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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).

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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.

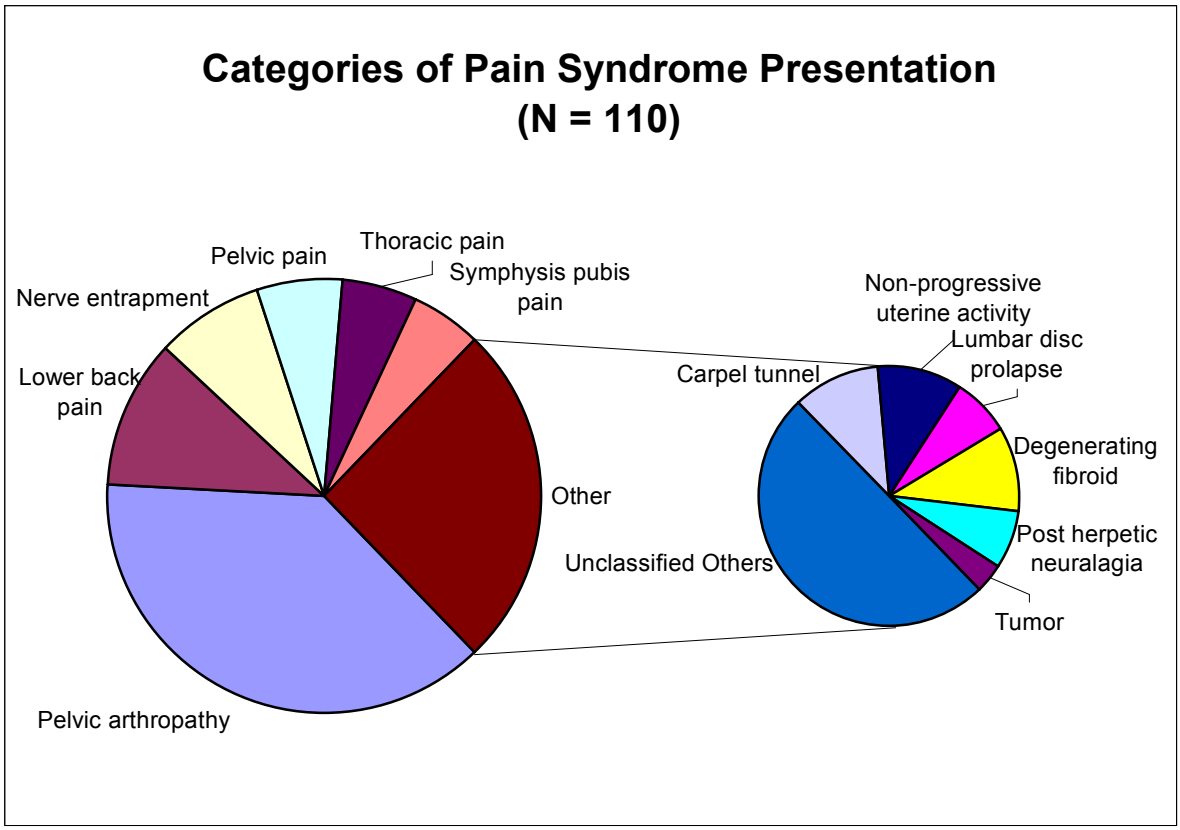
In a study of 870 women referred to physical therapy for pain during pregnancy, over 76% of their women complained of pain over the sacroiliac joints and 57% complained of pubic symphysis pain (11). A correlation was found in those women with previous low back pain and pelvic pain, higher pre and end 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, carpel tunnel syndrome and lumbar disc prolapse.



(12)

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).

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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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