AANA Journal Course
Update for Nurse Anesthetists

4
6 CE Credits*

Gender Differences in Pain: Does X = Y?

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Increasing evidence suggests that men and women differ in their responses to pain. Women report intense pain more often than men afflicted with similar ailments. A variety of psychological, cellular, and hormonal modulations have important roles in the experience of pain. The aims of this course are to update anesthesia providers about the differences between genders in pain sensitivity and treatment and to elucidate the complex aspects of the biology of such differences. Providers need to understand and anticipate gender as a potential factor in pain response and opioid requirements. Continued research in this area may someday provide gender-specific medications for pain treatment and a better understanding of certain prevalent pain conditions between genders.

Keywords: *Analgesia, gender, pain.*

Objectives

At the completion of this course, the reader should be able to:

1. Describe psychological factors that influence pain between genders.
2. Understand the influential role that sex hormones have on pain.
3. Describe factors that may alter pain during pregnancy.
4. Elucidate gender differences in postoperative pain.
5. Understand anesthetic implications and the influence of sex hormones on minimum alveolar concentration of the inhaled anesthetics.

Introduction

Evaluation and treatment of pain is a primary responsibility of anesthesia providers. Increasing evidence suggests that men and women differ in their response to pain. Clinical and experimentally induced pain experiences have been reported to differ among gender over a range of etiologies from arthritis to surgical recovery. Women report pain more often and with more intensity than do men with similar ailments.[1] Pain has been described as an "ensemble act" (Figure 1) with cellular, molecular, genetic, physiological, psychological, and social factors jointly processing the signal to create the circumstances that the person experiences as pain. Numerous investigations have reported greater prevalence of certain pain conditions in women than in men (Table).[2-9] The most significant gender differences are noted in the autonomic nervous system–linked comorbid medical conditions such as migraine,[2] temporomandibular disorders,[3] irritable bowel syndromes,[4] and rheumatoid arthritis and fibromyalgia.[5-7] The aims of this course are to update and inform anesthesia providers about gender-based differences in pain sensitivity and treatment and to elucidate the complex aspects of the biology of such differences.

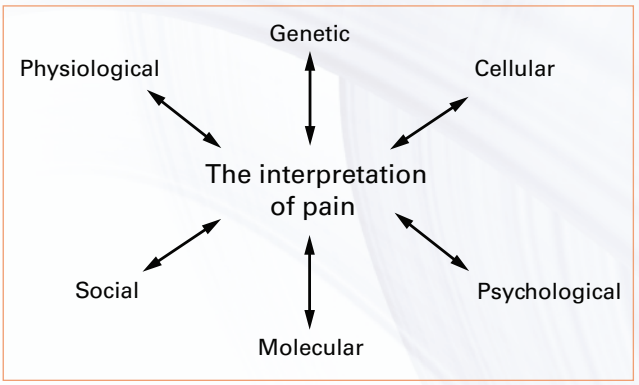

Figure 1. The "Ensemble Act" of Pain: Interacting Factors
No singular factor is responsible for the perception and response to pain. A multiplicity of factors combine to create an environment and an experience that is different between men and women.

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History of Female Participation in Pharmacological Testing

In 1977, the Food and Drug Administration (FDA) ruled that "women of childbearing potential" be excluded from early clinical trial phases. Many pharmaceutical companies interpreted this mandate as an exclusion from all clinical trials. The result was a lack of inclusion of women in testing, which blinded research as to gender differences in medication dosing and response.[10] In 1993, Congress passed the National Institutes of Health Revitalization Act. Subsequently, the FDA lifted the research ban on including women in testing and later provided guidance to drug developers to ensure that effects on women were properly evaluated and researched.[10] This guidance emphasized the FDA's expectations that women would be appropriately represented in clinical trials and that new drug applications would include analyses capable of identifying potential differences in drug actions or efficacy between genders.[10] Since then, much research has been devoted to identifying the causative factors and influences of gender differences in relation to pain.

Psychological Factors in Pain

Psychosocial factors may have a role in the gender pain relationship. One reason women report more pain may be due to early childhood socialization and gender-role expectations. Stereotypically, girls are allowed to be emotional and express pain behavior openly, whereas boys are expected to be brave and stoic.[1,11] Researchers have examined the influence of anxiety in relation to pain sensitivity and found that high anxiety is associated with enhanced pain reported in women, but not in men.[12] Three female-specific factors may account for women's greater sensitivity to pain, including hypervigilance, greater body-monitoring, and higher prevalence of anxiety and depression.[13] Women may experience more pain throughout their lifetime due to biological events such as menstruation and childbirth and, as a result, may develop a greater awareness of pain over time.[14]

Technological advancements have allowed researchers to systematically examine the biological differences in pain between genders. In an elegant study using positron emission tomography (PET) scan, Paulson et al[15] studied increases in blood flow and cerebral activation patterns during pain perception. With 20 volunteers, 10 male and 10 female, the subjects were instructed to discriminate between the intensity of innocuous and noxious heat stimulations (40°C and 50°C, respectively) applied to the forearm. Two findings were noted. The first response was an overlap in spatial and intensity patterns of cerebral and cerebellar activation in response to pain in males and females. This finding provides evidence that there are consistent and identifiable cerebral responses associated with painful stimulation in humans. In the second finding it was noted that females verbally perceived the 50°C heat stimulus as more intense compared with males. The authors assimilated this difference with greater activation in the thalamus, anterior insula, and contralateral prefrontal cortex of females as evidenced by the PET scan. The difference found within the prefrontal cortex may be responsible for the affective, or psychological, differences seen between genders in pain perception.[16] This study associated differences in pain perception with differences in PET scan processing of brain nociception.

Female prevalence	Male prevalence
Postdural puncture headache	Duodenal ulcer
Temporomandibular pain	Ankylosing spondylitis
Fibromyalgia	Postherpetic neuralgia
Irritable bowel syndrome	Cluster headache
Raynaud disease	Pancreatic disease
Migraines	
Multiple sclerosis	
Rheumatoid arthritis	

Table. Prevalence of certain painful conditions between genders[2-9]

Many psychological factors can contribute to the sensation and expression of pain, but are there any objective signs to determine the extent of pain that an individual is experiencing? In the operating room, vital signs and pupil size are frequently used to determine painful responses and analgesia. Ellermeier and Westphal,[17] using an objective measure of pain, studied gender differences in the pupillary response to pain. An infrared video pupillometer recorded pupillomotor activity in response to a painful pressure stimulus. Sixteen participants—8 female, 8 male—first passed a screening test to ensure their suitability for pupilometry (eg, no gross anomalies in shape or infrequent eye blinks). The experiment consisted of a 15-minute dark adaptation period followed by asking the participant to fixate on an illuminated screen. The screen brightness was then adjusted to set the subject's pupil diameter to 30 mm^2 as a starting value. An application of pressure was then applied to the finger, and pupillary measurements were obtained. In addition, each participant was asked to verbally rate the pain. The authors found the following: (1) Females verbally rated their pain higher at pressures equal to those for males. (2) The effect of painful pressure on pupil dilation grew at a faster rate among females compared with males. The significance of this test demonstrates a gender difference at the level of the autonomic nervous system, a response that is beyond voluntary control.

Role of Gonadal Hormones in Pain

The influence of hormones in pain response between

genders has received much scrutiny. The developmental profile of some types of pain such as temporomandibular pain,[18] migraines,[7,18] and tension headache[19] clearly parallels hormonal changes during the menstrual cycle (Figure 2).[20,21] Aside from their function in reproduction, sex hormones and their receptors that are widely distributed throughout the central nervous system have demonstrated modulatory effects on the central opioid system to responses in pain.[7,17,22-26] High densities of estrogen receptors functionally related to endorphin receptors have been found within the hypothalamus, an area with a high density of neuroendocrine and centrally projecting neurons.[27] This may explain the decreased sympathetic outflow associated with estrogens.[28] Estrogens have also been found to induce mu-opioid receptor activation within the preoptic nucleus and posterodorsal medial amygdaloid nucleus (areas responsible for thermoregulation and sex behavior, respectively).[29] This effect can be blocked by the mu-opioid antagonist naltrexone,[29] which further demonstrates these hormone-opioid receptor interrelationships.

Some authors have been unable to identify differences in the pain response across the menstrual cycle.[14,30-32] Significant interindividual and intraindividual hormonal concentration fluctuations may partly explain these inconsistencies. This can cause difficulty in relating pain with various stages of the menstrual cycle.[31,32] Another confounding factor is the complex interactions between progesterone and estrogen. Stenning et al[30] studied the pain response across the menstrual cycle phases using a cold pressure test. In this study, a demonstration of variations in pain perception that correlate with the fluctuating concentration ratios of estrogen and progesterone was conducted. The researchers reported that with lower levels of estrogen, progesterone was pronociceptive. Pain thresholds were decreased, and pain intensities increased during the midluteal phase when progesterone levels were relatively higher than estrogen levels. The authors speculated that the pronociceptive response may not be due to the overall concentration of progesterone, but rather to the sudden drop in the concentration as seen at the very end of the luteal phase (see Figure 2); with elevated levels of estrogen and progesterone, there is an antinociceptive effect. This effect is seen during pregnancy and may account for pregnancy-induced increases in tolerance to nociception.

Pregnancy

It is known that pregnancy induces a myriad of hormonal and physiological changes.[23] One sequela of the activation of female reproductive processes is an elevated maternal pain threshold. Elevated pain thresholds continue to rise throughout late pregnancy and the parturient period. The most notable elevations are seen in the last 18 days of the third trimester.[8,23] This timing of antinociceptive response may account for a woman's ability to better tolerate the pain of childbirth.

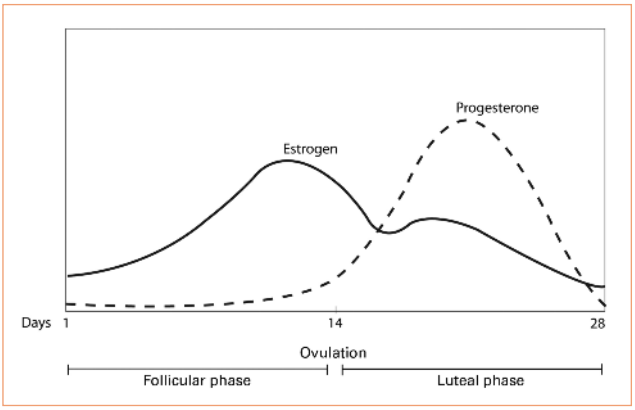

Figure 2. Hormone Fluctuations During the Menstrual Cycle

Estrogen and progesterone concentrations rhythmically change across the menstrual cycle.[20,21] Changes in both the concentration and relative ratio to each other may play a role in pain.

Several theories have been proposed throughout the literature to account for the antinociceptive response of pregnancy. One theory includes stimulation of the internal sensory system of the uterus. Researchers have found that cutting the hypogastric nerve (the major uterine afferent) significantly attenuates the analgesia of pregnancy.[33] It has also been suggested that a synergistic interaction between spinal kappa and delta opioid receptors is augmented during pregnancy.[23] Similarly, an interaction of hormones on descending noradrenergic pathways (originating from the pons) terminating on spinal alpha$_2$-adrenergic receptors may have a role in the antinociceptive response of pregnancy.[34] Most likely, it is a synergism of multiple organ systems collaborating to create an environment enhancing a woman's ability to endure the bodily changes and pains of pregnancy and parturition.

Gender Differences in Opioid Analgesia

Gender differences are not limited to pain perception, but may also extend to the biological response to analgesics. It is not surprising to see differences between genders in their response to opioid-induced analgesia. There are many genetic differences between genders. Genes encode not only gonadal steroid hormone systems (which can influence opioid systems as described earlier), but may also encode many biologic factors that directly influence opioid analgesia (ie, opioid receptor expression and enzymes responsible for their metabolism).[8] Genetic research is ongoing, and someday we may more fully understand the roles of these small molecules between genders.

A multiplicity of research involving sex differences in response to analgesics has been carried out in nonhuman species to negate the effects of gender-role expecta-

tions.[35,36] Cicero et al[37] defeminized female rats by administering testosterone on the first and second postnatal days. Krzanowska et al[38] demasculinized male rats via orchiodectomy on the first and second postnatal days. In both studies, the neonatally manipulated rats were then tested for sensitivity to morphine-induced analgesia 3 months later in the adult stage. Some conclusions can be made from these laboratory studies. The neonatally androgenized females had greater morphine sensitivity than the female control group and equivalent sensitivity compared with normal adult males, whereas the neonatally orchidectomized males had lesser morphine sensitivity than the male neonatal control group but equivalent sensitivity compared with normal adult females.[37,38] In other words, the neonatal gonadal hormone manipulations eliminated the apparent differences in sensitivity to morphine analgesia normally observed in adult rats. These studies suggest that the neural substrates involved in opioid analgesia are sensitive to gonadal steroid hormones during development. However, the suitability of nonhuman species to human application is always suspect.

Differences between the genders have likewise been noted. Zubieta et al[25] found that mu receptors in the healthy female brain are activated differently from those in the healthy male brain. The authors, using PET, studied brain activity in women and men in response to a painful stimulus and in the presences of carfentanil, a mu-specific opioid agonist. The authors injected a hypertonic saline solution into the masseter muscle with volume adjusted such that the women's pain response was similar to men's. The results demonstrated that at baseline, women showed greater mu-opioid binding in the amygdala, an area that is involved in emotions, as compared with men. A different effect was noted in response to the painful stimulus. The male test subjects had a larger magnitude of mu-opioid activation than did female test subjects in the anterior thalamus, ventral basal ganglia, and amygdala during the concomitant painful stimulus. These data demonstrate that at equivalent levels of pain intensity, men and women differ in the magnitude and response of the mu-opioid system in distinct brain nuclei.

Gender Differences in Postoperative Pain

Multiple research investigations have identified differences between genders and postoperative pain.[24,39-43] In general, findings have indicated that female patients are more susceptible to pain in the immediate postoperative period. Cepeda and Carr[24] conducted a prospective cohort study involving 700 patients in the postanesthesia care unit who had undergone general anesthesia for various surgical procedures. The aim of the study was to compare gender differences in pain scores and the dose of morphine to achieve relief of pain as noted by a visual analog score of less than 30 on a 0 to 100 scale. After adjusting for the type of surgery and age, the authors found higher levels of pain intensity and a 30% greater morphine requirement to achieve a similar degree of pain relief among female patients. Comparable findings demonstrating lower thresholds and higher intensities of pain have likewise been reported in the literature in studies of male and female patients having similar surgical procedures, including laparoscopic cholecystectomy,[43] thoracotomy,[42] and arthroscopy.[41]

Gender Influence on Minimum Alveolar Concentration

It is unclear whether gender influences the effects of anesthetic requirements between males and nonpregnant females. Current evidence suggests that the minimum alveolar concentration (MAC) of inhaled anesthetics may possibly be influenced by gender. Greif et al[44] found that females required higher desflurane concentrations compared with males to prevent movement to noxious electrical stimulation. However, other studies have been unable to identify differences between genders when considering desflurane, diethyl ether, halothane, methoxyflurane, and sevoflurane.[45] Further research is indicated to clarify gender differences in MAC between males and nonpregnant females.

Pregnancy has long been recognized for its modulation of anesthetic requirements. The hormonal changes associated with pregnancy are known to increase the potency (ie, decrease the MAC) of the inhaled anesthetics.[46-48] This effect is likely due to increased levels of progesterone.[46] Interestingly, progesterone has also been found to induce sleep in humans.[49] One explanation for the decreased MAC of the inhaled anesthetics in the presence of progesterone may be an alteration in the plasticity of the γ-hydroxybutyric acid$_A$ ($GABA_A$) receptor complex.[50] The $GABA_A$ receptor complex is one of many postulated sites of action of inhaled anesthetics.[50,51]

Conclusion and a Look to the Future

Pain difference between genders is an exciting area of study that has recently received much scientific scrutiny. Although further research in this area is expected, we can see the clinical relevance of gender differences in response to pain. As we ask our female patients routine questions about their last menstrual period, we may now be more attuned to possible alterations in opioid requirements. It is essential that providers understand and anticipate gender as a factor in pain response and opioid requirements. Continued research in this area may someday provide gender-specific pharmacogenotyping, a process in which medications can be tailored to precise gender requirements at the molecular level.

REFERENCES

1. Lamberg L. Venus orbits closer to pain than Mars: Rx for one sex may not benefit the other. *JAMA.* 1998;280(2):120-124.
2. Ashkenazi A, Silberstein S. Menstrual migraine: a review of hormonal

causes, prophylaxis and treatment. *Expert Opin Pharmacother.* 2007; 8(11):1605-1613.
3. LeResche L, Mancl L, Sherman J, Gandara B, Dwarkin S. Changes in temporomandibular pain and other symptoms across the menstrual cycle. *Pain.* 2003;106(3):253-261.
4. Lee O, Mayer E, Schmulson M, Chang L, Naliboff B. Gender-related differences in IBS symptoms. *Am J Gastroenterol.* 2001;96(7):2184-2193.
5. LeResche L. Epidemiologic perspectives on sex differences in pain. In: Fillingim R, ed. *Sex, Gender and Pain.* Seattle, WA: IASP Press; 2000: 233-250.
6. Unruh A. Gender variations in clinical pain experience. *Pain.* 1996; 65(2-3):123-167.
7. Craft R. Sex differences in opioid analgesia: "from mouse to man." *Clin J Pain.* 2003;19(3):175-186.
8. Craft RM, Mogil JS, Aloisi AM. Sex differences in pain and analgesia: the role of gonadal hormones. *Eur J Pain.* 2004;8(5):397-411.
9. Berkley KJ. Sex differences in pain. *Behav Brain Sci.* 1997;20(3):371-380.
10. Merkatz RB, Temple R, Sobel S, Feiden K, Kessler DA. Women in clinical trials of new drugs: a change in food and drug administration policy. *N Engl J Med.* 1993;329(4):292-296.
11. Fearon I, McGrath PJ, Achat H. "Booboos": the study of everyday pain among young children. *Pain.* 1996;68(1):55-62.
12. Keogh E, Hamid R, Hamid S, Ellery D. Investigating the effect of anxiety sensitivity, gender and negative interpretative bias on the perception of chest pain. *Pain.* 2004;111(1-2):209-217.
13. Rollman GB, Abdel-Shaheed J, Gillespie JM, Jones KS. Does past pain influence current pain: biological and psychosocial models of sex differences. *Eur J Pain.* 2004;8(5):427-433.
14. Fillingim RB, Ness TJ. Sex-related hormonal influences on pain and analgesic responses. *Neurosci Biobehav Rev.* 2000;24(4):485-501.
15. Paulson PE, Minoshima S, Morrow TJ, Casey KL. Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. *Pain.* 1998;76(1-2):223-229.
16. Derbyshire SW, Nichols TE, Firestone L, Townsend DW, Jones A. Gender differences in patterns of cerebral activation during equal experience of painful laser stimulation. *J Pain.* 2002;3(5):401-411.
17. Ellermeier W, Westphal W. Gender differences in pain ratings and pupil reactions to painful pressure stimuli. *Pain.* 1995;61(3):435-439.
18. Gintzler AR. Endorphin-mediated increases in pain threshold during pregnancy. *Science.* 1980;210(4466):193-195.
19. Kappius RE, Goolkasian P. Group and menstrual phase effect in reported headaches among college students. *Headache.* 1987;27(9):491-494.
20. Staley K, Scharfman H. A woman's prerogative. *Nat Neurosci.* 2005; 8(6):697-699.
21. Kasper D, ed. *Harrison's Principles of Internal Medicine.* 16th ed. New York, NY: McGraw-Hill Companies, Inc; 2006.
22. Wang X, Traub RJ, Murphy AZ. Persistent pain model reveals sex difference in morphine potency. *Am J Physiol Regul Integr Comp Physiol.* 2006;291(2):R300-R306.
23. Dawson-Basoa M, Gintzler AR. Gestational and ovarian sex steroid antinociception: synergy between spinal kappa and delta opioid systems. *Brain Res.* 1998;794(1):61-67.
24. Cepeda MS, Carr DB. Women experience more pain and require more morphine than men to achieve a similar degree of analgesia. *Anesth Analg.* 2003;97(5):1464-1468.
25. Zubieta J, Smith YR, Bueller JA, et al. Mu-opioid receptor–mediated antinociceptive responses differ in men and women. *J Neurosci.* 2002;22(12):5100-5107.
26. Ji Y, Murphy AZ, Traub RJ. Sex differences in morphine-induced analgesia of visceral pain are supraspinally and peripherally mediated. *Am J Physiol Regul Integr Comp Physiol.* 2006;291(2):R307-R314.
27. Kelly M, Qiu J, Rønnekleiv OK. Estrogen modulation of G-protein–coupled receptor activation of potassium channels in the central nervous system. *Ann N Y Acad Sci.* December 2003;1007:6-16.
28. Gingerich S, Krukoff TL. Estrogen in the paraventricular nucleus attenuates L-glutamate–induced increases in mean arterial pressure through receptor β and NO. *Hypertension.* 2006;48(6):1130-1136.
29. Eckersell CB, Popper P, Micevych PE. Estrogen-induced alteration of mu-opioid receptor immunoreactivity in the medial preoptic nucleus and medial amygdala. *J Neurosci.* 1998;18(10):3967-3976.
30. Stening K, Eriksson O, Wahren L, Berg G, Hammar M, Blomqvist A. Pain sensations to the cold pressor test in normally menstruating women: comparison with men and relation to menstrual phase and serum sex steroid levels. *Am J Physiol Regul Integr Comp Physiol.* 2007;293(4):R1711-R1716.
31. Becker JB, Arnold AP, Berkley KJ, et al. Strategies and methods for research on sex differences in brain and behavior. *Endocrinology.* 2005;146(4):1650-1673.
32. Sherman JJ, LeResche L. Does experimental pain response vary across the menstrual cycle? a methodological review. *Am J Physiol Regul Integr Comp Physiol.* 2006;291(2):R245-R256.
33. Gintzler AR, Peters LC, Komisaruk BR. Attenuation of pregnancy-induced analgesia by hypogastric neurectomy in rats. *Brain Res.* 1983;277(1):186-188.
34. Liu NJ, Gintzler AR. Gestational and ovarian sex steroid antinociception: relevance of uterine afferent and spinal α_2-noradrenergic activity. *Pain.* 1999;83(2):359-368.
35. Kallai I, Barke A, Voss U. The effects of experimenter characteristics on pain reports in women and men. *Pain.* 2004;112(1-2):142-147.
36. Criste A. Gender and pain. *AANA J.* 2002;70(6):475-480.
37. Cicero TJ, Nock B, O'Connor L, Meyer ER. Role of steroids in sex differences in morphine-induced analgesia: activational and organizational effects. *J Pharmacol Exp Ther.* 2002;300(2):695-701.
38. Krzanowska EK, Ogawa S, Pfaff DW, Bodnar RJ. Reversal of sex differences in morphine analgesia elicited from the ventrolateral periaqueductal gray in rates by neonatal hormone manipulations. *Brain Res.* 2002;929(1):1-9.
39. Guth AA, Hiotis K, Rockman C. Influence of gender on surgical outcomes: does gender really matter? *J Am Coll Surg.* 2005;200(3):440-455.
40. Logan DE, Rose JB. Gender differences in post-operative pain and patient controlled analgesia use among adolescent surgical patients. *Pain.* 2004;109(3):481-487.
41. Rosseland LA, Stubhaug A. Gender is a confounding factor in pain trials: women report more pain than men after arthroscopic surgery. *Pain.* 2004;112(3):248-253.
42. Ochroch EA, Gottschalk A, Troxel AB, Farrar JT. Women suffer more short and long-term pain than men after major thoracotomy. Clin J *Pain.* 2006;22(5):491-498.
43. Uchiyama K, Kawai M, Tani M, Ueno M, Hama T, Yamaue H. Gender differences in postoperative pain after laparoscopic cholecystectomy. *Surg Endosc.* 2006;20(3):448-451.
44. Greif R, Laciny S, Mokhtarani M, et al. Transcutaneous electrical stimulation of an auricular acupuncture point decreases anesthetic requirement. *Anesthesiology.* 2002;96(2):306-312.
45. Eger EI II, Laster MJ, Gregory GA, Katoh T, Sonner JM. Women appear to have the same minimum alveolar concentration as men: a retrospective study. *Anesthesiology.* 2003;99(5):1059-1061.
46. Palahniuk RJ, Shnider SM, Eger EI II. Pregnancy decreases the requirement for inhaled anesthetic agents. *Anesthesiology.* 1974; 41(1):82-83.
47. Chan MT, Mainland P, Gin T. Minimum alveolar concentration of halothane and enflurane are decreased in early pregnancy. *Anesthesiology.* 1996;85(4):782-786.
48. Gin T, Chan MT. Decreased minimum alveolar concentration of isoflurane in pregnant humans. *Anesthesiology.* 1994;81(4):829-832.
49. Merryman W, Boiman R, Barnes L, Rothchild I. Progesterone anesthesia in human subjects. *J Clin Endocrinol Metab.* 1954;14(12):1567-1569.
50. Lovick TA, Griffiths JL, Dunn SM, Martin IL. Changes in GABA(A) receptor subunit expression in the midbrain during the oestrous cycle in wistar rats. *Neuroscience.* 2005;131(2):397-405.
51. Kier LB. A theory of inhaled anesthetic action by disruption of ligand diffusion chreodes. *AANA J.* 2003;71(6):422-428.

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