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.
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. 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). The most significant gender differences are noted in the autonomic nervous system–linked comorbid medical conditions such as migraine, temporomandibular disorders, irritable bowel syndromes, and rheumatoid arthritis and fibromyalgia. 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.
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. 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. 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. 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. 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. 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. 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.

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. 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. This study associated differences in pain perception with differences in PET scan processing of brain nociception.

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, 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 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 naloxone. \(^{29}\) 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 pronounced. 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.

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 alpha2-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). \(^{35}\) 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-
Cepeda and Carr conducted a prospective cohort study involving 70,000 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, thoracotomy, and arthroscopy.

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. 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. 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 (i.e., decrease the MAC) of the inhaled anesthetics. This effect is likely due to increased levels of progesterone. Interestingly, progesterone has also been found to induce sleep in humans. 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 (GABA) receptor complex. The GABA receptor complex is one of many postulated sites of action of inhaled anesthetics.

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


