IN THEIR EXCELLENT RECENT REVIEW ENTITLED, “WOMEN’S SLEEP IN HEALTH AND DISEASE,” DZAJA, PORKKA-HEISKANEN, AND THEIR COLLEAGUES make the point that, while a large amount of information about sleep has been obtained over the past 50 years, “…there are numerous areas of considerable ignorance. One of these concerns, the particularities of sleep in women.” The lack of basic research on the effects of sex (i.e., the genetic make-up of the individual, not the act itself) on sleep is of particular concern given our almost total lack of understanding on the importance of women’s sleep in health and disease. The findings of Zhang and Wing in a paper in this issue of SLEEP, reporting on a meta-analysis approach to investigate sex differences in the risk of insomnia, supports the clear need to develop a better understanding of how sex influences sleep. The meta-analysis involved 31 published epidemiologic studies and more than 1.25 million subjects. The conclusion: as has been found in most epidemiologic studies, there is an increased risk (a risk ratio of 1.41) for insomnia in females, as compared with males. While it is likely that many cultural, sociologic, socioeconomic, and other environmental factors could underlie some of the sex-based differences in insomnia, the clear evidence that the reproductive-hormone environment can influence various sleep-wake parameters suggests a role, as well as for the genome and other biologic factors on women’s sleep in health and disease.

Although there are a number of reports indicating that sleep in humans is greatly influenced by sex, the mechanisms underlying these differences remain poorly understood. Given the potential importance of sex-specific differences in normal and pathophysiologic sleep-wake states, there is a clear need to develop animal models to determine the mechanisms responsible for the effects of sex on sleep. Surprisingly, few studies directly examining the influence of sex on sleep and wakefulness in animal models have been reported.

The influence of reproductive neuroendocrine and/or endocrine processes on sleep could be occurring at a number of developmental and/or age-related steps. In rodents, the sex-hormone environment around the time of birth plays a major role in “organizing” the neural circuitry responsible for generating a variety of sex-influenced behaviors later in life, including sex-specific mating behavior, aggression, arousal, and stress responses. Thus, the “activation” of many sex-related behaviors by the steroid-hormone environment during later pubertal and adult life is dependent on the “organizational” effects of the sex steroids during the perinatal environment. To date, however, no attempts have been made to examine the role of early steroid-based organizational events in mediating sex-specific effects on the sleep-wake cycle.

Puberty is another time when major changes or differences arise in the reproductive-hormone environment. In humans, sex-related differences in sleep patterns have been observed during early (10-13 years old) and late (13-14 years old) adolescence, although there is little information regarding the cultural versus biologic bases for these differences. Nevertheless, a number of studies have been carried out, particularly by Carskadon and her colleagues, to indicate that both the homeostatic and circadian regulation of sleep are influenced by pubertal events. For example, a recent study found that sleep intensity, as measured by non-rapid eye movement (NREM) delta activity, was stable between 9 and 12 years of age in male subjects, whereas NREM delta activity decreased in female subjects during this time period. The authors interpreted these results to indicate that the maturation of the change in NREM delta activity to the adult-like condition occurs at an earlier age in females than in males.

The reproductive-hormone environment in adults is characterized by stable levels of the gonadotropins and testosterone in the male and by the presence of regular cyclicity in the hypothalamic-pituitary-gonadal axis of the female. Sleep patterns differ across the menstrual or estrous cycle, as well as during pregnancy or following menopause as the levels of estrogen and/or progesterone are altered. In middle to old age, women have consistently been shown to have greater amounts of NREM (stages 3 & 4) sleep and NREM delta activity, as compared with age-matched men. In addition, major sex differences in the nocturnal profiles of growth hormone and prolactin and their relationship to sleep electroencephalogram variables are present in healthy older adults, and, when normalized, delta activity in older women is lower than in older men. Estrogen replacement therapy results in improved sleep in menopausal women who do not report symptoms such as hot flashes, and estrogen replacement therapy increases slow-wave activity in postmenopausal women. In men, aging brings about a gradual decline in testosterone production, often referred to as the andropause, and sleep disturbances are a common complaint in men receiving anti-testosterone treatment for prostate cancer, as well as in women receiving anti-estrogen treatment in response to breast cancer. Taken together, these data indicate that changes in sleep that occur throughout the lifetime depend on interactions between age and sex.

Given that (1) the sleep-wake cycle undergoes profound changes from birth to advanced age, (2) the reproductive-hormone environment also undergoes profound changes from birth to advanced age, and (3) reproductive hormones can influence
sleep, it is surprising that the influence of sex and the importance of sex for normal and pathologic sleep-wake states is not more of a major focus of both clinical and basic research.

In addition to any direct effects of the reproductive-hormone environment on sleep, the effects could be indirect because the hormonal environment may alter the response to environmental factors (i.e., response to stress), which influence sleep. Regardless of direct or indirect effects, studies such as the one from Zhang and Wing emphasize that sleep researchers need to make greater efforts to understand the effects of sex on human sleep and its pathophysiologic implications. In addition, animal models are needed to elucidate the molecular, cellular, and physiologic mechanisms by which the sex-related neuroendocrine environment influences the sleep-wake cycle. The latter such studies would provide information that could be translated from the bench to the bedside as sleep researchers address important questions regarding the influence of the reproductive sex-hormone environment on the human sleep-wake cycle. It is important to develop a better understanding of how sex affects sleep in adults and, based on Mary Carskadon’s work, even in children.

REFERENCES