# HORMONAL FACTORS

### What We Know

- 1. A consensus is emerging from the literature that the likelihood of suffering an ACL injury is not evenly distributed across the menstrual cycle; instead, the risk of suffering an ACL disruption is greater during the preovulatory phase of the menstrual cycle than in the postovulatory phase.<sup>1–5</sup> During the preovulatory phase, hormone levels are changing dramatically, falling to their nadirs with the onset of menses and once again rising rapidly near ovulation.
- 2. Evidence exists for sex hormone receptors (estrogen, testosterone, and relaxin) on the human ACL.<sup>6–10</sup>
- 3. Evidence exists for sex hormone receptors (estrogen, testosterone) on skeletal muscle.<sup>11–13</sup>
- 4. Large individual variations in female hormone profiles should be appreciated in study designs.<sup>14</sup>
- 5. Consistent with individual variability in hormone profiles, the magnitude of change in laxity (ie, anterior knee laxity, genu recurvatum) that females experience across the menstrual cycle varies substantially<sup>15</sup> (abstract 19).
- 6. Because of the individual variability in hormone profiles across the menstrual cycle, a single measurement within a single phase (even with hormonal

confirmation) is not adequate to accurately characterize the same hormone profile or time point in a particular phase of the menstrual cycle for all females.

- 7. The mechanical and molecular properties of the ACL are likely influenced not only by estrogen but by the interaction of several sex hormones, secondary messengers, remodeling proteins, and mechanical stresses. 7,10,14,16-18
- A time-dependent effect exists for sex hormones and other remodeling agents to influence a change in ACL tissue characteristics.<sup>10,14</sup>
- 9. Some evidence in animal models suggests interactions among mechanical stress, hormones, and altered ACL structure and metabolism.<sup>19–21</sup>

## What We Don't Know

- 1. What is the underlying mechanism for the increased likelihood of ACL injury in the preovulatory phase?
- 2. How do ACL injury rates vary in females who are eumenorrheic or oligomenorrheic or using oral con-traceptives?
- 3. What are the effects of sex hormones on ACL structure, metabolism, and mechanical properties? The influence of hormones on ACL biology has been examined in a variety of animal models<sup>21–30</sup> and

relatively few human studies,<sup>18,31</sup> but a consensus is lacking due to variations in study designs and the varieties of species examined.

- 4. What is the role of hormones on skeletal muscle structure and function in controlling dynamic motion? What, if any, changes occur in neuromuscular and biomechanical risk factors across the menstrual cycle? Although previous authors have suggested that cyclical changes in neuromuscular and biomechanical control may be negligible,<sup>32–34</sup> these results may be incomplete due to the individual variations in hormone profiles (see What We Know, items 3–5).
- 5. Does the rate of increase or time duration of amplitude peaks in hormone fluctuations play a role in soft tissue changes?
- 6. For those females who experience changes in knee laxity across the menstrual cycle, what are the clinical implications of these changes on weight-bearing knee joint stability and neuromechanics?
- 7. What are the interactions among mechanical stress on the ACL, hormone profiles, and altered ACL structure and metabolism in physically active females?

#### Where We Go From Here

- 1. We must continue to consider the interactive effect of all relevant hormones on soft tissue structures and ACL injury risk.
- 2. The mechanisms by which sex hormones may explain sexspecific differences in ACL structure, metabolism, and mechanical properties that have been observed (also see Anatomical and Structural Factors) should be defined.
- 3. More studies using research designs relevant to the healthy, physically active female are needed to examine hormonal effects on ACL structural, metabolic, and mechanical properties.
- 4. When examining hormonal influences on knee joint function and ACL injury risk, females using oral contraceptives and those with irregular menstrual cycles (amenorrhea and oligomenorrhea) should also be investigated. The type of contraceptive should be documented and both the endogenous and exogenous levels of sex hormones evaluated.
- 5. Future studies of hormone risk factors should focus more on individual results, rather than mean values, as much variability exists in individual menstrual cycle characteristics.
- 6. Improved methods of measuring individual hormone profiles to better assess the complex roles of hormones in soft tissue changes should be developed. We need to verify phases of the cycle with actual hormone measures and consider all relevant hormones, including estrogen, progesterone, and possibly others. To confirm that the desired time in the cycle or a particular phase is truly captured in future study designs, hormone samples should be taken over multiple days rather than measured at a single time point.

- 7. When making female-to-male comparisons, factors should be assessed during the early follicular phase, when hormone levels are at their nadirs (preferably 3–7 days postmenses) to decrease the potential for cyclic hormonal fluctuations to confound the anatomical, neuromuscular, and biomechanical outcomes of interest.
- 8. The interaction among hormones, mechanical loading, and ACL mechanical properties in the physically active female should be examined.

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