds (thermal, mechanical, electrical stimuli)
- Brain Neuroimaging. Observations from brain imaging in IBS suggest a compromised activation of pain inhibition circuits including those of the cortico-pontine circuit but increased activation of limbic and paralimbic circuits that may be related to pain facilitation.

Prognosis and Treatment:

- IBS typically lasts for the entire life of the patient, though a mild control of the symptoms can be achieved through treatment.
- Treatment is typically multimodal. It involves: dietary factors (careful analysis of potential food triggers); traditional pharmacologic therapy (including bulking agents, antispasmodics, tricyclic antidepressants and other psychotropic agents, and laxatives), serotoninergic agents [5-HT3 receptor antagonists, 5-HT4 receptor agonists, combination 5-HT4 agonist and 5-HT3 antagonist]; antidepressants; behavioral and psychological therapy.

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Fibromyalgia Syndrome (FMS)

Definition:
Fibromyalgia Syndrome is defined as a common rheumatologic syndrome characterized by chronic, diffuse musculoskeletal pain and tenderness with a number of associated symptoms among which sleep disturbance and affective dysfunction are particularly frequent.

Epidemiology and Economics:
- This syndrome affects 2% of the general population.
- It occurs in all ages, ethnic groups and cultures.
- Its gender distribution is nearly equal in childhood, but is up to sevenfold more common in females than males in adult age (50-60 years).
- FMS’s impact on an individual’s quality of life and physical function is substantial, comparable with that of rheumatoid arthritis (RA).
- Over 30% of FMS patients are forced to accept shorter work hours or less physically demanding work to maintain employment.
- In the USA about 15% of patients currently receive disability funding because of their symptoms.

Pathophysiology:
The pathophysiology of FMS is not completely clarified, a number of neuroendocrine\(^1\), neurotransmitter\(^2\) and neurosensory\(^3\) disturbances have been implicated in its generation. The exposure of a genetically predisposed individual\(^4\) to a variety of environmental stressors is supposed to lead to the development of FMS.
- **Neuroendocrine disturbance:** dysfunction of the hypothalamic-pituitary-adrenal axis, including blunted cortisol responses and lack of cortisol diurnal variation; abnormal growth hormone regulation.
- **Neurotransmitter disturbance:** decreased serotonin in the central nervous system, elevated levels of spinal fluid substance P and nerve growth factor, decreased dopamine transmission in the brain.
- **Neurosensory dysfunction:** central amplification of pain and/or reduced antinociception (central sensitization, abnormalities of descending inhibitory pain pathways).
- **Genetic predisposition:** strong familial aggregation for FMS. Mode of inheritance most probably polygenic.

Evidence for a role of polymorphisms of genes in the serotoninergic, dopaminergic and catecholaminergic systems in the etiology of FMS.

Diagnostic criteria:
The present criteria for FMS diagnosis are those established by the American College of Rheumatology Committee in 1990, i.e.:
1. A history of widespread pain (involving all 4 limbs and the trunk) of at least 3 months duration and
2. Tenderness to digital palpation (with a pressure of 4 kg) in at least 11 of 18 (9 symmetrical) pre-determined body districts called tender points (TePs)*

* A tender point is defined as a site of exquisite tenderness in soft tissues which, in contrast to the Trigger Point of Myofascial Pain Syndromes, is not included in a taut, palpable band of muscle fibers, does not evoke a local twitch response under snapping palpation and does not refer pain at a distance when stimulated.

A critical revision of the above criteria has been proposed by the International Pain Community. New criteria will probably be established in the forthcoming years.

Clinical features and Instrumental Findings:
- FMS has either a gradual or a post-traumatic onset (physical injury, psychological stress).
- The spontaneous pain in FMS is described as a persistent, diffuse, deep, aching, throbbing, sometimes stabbing sensation in muscles; it can be recurrent but is most often continuous with periodical exacerbations.
- Clinical symptoms associated with muscle pain in FMS are: affective dysfunction, cognitive deficits, short-term memory loss; throbbing occipital pain of muscle contraction headache; lightheadedness, dizziness, syncope; non-
restorative sleep or chronic insomnia, nocturnal myoclonus, nocturnal bruxism; daytime tiredness resembling physical fatigue, prolonged morning stiffness, numbness, tingling, dysesthesia in hands and feet; abdominal/pelvic pain, diarrhea, constipation; frequency, urgency, sterile dysuria.

- A number of clinical conditions occur more frequently in FMS than in the general population (co-morbidities):
  - depression [40% in FMS vs 10% in controls and 20% in people hospitalized for another medical condition]
  - anxiety [45% in FMS vs 21% in patients with other chronic pain conditions and 51% in patients with FMS plus other disorders]
  - irritable bowel syndrome (IBS) [up to 70% in FMS vs 20% in controls]
  - dysmenorrhea, interstitial cystitis (IC), other rheumatic conditions (rheumatoid arthritis, lupus erythematosus, Sjogren’s syndrome), chronic fatigue syndrome, myofascial pain syndrome, low back pain, temporomandibular joint disorder

- FMS patients have abnormal reactivity to painful stimuli. They are *hypersensitive to painful stimuli* applied to somatic structures not only in painful sites but also in normal control areas; they exhibit lower than normal pain thresholds to thermal, mechanical, electrical and chemical stimuli at skin, subcutis and/or muscle level. They also have a reduction in nociceptive flexion reflex threshold compared to controls. The pain threshold to repeated intramuscular electrical stimulation is significantly lower for patients with FMS compared to control groups, indicating that the temporal nociceptive summation is more pronounced in the syndrome. Infusion of hypertonic saline evokes muscle pain with a longer duration in patients with FMS, and referred pain that spreads to a larger area than in controls.

- FMS patients have aberrant responses to pain seen on Functional Brain Neuroimaging. Resting brain blood flow studies have reported mixed findings for several brain regions, whereas decreased thalamic blood flow has been noted by several investigators. Recent studies also suggest an accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain?

Prognosis and Treatment

- FMS does not threaten the patients' life but can cause severe disability and thus substantially compromise the quality of life. Complete resolution of symptoms is almost never achieved, but significant improvement can be obtained with adequate therapy.

- Management of FMS is typically multimodal:
  - accepting attitude from both physician and patient
  - comprehensive clinical evaluation, accurate diagnosis
  - education for affected individuals, family, society
  - encourage patient to take an active role in self-care
  - psychological or psychiatric support, biofeedback training
  - physical therapies, physical modalities, exercise program
  - sparing use of medications proven to be effective (low-dose tricyclic antidepressants (mostly amitriptyline) or other serotonin reuptake inhibitors, sedative, hypnotic medication, analgesics (tramadol), antiepileptics (gabapentin, pregabalin)
  - regular monitoring and follow-up

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Sex and Gender Differences in Orofacial Pain

Orofacial Pain: Prevalence and Impact

- Acute (e.g., toothache, oral sores) and chronic (e.g., temporomandibular muscle and joint disorder or TMJD/TMD pain) orofacial pain are highly prevalent conditions.
- Most forms of orofacial pain are more common among women than men, and women report greater impact of oral pain.
- The most common form of chronic orofacial pain is TMJD pain, which affects approximately 10% of the population.
- TMJD is twice as common in women than men, and a greater proportion of women with TMJD seek treatment for this condition.
- Trigeminal neuralgia, while much rarer than TMJD, occurs roughly twice as often in women as in men.
- Burning mouth syndrome occurs at dramatically higher rates in women than men.

Experimental Models of Orofacial Pain

- Injection of certain chemicals into the masseter (jaw) muscles of healthy persons can produce pain similar that reported by patients with TMJD pain.
- Women report more intense, more widespread, and longer lasting pain after such injections.
- In response to experimental jaw pain, women show less activation of opioid receptors in their brain compared to men, suggesting a reduced ability to modulate facial pain using the endorphins.
- Administration of exogenous estrogen increased women’s ability to activate opioid receptors to modulate experimental jaw pain.

Sex Hormones and Orofacial Pain

- TMJD is most likely to occur in females during the reproductive years, such that sex differences in prevalence are smaller (or nonexistent) prepubertally and post-menopaually.
- Some evidence suggests that use of exogenous estrogens (e.g., oral contraceptives, hormone replacement) increases risk of TMJD.
- TMJD pain symptoms vary across the female menstrual cycle, and tend to lessen during pregnancy.

Other factors may impact sex differences in orofacial pain

- Chronic TMD pain is often co-morbid with other painful conditions, which are also more prevalent in women, such as: fibromyalgia, irritable bowel syndrome, and vulvar vestibulitis.
- Psychological factors have been associated with TMJD pain, including somatization, depression, and other indices of psychological distress, and women tend report higher levels of these factors than men in the general population.

What needs to be done?

- A better understanding for the reasons underlying sex differences in orofacial pain is needed.
- Whether women and men with orofacial pain respond differently to different treatments also needs to be determined.

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Global Year Against Pain in Women

real women, real pain

Pain in Women in Human Immunodeficiency Virus (HIV/AIDS)

- Pain in HIV/AIDS is highly prevalent, diverse and varied in syndromal presentation and it is associated with significant psychological and functional morbidity.
- Pain, in general, is more prevalent in women and is known to be more severe, frequent, widespread and of longer duration.
- Pain syndromes in HIV/AIDS may be related directly to HIV infection or immunosuppression, HIV therapies and those unrelated to AIDS or AIDS therapies and include peripheral neuropathy, extensive Kaposi's sarcoma, headache, oral, pharyngeal, abdominal and chest pain, arthralgias, myalgias, and painful dermatologic conditions.
- As there are more women with HIV, more women will experience pain and this includes unique pain syndromes of a gynecologic nature specifically related to opportunistic infectious processes and cancers of the pelvis and genitourinary tract.

Epidemiology

- Women represent the largest percentage of newly infected HIV-positive individuals throughout the world.
- The AIDS epidemic is worst in sub-Saharan Africa where on average three women are infected for every two men; among young people (15-24 years), the ratio widens to three young women for every young man.
- 80% of AIDS pain is under-treated. This is even more so in women who are often also under-diagnosed. In poor resource countries such as Africa, South America and Asia, there may be limited access to antiretroviral therapy (ART) and palliative care.

Barriers

- Barriers that interfere with pain management by clinicians are lack of knowledge about pain management and access to pain specialists, reluctance to prescribe opioids, concern about drug addiction or abuse, lack of psychological support and drug treatment services.
- Women experience barriers to accessing treatment programs due to prejudice and inequality in the treatment of women and children (especially female) and this may include poverty, abuse, conflict due to war and violence.
- Women often experience lack of information and may have limited understanding, especially in developing countries, that their painful conditions may be part of their HIV disease and that it is recognizable as such and treatable.
- Women often accept their pain experience and may not complain of pain or may accept under-treatment as the norm due to cultural expectations and therefore may dismiss pain and other symptoms as being normal.
- Women with, or without HIV/AIDS, are the ones who provide all the care. Most of the family resources are often devoted to caring for the husband or children.
- Stigma and discrimination is far stronger against women who risk violence, abandonment, ostracism, destitution and neglect from family and community. They may be blamed for the spread of disease even though the majority of them were infected by their only partner/husband.
- Clinical management is based on research on men and more knowledge and education on clinical management of HIV/AIDS and pain in women is required.

Predisposing factors

- Women's sexual rights are often violated, predisposing them to contracting HIV/AIDS due to poverty and male control over women's lives.
- A history of physical, sexual/childhood abuse is common with HIV infection, with up to two thirds of patients reporting a lifetime experience of abuse.
- Women experience poor reproductive, sexual and other health needs, nutrition and medical care.

Co-morbidities

- HIV-positive women were four times more likely (19.4%) to meet clinical criteria for current major depressive disorder than HIV-negative women (4.8%), with significantly more anxiety symptoms.
All forms of coerced sex increases risk of micro-lesions and therefore of sexually transmitted diseases; this includes harmful cultural practices such as genital mutilation and practices such as "dry" sex.

**Treatment and support**

- Opioid analgesics may be required for the management of severe pain and can be used in these patients, including the substance abusers, by following appropriate guidelines.
- Symptom management in HIV palliative care includes pain management and addressing fatigue, stress, depression and anemia.
- The nature of the disease, weak public health infrastructure and other factors mandate improved community-based palliative and end-of-life care. This includes increased government funding and support, higher standards of clinical training, improved pain control through drug policy advocacy, orphan care, income generation and food security.
- Reduce the vulnerability of women by improving their education; change social norms that perpetuate male attitudes and violence against women; increase the availability of treatment that will improve women’s conditions and reduce suffering; change attitudes and negative assumptions about women’s roles; improve their ability to own property and become economically independent; challenge discrimination against them and then women will become empowered to help themselves.

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Global Year Against Pain in Women
real women, real pain

Pain in Women in Developing Countries

Pain is ubiquitous in all societies and is a predictable consequence of events such as trauma and disease. Pain has significant health, socioeconomic and quality of life implications.

The prevalence of most types of pain may be much higher in developing countries than in developed countries for a variety of reasons such as very limited resources, poverty, ignorance and poor healthcare systems, policies and priorities.

Women in the developing world are more likely to suffer pain and are also less likely to be adequately treated than their male counterparts because of societal norms, culture, and governmental policies (1, 2).

There are some painful conditions which by nature occur only in women, such as menstrual pain, pain during pregnancy and childbirth, cancers of the female genital system, female genital mutilation and sexual violence and abuse. Typically, the range of diagnostic and treatment options is very limited.

People in developing countries commonly suffer a ‘double burden’ of both communicable and non-communicable diseases that significantly contributes to a high prevalence and burden of pain and suffering. Eighty percent of cancer patients in the developing world present with advanced incurable cancer and palliative care is often the only therapy.

The burden of disease from cancer of the cervix is substantial, in contrast to the developed world where it has become uncommon thanks to screening interventions. In Africa, it is estimated that 67,761 women die annually from the disease (4). The goal of comprehensive population screening and primary prevention with HPV vaccines remains a distant dream, and there are major challenges in delivering surgery, radiotherapy or pain control to those in need. Supplies of opioids for those with cancer pain are often problematic owing to restrictive legislation and unfounded anxieties on the part of professionals regarding the risk of addiction.

Maternal mortality rates are highest in the developing world accounting for 99% of all maternal deaths worldwide and with approximately half a million women still dying from (mostly preventable) pregnancy and childbirth-related causes (5). An African woman’s lifetime risk of dying from pregnancy-related causes is 1 in 16; in Asia 1 in 65; and in Europe 1 in 1,400. These data conceal a much larger burden of complications and suffering that occur without medical assistance and care.

The developing world, particularly sub-Saharan Africa is the most affected by the HIV/AIDS epidemic with three-fourths of the total worldwide cases. The advent of this epidemic has resulted in a dramatic increase in the incidence of tuberculosis and AIDS-related cancers. The prevalence of pain in HIV/AIDS is very high. In contrast to the developed world, the prevalence of HIV/AIDS is significantly higher in women in developing countries. Gender inequality is the major reason for women’s vulnerability to HIV infection (2).

Working and employment conditions may differ between the sexes. Women are more likely to work in the informal sector where they are often exposed to harmful working environment, inadequate social benefits, greater risk of discrimination and physical and sexual harassment.

Given the very limited resources and fragile health systems stretched by the huge disease burden, pain management in women in developing countries is seen as a very low priority. It would therefore be valuable if it became more universally recognized how good pain management can improve a country’s economy.

There are recognized gender disparities in health and healthcare in general and in pain management in particular (1-3). We need to urgently address and eliminate this gender disparity in healthcare by empowering women so that they can protect and enhance their health and quality of life.

Violence against women (Gender-based violence)

The United Nations defines violence against women, also known as gender-based violence, as ‘any act that results in, or is likely to result in physical, sexual or psychological harm or suffering to women, including threats of such acts, coercion or arbitrary deprivations of liberty, whether occurring in public or private life’(1).

Violence against women is usually both a cause and consequence of discrimination against women.

Violence against women is a major health problem as well as a violation of women’s human rights.

It is prevalent worldwide with far-reaching health, economic and social ramifications and is rooted in gender inequality (1, 2).

Violence against women has significant consequences and costs for women, their families and the society as a whole. It is a major contributor to illness, death, pain, suffering, social isolation, loss of employment and productivity and restriction of freedom.

Violence against women is of various types and can take place in a variety of settings including the family, the community, state custody, and armed conflict. The most common form of physical violence experienced by women worldwide is physical violence by an intimate partner, otherwise called domestic violence. Forced or coerced sex or rape is an example of violence. Violence is an important factor in the transmission of sexually transmitted diseases including HIV, unintended pregnancies and often unsafe abortions (1-3).

Discriminatory social norms and traditional practices in some regions put women in a subordinate position, and at increased risk of reproductive health hazards and even disability and death. These harmful practices include sex selective abortions, female infanticide, female genital mutilation/cutting, neglect of the girl child, early and forced marriage, wife inheritance, violence and discrimination against widows, dowry-related violence, prostitution, and human trafficking mainly for sex exploitation.

Sexual harassment and violence is common in the workplace, educational institutions, correctional institutions, and also in sports. In areas of armed conflict and natural disasters, women are at greater risk of physical and sexual violence (1, 3).

In some societies violence against women is so common that women have come to accept that such acts are ‘normal’ and ‘acceptable’ (1-3). Abused women are often reluctant to seek help because safe and supportive facilities are usually not available. Fear and stigmatization may make women reluctant to disclose their pain and suffering (2).

There are established international laws and policies in place to address and tackle this major public health and human right issue (1-3), but the fact that the problem persists indicates that the laws and legislation, if and where they do exist, are not being effectively implemented.

To effective curb this menace, a multi-sectoral approach, involving the health, legal and social services, must be adopted. There must be a demonstration of political commitment and availability of adequate resources to provide these necessary services. Gender-based violence can only be eradicated by addressing gender discrimination and promoting women’s equality and empowerment. Legislation must criminalize all forms of violence against women and must be properly and effectively implemented.

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Children with Chronic Pain: Sex and Gender Differences

Prevalence

- Chronic pain is a major problem for many children and adolescents, causing significant suffering, disability, anxiety and emotional distress.
- Chronic pain may develop from injury, disease, psychological factors, or from an unknown etiology.
- The prevalence of childhood chronic pain increases generally with age, but certain pain conditions affect girls more than boys. For example, clinical referrals indicate that Complex Regional Pain Syndrome - Type 1 has a female to male ratio of ~ 9:1, affecting children primarily in their pre- and early teen years.

Etiologic and Risk Factors

- Chronic pain generally has multiple causes, often with both nociceptive and neuropathic components, rather than a single cause. Psychosocial factors (cognitive, behavioral, and emotional) typically contribute to a child’s pain experience, emotional distress, and physical disability.
- Psychosocial factors may be different for girls and boys. For example, females show more internalizing behaviors with symptoms of depression and anxiety, while males show more externalizing and disruptive behaviors.
- Females may be at higher risk for continuing pain and report greater use of health care, medication, and non-drug methods of pain control.
- Much research is now focusing on determining the risk factors for developing chronic pain, especially why girls and pre- and early teens may be most vulnerable.
- While sex and gender-related differences have been noted in children's chronic pain behaviors and pain sensitivity (comparable to those for adults), we lack sufficient data to understand the interplay of biological, cultural and developmental factors in mediating such differences.

Pain Management

- Like adults, children with chronic pain usually require a multimodal therapeutic regimen comprised of drug, physical, and psychological therapies – to address the primary etiology and any environmental, family, and psychological factors that affecting children's pain and disability.
- However, we lack data from well-designed cohort studies and RCTs to support the overall efficacy of many interventions (both drug and non-drug therapies), as well as their sex- and age-based efficacy.

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