

Is it all about sex? Acupuncture for the treatment of pain from a biological and gender perspective

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Abstract

Pain is a unique personal experience showing variability where gender and sex related effects might contribute. The mechanisms underlying the differences between women and men are currently unknown but are likely to be complex and involving interactions between biological, sociocultural and psychological aspects.

In women, painful experimental stimuli are generally reported to produce a greater intensity of pain than in men. Clinical pain is often reported with higher severity and frequency, longer duration, and present in a greater number of body regions in women than in men. Women are also more likely to experience a number of painful conditions such as fibromyalgia, temporomandibular dysfunction, migraine, rheumatoid arthritis and irritable bowel syndrome. With regard to biological factors, quantitative as well as qualitative differences in the endogenous pain inhibitory systems have been implicated, as well as an influence of gonadal hormones. Psychosocial factors like sex role beliefs, pain coping strategies, and pain related expectancies may also contribute to the differences. Being exposed to repeated painful visceral events (eg menses, labour) during life may contribute to an increased sensitivity to, and greater prevalence of, pain among women.

When assessing the outcome of pharmacological and non-pharmacological therapies in pain treatment, the factors of gender and sex should be taken into account as the response to an intervention may differ. Preferably, treatment recommendations should be based on studies using both women and men as the norm. Due to variability in results, findings from animal studies and experiments in healthy subjects should be interpreted with care.

Keywords

Acupuncture, oestrogens, gender, pain, sex differences, testosterone.

Introduction

One of the best known examples of records of women in pain is the work of the Mexican artist Frida Kahlo (1907-1954), who had a gift for communicating her pain to the world through painting. When she was 18, she was hurt in a bus accident that scarred her for life. Her spinal column and pelvis were broken in three places. She was skewered by a metal handrail that entered her hip and exited through her vagina. Most of her paintings were self portraits describing her life and pain after the accident (Figure 1). Her paintings are often violent looking, bloody, and severe but represent what was happening to her. She purged her pain and suffering on canvas. She said, 'I paint self portraits because I am the person I know best. I paint my own reality'.

Frida Kahlo lived her life to the fullest, despite immense pain, handicaps, and suffering. She was an amazing woman in her own right, for what she had endured, how she persevered, and for how she was and still is an inspiration and example of strength to other women (and men) in pain.

Pain is a subjective experience with many dimensions and is therefore not comparable between individuals. In addition to the variability of pain due to personal experience, the fact of being a woman or a man may also have a great influence on individual differences in perceived pain.

On 15 October 2007, the International Association for the Study of Pain, IASP, announced the launch of the Global Year Against Pain 'Real Women, Real Pain' campaign to draw attention to

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Figure 1 'The Broken Column' ('La Columna Rota') by Frida Kahlo; 1944, oil on masonite. © 2007 Banco de México Diego Rivera & Frida Kahlo Museums Trust. Av Cinco de Mayo No 2, Col Centro, Del Cuauhtémoc 06059, México, DF.

the significant impact of chronic pain on women and the need for an increase of knowledge in the field.¹ In the present review and tutorial we address sex and gender aspects of pain and some common female visceral pain conditions in relation to effects of acupuncture.

Women and men in pain

Epidemiological studies have recently reported that the prevalence of pain, the burden of pain and the use of analgesics is greater in women than men.²⁻⁴ Women report pain to be of a higher severity and frequency, longer duration, and present in a greater

number of body regions as compared with men. Also, women appear more prone to a number of painful conditions such as fibromyalgia, temporomandibular dysfunction, migraine, rheumatoid arthritis and irritable bowel syndrome.⁵

In the field of pain research, females have generally been excluded from experimental and clinical studies up to now, possibly because of the extra variability in the results introduced by the menstrual cycle. Furthermore, basic science studies continue to use male rodents almost exclusively as research subjects.⁶ This gender bias influences research results and could lead to inappropriate and questionable generalisations of research findings, based on the male as the norm.⁷⁻⁹

When testing women's and men's response to a painful experimental stimulus, it has been found that women generally report pain at lower stimulus intensity and have a lower tolerance to pain as compared with men, although this partly depends on the type of stimulus used.⁵ The same pattern has been described in studies with rodents where the females exhibited greater sensitivity to a range of noxious stimuli and greater responsiveness in experimental nociceptive models than male rats.¹⁰

In this article, we describe how the complex mechanisms underlying these differences are influenced by interacting factors such as biological (genetics, gonadal hormones, differences in the function of endogenous pain inhibition), psychological (anxiety, depression, cognition, behavioural) and psychosocial (age, ethnicity, family history, gender roles) factors that all contribute to differing perceptions of pain.⁵⁻¹¹

Gender and sex

Gender, in everyday usage, refers to the differences between men and women without any assumptions in respect to biology. The definitions of gender and gender identity differ in theory. In popularised and scientifically based tradition, sex is what you are biologically while gender is what you grow to be socially. For example gender identity is your own sense or conviction of maleness or femaleness; and gender role is the cultural typecast of what is masculine and feminine.

Gender differences in the processing of emotions may explain why women are more sensitive to negative threat while men respond to positive

pleasurable stimuli.¹² Also, expectation may play a key role when being exposed to pain for the first time.¹³ The gender role stereotypes of social norms may also contribute to the differences in pain (ie the ideal man is masculine and tolerates more pain; the ideal woman is feminine and tolerates less pain). Men who identify strongly with the male gender role stereotype showed significantly greater pain tolerance than high-identifying women, while no differences existed between low-identifying men and women.¹⁴ Furthermore, therapist patient interaction has been reported to be influenced by gender. Men examined by a woman reported less pain than when the examination was carried out by a man. Women on the other hand, were not as sensitive to gender in their reports of pain as men were.¹⁵ The effects of the examiner's gender in testing of pain thresholds followed the same pattern.¹⁶

Like the variety of meanings of the word *gender*, the word *sex* has different meanings, eg to describe male and female duality of biology and reproduction, but also to describe erotic behaviour between humans. Sex dependent differences in pain, both in humans and in animal models, are well established,¹⁷⁻²³ where causality with respect to sex is known to operate from chromosome to gonads, and from gonads to hormones.²⁴

This sexual dimorphism also includes differences in central processing as well as involvement of different signalling pathways.²⁵⁻³⁰ In addition, inflammation and inflammatory diseases are sexually dimorphic, though the underlying causes are poorly understood.¹⁰ Although many factors are likely to contribute to the observed differences in nociception and pain, sex hormones are suggested to be key factors.^{20,30-34} For instance, Naliboff and collaborators reported that male and female patients with irritable bowel syndrome (IBS) differ in activation of brain networks in response to anticipated aversive visceral stimuli.³⁵ These observed differences in IBS may be attributed to the effect of gonadal hormones on gastrointestinal motility and sensory processing.³⁶

Causality aspects of sex differences

Chromosomes

Gonads start developing as a common precursor in the form of gonadal ridges that are subsequently differentiated into male or female sex organs. The SRY gene, located on the Y chromosome and

encoding the testis determining factor, determines the direction of this differentiation.

Gonads

The gonads – testes in males and ovaries in females – are the organs that make gametes, ie haploid germ cells. In addition, the gonads function like glands producing steroid sex hormones, identical to those produced by adrenal cortical cells. The major distinction is the source and relative amounts produced. The testes produce spermatozoa and secrete androgens, predominantly testosterone. The ovaries produce ova and secrete oestrogen and progesterone. In 2004, Craft and collaborators reported that the ‘male’ hormone testosterone has an antinociceptive effect while the ‘female’ hormone oestrogen has a pronociceptive effect.³⁷ The present review is focused on women in pain and therefore also on oestrogens.

Hormones

Testosterone is produced in the largest amounts by the Leydig cells in the testes. It is also synthesised in far smaller quantities by the thecal cells of the ovaries and by the placenta, as well as by the zona reticularis of the adrenal cortex in both sexes. In general, androgens, like testosterone, promote protein synthesis and growth of those tissues with androgen receptors. Like most hormones, testosterone is supplied to target tissues in the blood where much of it is transported bound to a specific plasma protein, sex hormone binding globulin (SHBG). The effects of testosterone are mediated by two main mechanisms: by activation of the androgen receptor (directly or as 5α -dihydrotestosterone), or by conversion to oestradiol and activation of oestrogen receptors (ERs).

Free testosterone is transported into the cytoplasm of target tissue cells, where it can bind to the androgen receptor or be reduced to 5α -dihydrotestosterone by the cytoplasmic enzyme 5α -reductase. 5α -dihydrotestosterone binds to the same androgen receptor even more strongly than testosterone, so that its androgenic potency is about 2.5 times that of testosterone. The testosterone receptor or 5α -dihydrotestosterone receptor complex undergoes a structural change that allows it to move into the cell nucleus and bind directly to specific nucleotide sequences of the chromosomal DNA (hormone

response elements) and influence the transcriptional activity of certain genes, resulting in up or down regulation of specific gene transcription, producing the androgen effects.

Up regulation or activation of transcription results in increased synthesis of messenger RNA which in turn is transcribed by ribosomes to produce specific proteins (*genomic* effect). Thus, changing levels of specific proteins in cells is one way that androgen receptors control cell behaviour. The androgen receptor also has additional functions independent of DNA binding (*non-genomic* effects). Greatly differing amounts of testosterone account for a share of biological differences between males and females throughout life: ie prenatally, during puberty and the adult period of life.

Oestrogen is the primary female sex hormone and is produced mainly by developing follicles in the ovaries, the corpus luteum, and the placenta. The three major naturally occurring oestrogens in the female body are oestradiol, oestriol, and oestrone, all produced from androgens through actions of enzymes. The conversion of testosterone to the dominant oestrogen oestradiol, and of androstenedione to oestrone, is catalysed by the enzyme aromatase. From menarche the primary oestrogen is 17β -estradiol with varying levels related to the menstrual cycle. In postmenopausal women more oestrone is present than oestradiol. Some oestrogens are also produced in smaller amounts by other tissues such as the liver, adrenal glands, and the breasts. These secondary sources of oestrogens are especially important in postmenopausal women.

Oestrogen receptors

There are two types of oestrogen receptor (ER), ER α and ER β . Both types of ERs are distributed in regions of the CNS and peripheral nervous system which are involved in pain perception, including spinal dorsal horn neurons and dorsal root ganglia (DRG) neurons.³⁸⁻⁴² The two receptor forms are co-expressed in many cell types and may therefore form ER α ($\alpha\alpha$) or ER β ($\beta\beta$) homodimers or ER $\alpha\beta$ ($\alpha\beta$) heterodimers. The main functions of the ERs α and β is a DNA binding transcription factor regulating gene expression. However the ERs also have additional functions independent of DNA binding.

Oestrogens - non-genomic and genomic actions

Oestrogens readily diffuse across the cell membrane and interact with ERs inside the cell. By regulating activities and expressing levels of key signalling molecules, oestrogens control mechanisms that are responsible for crucial cellular functions. Ligand binding to an ER leads to conformational changes that regulate the receptor activity, and its interaction with other proteins and DNA.

In the cytoplasm, receptor interactions with kinases and scaffolding molecules regulate cell signalling cascades (*extranuclear/non-genomic action*). In the nucleus, oestrogens control a repertoire of co-regulators and other auxiliary proteins that are associated with the ERs, which in turn determine the nature of regulated genes and level of their expression (*genomic action*). The combination of genomic and non-genomic actions of oestrogens ultimately confers the cell-type and tissue-type selectivity.²⁴ For example, 17 β -estradiol (E2) is a circulating steroid hormone that has marked biological effect on many cells and tissues, including nociceptive neurons.^{39:42-45} Thus oestrogen can act on the nociceptive neuron directly.⁴⁶

Surprisingly, in cultured DRG neurons, the action of oestrogen is very fast. One minute's preincubation with oestrogen abolishes the translocation of PKC3 (protein kinase C3) in cultured, male-derived sensory neurons, suggesting that a transcription-independent mechanism is involved. Fast actions of sex hormones have been shown also in other systems.⁴⁷ A physiological role for such fast concentration changes might exist in pain pathways.

Aromatase

The oestrogen-producing enzyme aromatase is present in the dorsal horn of the spinal cord,⁴⁸ where peripheral nociceptive neurons terminate and pain signals are modulated. Aromatase activity was recently found to be involved in the establishment of thermal nociceptive threshold.⁴⁸ Having the oestrogen-producing enzyme and the ERs adjacent to each other opens the possibility that concentration changes occur rapidly and only on a very local level, which therefore might not be reflected in changes of the more constant plasma levels. Indeed, a local rise in oestrogen by injection into the rat hindpaw results in decrease of mechanical hyperalgesia induced by intracellular signalling molecules.⁴⁶ Thus,

gonadal hormones could potentially have fast, local regulatory functions beyond their classical organism-wide actions on gene transcription. These hormones may have a dual pro-nociceptive action: a slow genomic and a rapid non-genomic action. It is likely that part of this non-genomic effect is mediated by changes in N-methyl-D-aspartic acid receptor (NMDAR) expression and activity.^{39:42:49}

N-methyl-D-aspartic acid receptor

NMDARs are glutamate and glycine-gated cation channels that play an essential role in neuroplasticity functions and are expressed by nearly all DRG neurons.⁵⁰ Direct stimulation of peripheral afferent nerve terminal fields with NMDAR agonists causes nociception and pain,⁵¹⁻⁵⁴ and is also involved in a temporal context.^{46:55-56} Visceral nociceptive responses have greater sensitivity to peripherally administered NMDAR antagonists than those arising from somatic tissues implying a greater role of these NMDARs in visceral pain transmission.⁵⁷⁻⁵⁸

In peripheral tissue, stimulation of NMDARs causes release of the neuropeptides like substance P (SP) and calcitonin gene-related peptide (CGRP) from capsaicin-sensitive peripheral nerve terminals.⁵⁷ These neuropeptides and growth factors contribute to neurogenic inflammation.⁵⁹⁻⁶⁴

Stimulation of NMDARs in the spinal cord also mediates release of neuropeptides and of brain-derived nerve growth factor,⁶⁵⁻⁶⁸ that may have important effects in the development of long term central sensitisation, and thereby the maintenance of chronic pain.⁶⁹ Clinically, this may be reflected by a greater degree of temporal summation to repeated noxious stimulation ('wind up') in women compared with men.³¹⁻³² Although temporal summation as measured clinically is short lived, it is increased in female patients with chronic pain disorders such as irritable bowel syndrome and fibromyalgia.^{70:71} Thus, mechanisms underlying temporal summation are likely to be involved in longer lasting forms of pain.

In a recent study, McRoberts and collaborators compared the activity of NMDARs expressed on male and female DRG neurons in short term culture and examined the effect of immediate ER stimulation.⁷² The results showed that small to medium sized cultured DRG neurons from female rats have significantly larger NMDAR currents than

those observed in neurons from male rats. The second finding was that addition of 17β -estradiol caused a rapid increase in NMDAR currents that was more pronounced in female than male derived neurons. These results could be due to increased expression of NMDARs, or could be due to greater activity of the individual NMDAR channels in female neurons.⁷³⁻⁸⁰ These results, demonstrating increased expression of NMDAR activity in female neurons, may help to explain sex based differences in glutamate mediated nociceptive responses in humans.⁸¹ Both intramuscular and subcutaneous injection of glutamate produces primary and secondary pain responses in humans with greater effects in women than men.^{52,82-84} Also, women have a greater number of pain mediating receptors – NMDA receptors – which may be activated by female gonadal hormones.⁸⁵⁻⁸⁸ Another aspect that has been investigated is the role of the adrenergic receptors.

Adrenergic receptors

In male rats, activation of the β 2-adrenergic receptor induces protein kinase C3 (PKC3) – as well as protein kinase A (PKA) and extracellular regulated kinase 1/2 (ERK1/2) – dependent mechanical hyperalgesia. In contrast, in female rats, β 2-adrenergic receptor mediated sensitisation does not require PKC3,²⁰ indicating that this phenotype is dependent on systemic oestrogen levels.

Also, recently it has been reported that activation of α 2-adrenoceptors produces sex specific, oestrogen dependent modulation of nociception in the trigeminal region of the rat,⁸⁹ suggesting that a decreased α 2-adrenoceptor-mediated inhibition could be one of the factors responsible for the higher prevalence of pain syndromes in females.

Genetic differences

Genetic differences could also contribute to the variations in perceived pain between women and men. It was recently reported that the gene melanocortin-1 receptor (MC1R) mediates gender specific analgesia in that women with two variant MC1R alleles, red hair and fair skin, display significantly greater analgesia, from the κ -opioid, pentazocine than other women and men.⁹⁰

Gender, sex and endogenous pain inhibitory systems

Both inhibitory and facilitatory functions of the endogenous pain modulatory systems have been described.⁹¹⁻⁹⁴ Diffuse noxious inhibitory control, DNIC, a part of the inhibitory system,⁹² has been shown to be malfunctioning in females suffering from fibromyalgia syndrome (FMS). The described deficiency in activating the pain inhibiting circuits in the DNIC system might possibly be one reason why more women suffer from FMS than men.⁷¹

A number of different neurotransmitters, such as opioids and monoamines, have been suggested to play a key role in the inhibitory circuits.⁹⁵⁻⁹⁶ It has been reported that there are sex related differences in the κ -opioid system.⁹⁷ The collected data from the study of Zubieta and collaborators demonstrate that at matched levels of pain intensity, the magnitude and direction of response of the κ -opioid system differs between men and women in distinct brain nuclei.⁹⁷

Sex differences in analgesic responses to opioids have received increasing attention recently.⁹⁸ In general, male rodents show a more robust response to opioid analgesics compared with females.⁹⁹ However, these effects are influenced by the specific nociceptive test used, as well as the opioid agonists studied. In a study by Bernal and collaborators it is suggested that sex related variations could be explained by a difference in the κ -opioid receptor density in the midbrain periaqueductal gray (PAG) region.¹⁰⁰

Evidence of sex differences in analgesia is reported in studies where κ -agonist is administered to patients following oral surgery. These data indicate that κ -opioids have a more pronounced analgesic effect in women than in men,²³ with dose-response characteristics.¹⁰¹

Gender dependent responses to sensory stimulation

In order to activate the endogenous pain inhibitory mechanisms, different modes of sensory stimulation (eg acupuncture) have been used.^{91,102} The systems will respond differently depending in what context the stimulation is applied and the type of condition treated but possibly also even the patient's sex or gender. Interestingly, acupuncture has been suggested to induce an up regulation of ER β and down

regulation of ER α .¹⁰³ Also, acupuncture has been shown to modulate 17 β -estradiol levels in plasma.^{104;105}

The documentation of possible gender related pain alleviating effects of acupuncture and other types of sensory stimulation (eg transcutaneous electrical nerve stimulation – TENS) is sparse.

In a previous study we detected a gender related effect of TENS and vibration indicating that women respond with an increase of the pain threshold while men do not.^{106;107} We have also observed a similar pattern in healthy individuals subjected to acupuncture (unpublished data).

In a subgroup analysis of the published data of Näslund and collaborators concerning the pain alleviating effect of acupuncture on anterior knee pain, we could not find a difference in treatment effects between women and men, ie the significant decrease of rated pain was present in both groups even six months after the acupuncture treatments had ended.¹⁰⁸ This would suggest that there is a difference between experimental and clinical pain and probably between different pain states.

Effects of acupuncture in women with visceral pain

Dysmenorrhoea

Painful menstruation is a cyclical condition that adversely affects the woman's wellbeing. Its pathogenesis is not always understood. Prostaglandins seem to be intimately involved in primary dysmenorrhoea although the underlying cause for their excessive secretion is not fully understood. Abnormalities in plasma steroid levels could account for the disturbance, especially significantly elevated plasma levels of oestradiol in the luteal phase. Higher plasma levels of vasopressin in women with dysmenorrhoea suggest a possible aetiological role in the uterine prostaglandin synthesis. Apart from pharmacological agents, several techniques have been used for pain alleviation including acupuncture.^{109;110} In 2003, a systematic review of controlled trials of acupuncture or acupressure for gynaecological conditions concluded that acupuncture and acupressure appear promising for dysmenorrhoea.¹¹¹ Furthermore, it was recently reported that the therapeutic effect of superficial needling at *Sanyinjiao* (SP6) in primary dysmenorrhoea is effective and better than that of

indomethacin or ibuprofen.¹¹²⁻¹¹⁴ Also, acupressure on SP6 has been shown to induce an alleviation of primary dysmenorrhoea,¹¹⁵ and was therefore recommended for self care.¹¹⁶

Pelvic pain during pregnancy

Many women experience back or pelvic pain during pregnancy, generally with increasing intensity as pregnancy advances. The pain often interferes with daily activities, health related quality of life and sometimes disturbs sleep. The precise aetiology of the pain is still unknown but altered posture due to enlargement of the uterus and decreased stability of lumbar and pelvic ligaments due to hormonal changes have been proposed as probable causes. Suggestions to help manage the pain are varied and include special pregnancy exercises, frequent rest, hot and cold compresses, a supportive belt, massage, acupuncture, chiropractic, aromatherapy, relaxation, herbs, yoga and Reiki. Pennick and Young concluded that specifically tailored strengthening exercise and acupuncture may be effective with minor and transient adverse effects.¹¹⁷ Recently, we carried out a prospective randomised controlled single blind study in pregnant women with pelvic pain.¹¹⁸ After acupuncture stimulation, significant systematic group changes towards lower levels of pain intensity at rest and in daily activities as well as in rated emotional reaction and loss of energy were seen. The results also showed additional individual changes in most variables. Furthermore, no differences between the effects induced by the superficial and deep acupuncture stimulation modes were observed. We concluded that acupuncture stimulation that is individually designed may be a valuable treatment strategy to ameliorate suffering in the condition of pelvic pain in late pregnancy.¹¹⁸ This suggestion is supported by other studies.¹¹⁹⁻¹²¹

Chronic pelvic pain

Chronic pelvic pain in adolescents accounts for 10% of outpatient gynaecology visits, and 70% of adolescent patients whose pelvic pain is unresponsive to initial therapy suffer from endometriosis. Case reports provide preliminary evidence that acupuncture may be an acceptable and safe adjunctive treatment therapy for some patients with endometriosis related pelvic pain refractory to standard therapies directed at endometriosis.¹²²

In a recent study by Sun and Chen,¹²³ the therapeutic effect of acupuncture for treatment of endometriosis in 90 women was evaluated. They reported that a *Shu-Mu* point combination needling method resulted in pain alleviation, with a lower adverse effect rate than the Western medicine group in the study. Also, ear acupuncture has been tried successfully in dysmenorrhoea due to endometriosis.¹²⁴

Painful bladder syndrome

Painful bladder syndrome/interstitial cystitis and endometriosis share some similar symptoms.¹²⁵ In 2003, Alraek and Baerheim reported that acupuncture treatment has a pain relieving effect in some types of recurrent cystitis.¹²⁶

Irritable bowel syndrome (IBS)

Acupuncture has been used as a therapy for various painful gastrointestinal disorders, including irritable bowel syndrome (IBS). However, there is scant information on the effect of acupuncture on gut physiology. Experimental and clinical studies have shown that both 'sham acupuncture' and acupuncture-like stimulation reduce the perception of visceral pain without affecting the visceral tone (distensibility).¹²⁷⁻¹²⁹ This central effect, ie the reduced perception of pain, has been suggested to be mediated by opioids.¹³⁰

Interestingly, Schneider and collaborators reported that both acupuncture and the 'sham' control significantly improved quality of life in patients with IBS, with no differences between the groups.¹³¹ Post hoc comparison of responders and non-responders in both groups combined revealed a significant prediction of the 'placebo' (our term) response by two subscales of the functional digestive diseases quality of life questionnaire (sleep, coping). Schneider and co-workers concluded that the effect of acupuncture in IBS is primarily a 'placebo' response. They suggested that the 'placebo' response may be predicted by high coping capacity and low sleep quality in individual patients. Similar results and conclusions have previously been reported in studies of the effect of acupuncture in IBS.¹³²

We have previously questioned conclusions based on so called randomised controlled trials using sham procedures such as 'placebo needles', superficial needling or needling outside the affected area.¹³³⁻¹³⁷ Despite claims of being inert there is now

strong evidence suggesting that this is not the case but additional modulatory systems seem to be affected when using acupuncture. Taken together it appears that a major effect of acupuncture, superficial needling and 'sham acupuncture' may be attributed to deactivation of function in limbic structures resulting in reduced affective components of pain.

Assisted reproductive technology

In a recent paper in *Acupuncture in Medicine*, Stener-Victorin and Humaidan discussed the use of acupuncture as an analgesic method during oocyte aspiration.¹³⁸ Pain during oocyte aspiration is caused by the passage of the needle through the vaginal wall and by mechanical stimulation of the ovary. The pain perceived is often compared to the intense pain perceived during menstruation. Oocyte aspiration is usually quick, and the analgesic method used must be both effective and safe. Recently, studies to evaluate both the pain relieving effect of electroacupuncture (EA) during oocyte aspiration and the effect of EA on the number of pregnancies have been published.¹³⁹⁻¹⁴² EA was found to induce pain relief similar to that induced by a fast acting opioid during oocyte retrieval and to have fewer negative side effects.¹⁴²⁻¹⁴³ Also, the results suggest that acupuncture may have a positive effect and no adverse effects on pregnancy outcome.

Conclusion

Pain is a unique individual experience showing a degree of variability dependent on gender and sex. The mechanisms underlying the differences between women and men are currently unknown but are likely to be complex, involving interactions between biological, sociocultural and psychological aspects.

Sex differences may also explain why women are more sensitive to pain. During life women are exposed to repeated painful visceral events (eg menses, labour) which may result in a greater prevalence of pain.

When assessing the outcome of pharmacological and non-pharmacological treatments in pain treatment, gender and sex aspects should be taken into account as the response to an intervention may differ and treatment recommendations should preferably be based on studies using both women and men as the norm. Due to variability in results,

findings from animal studies and experiments in healthy subjects should be interpreted with care.

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