Chapter 2
Hormonal Influence on the Neuromusculoskeletal System in Pregnancy

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Background of Hormones to Be Discussed

Estrogen

The most potent estrogen produced in the human body is 17 beta-estradiol (estradiol) [1]. In the nonpregnant female, estrogen is produced predominantly by the ovaries and it peaks just prior to ovulation [2] (Fig. 2.1). During pregnancy, estrogen is produced primarily from the placenta and its role is to promote fetal growth and well-being [3–5]. Estradiol has been shown to dramatically increase throughout pregnancy (Fig. 2.2) [6] and to decrease at time of parturition and during lactation [7]. Decreased estrogen levels during lactation seem to result from prolactin-mediated suppression of gonadotropin-releasing hormone, luteinizing hormone, follicular-stimulating hormone but not changes in parathyroid hormone (PTH), or 1,25-dihydroxyvitamin D [7, 8]. Estrogen modulates several neuromusculoskeletal tissues, including bone, cartilage, ligament, myotendinous unit, and the nervous system (Fig. 2.3).

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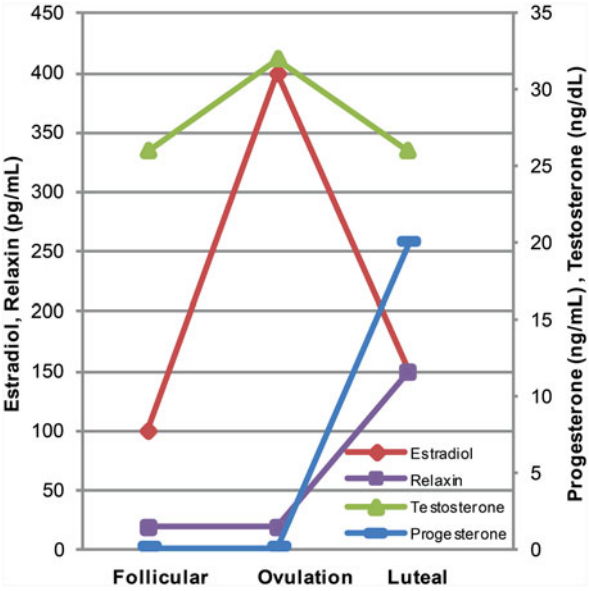

Fig. 2.1 Typical fluctuations of hormones across the menstrual cycle. There is significant intra-person variation in the concentrations of the hormones, so this graph represents the upper level of serum concentrations of estrogen, progesterone, testosterone, and relaxin (Data from: Ahrens, Annals of Epidemiology, 2014)

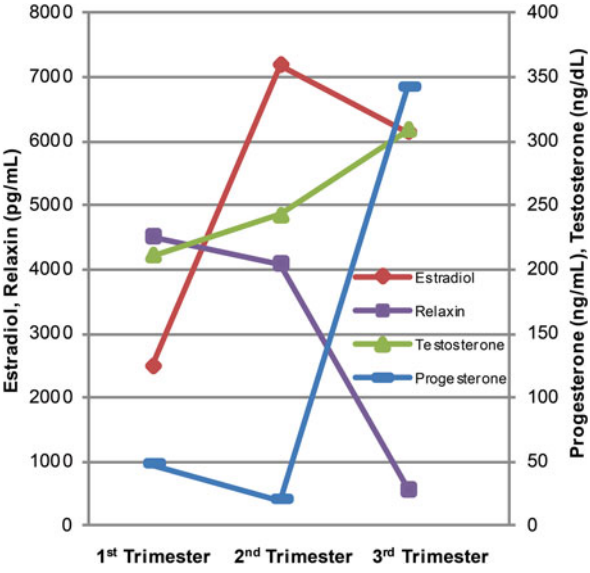

Fig. 2.2 Typical hormonal changes throughout pregnancy. There is significant intra-person variation in the concentrations of the hormones, so this graph represents the upper level of serum concentrations of estrogen, progesterone, testosterone, and relaxin (Data from: Abbassi-Ghanavati, Mina; Greer, Laura; Cunningham, F. Obstetrics & Gynecology. 114(6):1326-1331, December 2009; Vollestaad Man Ther 2012; Karger 1998; Kristiansson AJ OB Gyn 1996.)

Fig. 2.3 Neuromusculoskeletal tissues affected by estrogen

Progesterone

In nonpregnant women, progesterone is primarily produced by the corpus luteum during the luteal phase of the menstrual cycle [2] (Fig. 2.1). In the pregnant female, progesterone is initially produced by the corpus luteum, but after the first trimester, it is predominantly produced by the placenta [9]. Progesterone levels peak during the third trimester of pregnancy [10] (Fig. 2.2). Progesterone is essential for implantation and the maintenance of pregnancy and is often used pharmacologically to prevent miscarriage and to treat preterm labor [11]. Progesterone's role in the neuromusculoskeletal system is also through modulation of bone, cartilage, ligament, myotendinous unit, and the nervous system (Fig. 2.4).

Relaxin

Relaxin initially came into clinical and research interest in the 1920s when Hisaw found that the blood of pregnant guinea pigs and rabbits contained a factor that stimulated growth and softened the connective tissue that joined the pubic bones [12]. Thereafter, there was a period of uncertainty regarding relaxin's role as it was found that estrogen and progesterone could also relax the pubic bones [12]. However, the role of relaxin in pregnancy and in the musculoskeletal system has continued to receive much attention through animal as well as human studies [12].

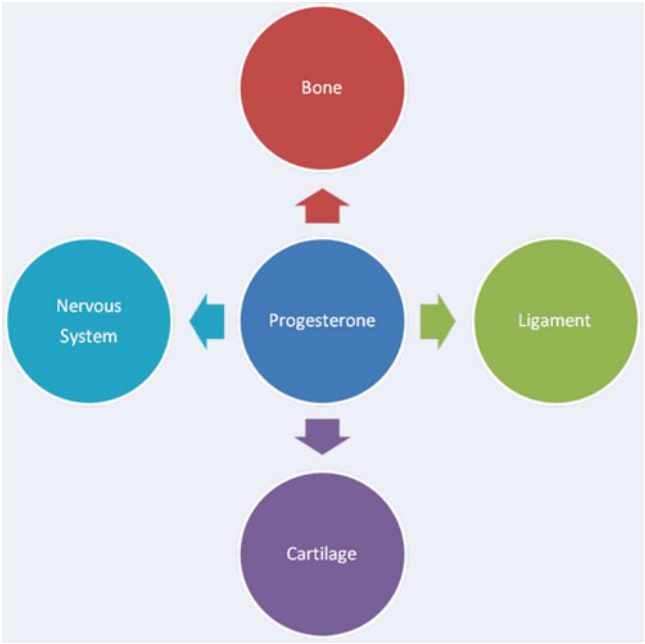

Fig. 2.4 Neuromusculoskeletal tissues affected by progesterone

Structurally, relaxin is related to insulin and insulin-like growth factor and is secreted from the corpus luteum and the placenta [13, 14]. In nonpregnant women, relaxin levels have been shown to increase during the luteal phase of the menstrual cycle [15] (Fig. 2.1). In pregnant women, relaxin levels have been found to increase early in the first trimester of pregnancy, peaking around the twelfth week of pregnancy [12, 16–18] (Fig. 2.2). Thereafter, relaxin levels steadily decrease to around 50 % of peak levels until approximately the 17th–24th week of pregnancy, after which the concentration stabilizes for the remainder of pregnancy [12, 16, 19]. Unlike other mammals, such as pigs and rats, there is no pre-labor relaxin surge in humans [20] and human relaxin levels are undetectable in the first few days postpartum [14]. In pregnant women, relaxin acts to remodel pelvic connective tissue and to inhibit uterine contractility [21]. In the neuromusculoskeletal system, relaxin appears to modulate a variety of tissues, including cartilage, ligament, bone, and the myotendinous unit (Fig. 2.5).

Testosterone/Androstenedione

In females, the ovaries and the adrenal glands produce testosterone. In nonpregnant women, testosterone levels peak during the ovulatory phase of the menstrual cycle [2] (Fig. 2.1) and in pregnant women, levels increase throughout pregnancy [22, 23] (Fig. 2.2). Levels become significantly greater than in nonpregnant females starting

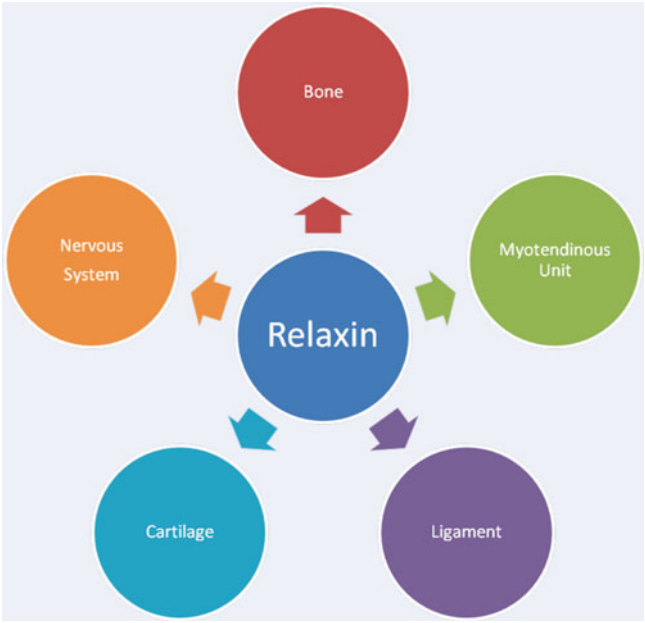

Fig. 2.5 Neuromusculoskeletal tissues affected by relaxin

during weeks 13–16 [23]. Androstenedione also increases during pregnancy but is only significantly elevated during weeks 13–16 and weeks 37–40 [22]. Up until week 28, the rise in free testosterone is thought to be due to a decrease in metabolic clearance and after week 28, production rate of free testosterone increases [22]. Testosterone and androstenedione reach their peak levels at time of parturition [23]. In the first few days after delivery, the levels decrease to those of nonpregnant females [23]. Testosterone modulates the neuromusculoskeletal system at the level of cartilage, ligament, bone, and the myotendinous unit (Fig. 2.6).

Prolactin

Prolactin is produced from the pituitary gland and plays a role in maintaining the corpus luteum during pregnancy and in synthesizing milk during lactation [24]. Prolactin begins to rise during the eighth week of pregnancy, peaks at ten times normal levels, and remains elevated in lactating women [25, 26]. Prolactin concentration depends on lactation status with higher levels of prolactin associated with longer duration of lactation [6, 25, 26].

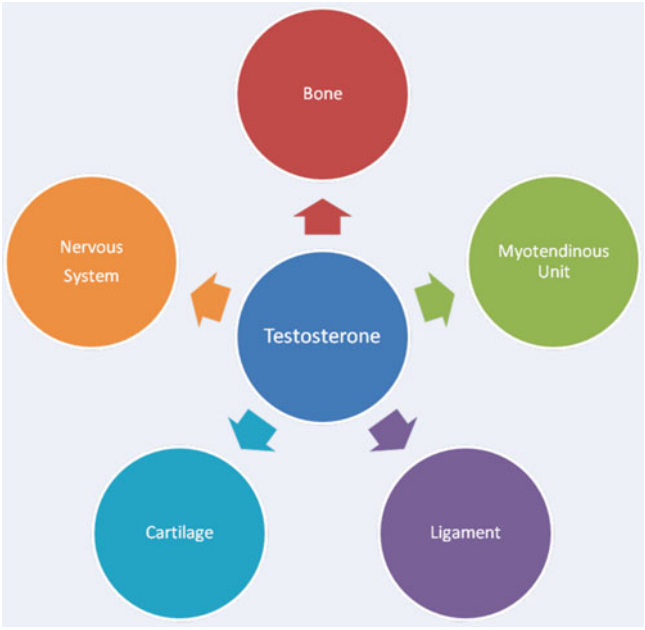

Fig. 2.6 Neuromusculoskeletal tissues affected by testosterone

Parathyroid Hormone

PTH is released from the parathyroid glands and its main role during pregnancy is to maintain calcium homeostasis [27]. PTH has been shown to decrease during mid-pregnancy and rise in late pregnancy in some studies [28]; however, others advocate levels are unchanged compared with those of nonpregnant females [6, 8]. Additionally, there is no consensus regarding PTH concentration in the postpartum phase or in lactating women, as levels have been shown to increase, decrease, or remain unchanged compared to nonpregnant controls [6, 29].

Parathyroid Hormone-Related Peptide

Parathyroid hormone-related peptide (PTHrP) is produced by many maternal tissues, including the placenta, uterus, lactating mammary gland, and fetal tissues during pregnancy. The dominant source is unclear [8, 30]. PTHrP concentration increases throughout pregnancy and continues to increase postpartum [31]. Particularly during early lactation, PTHrP levels increase and are inversely related to PTH concentration [29]. Elevated PTHrP levels have been found to be associated with breastfeeding status, elevated prolactin levels, and lower estradiol levels [7].

Vitamin D

Vitamin D is a secosteroid prohormone that is structurally similar to sex steroid hormones [9]. In addition to its role in regulating calcium homeostasis, animal studies suggest vitamin D is involved in regulating reproductive processes by influencing estrogen synthesis [9]. Also, low vitamin D levels during pregnancy may be associated with increased risk of various adverse pregnancy outcomes, including preeclampsia, gestational diabetes, preterm birth, and small for gestational age infants [32]. During pregnancy, serum 1,25-dihydroxyvitamin D increases early in gestation prior to the increase of PTH [6, 8, 28, 29] and is hypothesized to be predominantly placental in origin [29]. Increasing serum 1,25-dihydroxyvitamin D levels have been shown to be parallel with increasing calcium absorption during pregnancy [29]. With respect to other hormones of pregnancy, the literature has shown no significant association between serum 1,25-dihydroxyvitamin D levels with estradiol, progesterone, 17 hydroxyprogesterone, testosterone, androstenedione, insulin-like growth factor 1 (IGF-1), or PTH during early pregnancy [9, 33]. Nor was there any correlation between 1,25-dihydroxyvitamin D levels and estrogen, prolactin, or PTH levels during the remainder of pregnancy [6]. Postpartum, 1,25-dihydroxyvitamin D levels are similar to nonpregnant women regardless of lactation status [6, 29].

Insulin-Like Growth Factor 1

IGF-1 is produced from various cells and plays a role in promoting cell division and growth in various tissues including uterine leiomyomata [34, 35] and mammary tissue [36]. IGF-1 is suppressed in early pregnancy but peaks in the third trimester [6, 37, 38]. Postpartum, IGF-1 levels are suppressed and are lower in women who lactated for more than 4 months compared to controls and those who lactated less than 4 months [6].

Sex Hormone-Binding Globulin

Sex hormone-binding globulin (SHBG) is a glycoprotein with a strong affinity for estradiol. In studies of nonpregnant, menstruating women, SHBG has been found to increase when estradiol increases near ovulation and is thought to help maintain physiologic balance with progesterone [39]. In pregnant women, SHBG levels peak at parturition and then have a rapid decline in the postpartum period [40].

Bone

The key hormones that may affect bone metabolism in pregnant and lactating females include relaxin, estrogen, progesterone, testosterone, PTHrP, and PTH. Relaxin, estrogen, and various growth factors orchestrate the bone remodeling process [13].

Functional progesterone and testosterone receptors of osteoblast and osteoclast lineage, and estrogen receptors of osteoblast lineage exist in human bone cells [41, 42]. Estrogen has indirect and direct effects on bone metabolism and helps maintain a balance between osteoblastic and osteoclastic activity to overall reduce the rate of bone loss [41, 42]. The role of progesterone in maintaining bone health is less well understood than that of estrogen and seems to facilitate estrogen's effects on the skeletal system [42]. For instance, estradiol has been shown to stimulate osteoblast proliferation when used in combination with a pure progesterone [41]. Testosterone stimulates osteoblast proliferation, enhances osteoclast differentiation, and has been shown to have synergistic effects of improving bone mass when used pharmacologically with estrogen [42]. Relaxin is primarily an osteoclast-activating factor that increases bone resorption [13]. However, there is no evidence that higher concentrations of relaxin during pregnancy have any detrimental effects on bone density. On the other hand, there is some evidence to suggest that pregnant women with higher levels of estrogen and relaxin may correlate with increased prevalence of congenital hip dysplasia in neonates [13].

It has been suggested that pregnancy-related bone loss is primarily attributable to changes in estrogen status rather than resulting directly from increased calcium demands during pregnancy or lactation [29, 43]. Elevated estrogen during pregnancy protects against skeletal bone loss [43]. Some advocate that estrogen induces a buildup of a calcium "safety deposit" into the female skeleton from which calcium can be released into the bloodstream to serve the needs of the fetus and newborn during pregnancy and lactation [43].

PTHrP has been shown to increase 1,25-dihydroxyvitamin D and suppress PTH during pregnancy. Collectively, this may help regulate placental calcium transport and protect the maternal bone during pregnancy [8]. Specifically, PTHrP binds to the PTH receptor and stimulates renal calcium absorption [29] and the terminal fragments of PTHrP have been shown to inhibit osteoclast-induced bone resorption [8]. PTHrP is positively associated with increased levels of bone turnover markers, including osteocalcin and type 1 collagen N-telopeptide [7].

The high bone turnover rate during lactation may be related to the combination of low estradiol, high prolactin, high PTH and possibly high PTHrP levels [6, 29]. Changes in vitamin D levels during pregnancy have not been shown to be associated with bone loss during lactation [29]. Upon the resumption of menstruation with cyclic secretions of estrogen, bone mineral density is regained despite continued lactation [43].

Prolactin and PTHrP levels have been shown to be negatively associated with the rate of spine and femoral neck bone mineral density changes in postpartum women aged 20–40 years [7], even after accounting for breastfeeding status, other hormone levels, physical activity, and calcium intake [7]. However, increasing levels of estradiol have been shown to be associated with a positive change of bone mineral density in the spine in postpartum women aged 20–40 years [7]. Lastly, there has not been any proven long-term detrimental effect of pregnancy or lactation on the skeletal mass of mothers [43].

Cartilage

The main hormones that may affect articular cartilage in peripartum and postpartum females include estrogen, testosterone, progesterone, and relaxin. Estrogen and testosterone receptors have been localized in the chondrocytes of the articular cartilage of the knee and estrogen and progesterone receptors additionally in the synoviocytes of the synovial lining [26, 44–47]. While both males and females have testosterone receptors, testosterone has modulatory effects only on male chondrocytes [47]. In males, androgens have been shown to help protect against degradation in rheumatoid arthritis and may play a similar role in osteoarthritis; however, it is unclear if this is due to a direct result from testosterone or from locally produced estrogen [45]. In females, progesterone has been shown to have a role in the development and protection of cartilage [48], and estrogen has been shown to have both protective and detrimental effects on articular cartilage [47]. Animal models have shown antioxidant effects of estrogen in protecting the chondrocytes from reactive oxygen changes [47]. In human models, estradiol increases chondrocytes proliferation, stimulates type II collagen, and protects against osteoarthritis via direct protective actions on the chondrocytes [45]. Subjects with low estradiol were not only found to have increased incidence of arthritic changes, but also found to have greater pain associated with arthritis due to the lack of leukotrienes, which have pain mediating effects [47]. In the postpartum female, the rapid decline of estrogen after parturition may possibly contribute to joint pain. However, there is also evidence of detrimental effects of estrogen on chondrocytes. For example, intra-articular injections of estrogen in a rabbit model caused pathological changes of the articular cartilage consistent with osteoarthritis, including fibrillation and erosion of the articular cartilage leading to exposure of the subchondral bone [47]. Additionally, high levels of estrogen have been shown to lead to increased inflammatory effects of certain interleukins (IL 1beta) in rabbit models [47]. Progesterone, on the other hand, has been found to have anti-inflammatory effects in osteoarthritis [48].

Relaxin appears to decrease knee articular cartilage stiffness through induction of collagenase and metalloproteinase [13]. In an animal model, the collagen content of knee articular cartilage in pregnant rabbits had decreased RNA levels and decreased chondrocyte metabolism [13]. Thus, it is suggested that relaxin may play a role in women's propensity for joint disease [13].

Ligament

The key hormones that may affect ligaments during pregnancy and lactation are estrogen, progesterone, testosterone, relaxin, SHBG, and IGF-1. Multiple sex hormones have been investigated in nonpregnant females in order to determine causation or correlation between hormone levels, ligamentous laxity, and anterior cruciate

ligament (ACL) injuries since estrogen, progesterone, testosterone, and relaxin receptors have been found in the human ACL [13, 26, 39, 44, 49–52]. Despite increasing research in this area, the true modulatory effects of sex hormones are not known, partly because of the difficulty studying this topic and partly because several of these hormones likely act in concert with each other to affect the metabolic properties and function of ligaments.

Estrogen is the most well-studied hormone thought to affect ligaments. Women have been found to have greater knee and ankle laxity when compared to men [53, 54]. While some studies have shown no correlation of the acute fluctuations of estradiol, progesterone, and testosterone across the menstrual cycle with changes in knee or ankle laxity [45, 53–55], others have demonstrated a correlation [39, 56]. Research evaluating daily sex hormone levels in menstruating females has elucidated that approximately 60 % of increased ACL laxity across the menstrual cycle depends on the combined changes of estrogen, progesterone, and testosterone levels without correlation to any one specific hormone [56]. Primarily, this research revealed that when estrogen and testosterone levels peak in the setting of elevated progesterone, females experience a greater increase in knee laxity [56]. Evidence from animal and human studies in nonpregnant females suggests that estrogen may decrease collagen synthesis and fibroblast proliferation, leading to a reduced ability of the ligament to withstand load and increase injury risk [16, 26, 39, 49, 57–59]. Subsequently, several studies have noted increased rates of ACL injury in nonpregnant women during the follicular phase with rising and peak levels of estrogen [60, 61], while other studies have found conflicting results with respect to menstrual cycle phase [62]. These studies have been criticized for multiple limitations [63] and consensus is currently lacking [26] regarding the risk of ligamentous injury and menstrual cycle phase.

Relaxin leads to a marked local decrease in total collagen content by reducing the density and organization of collagen bundles [21, 26, 52, 64]. As collagen is the main load-bearing component of ligaments, changes in collagen could lead to changes in ligament integrity [52]. Relaxin has been implicated in altering the mechanical properties of the ACL in animal [13, 65] and human studies [13, 26, 66] via reduced ligament integrity and higher evidence of and risk for injury [13, 26, 66]. Yet other studies demonstrate that weekly variations of serum relaxin levels in eumenorrheic women are not associated with changes in the anterior translation of the knee [64]. Possibly the variable results can be explained by the influence of estrogen on the expression of relaxin receptors as estrogen priming increases the response of target organs to relaxin [52, 67].

Testosterone, progesterone, IGF-1, and SHBG additionally influence the mechanical properties and functions of ligaments. While testosterone has been associated with increased collagen content in capsular tissue and increased knee ligament repair strength [68], neither total nor free testosterone is an independent predictor of ACL stiffness [68]. Increased concentration of progesterone has been associated with increased fibroblast proliferation and collagen formation [39, 50], yet there is no direct relationship between progesterone levels and ACL stiffness [39]. Higher IGF-1 concentrations and lower serum markers of collagen production have been

shown to predict greater anterior knee laxity in both eumenorrheic women and women using contraceptives [69]. Lastly, SHBG is a glycoprotein that fluctuates with changes of estradiol and progesterone levels during the menstrual cycle [39]. SHBG modulates estrogen's effects on various target tissues including ligaments [39]. However, there is no significant correlation between ACL stiffness and estradiol, progesterone, or SHBG levels during various phases of the menstrual cycle [39].

The earliest evidence of possible increased joint and pelvic laxity during pregnancy dates back to the 1930s, when radiographs of the pubic symphysis demonstrated increased joint displacement in pregnant women [21]. Increased joint laxity over the course of pregnancy and postpartum has been shown [70–72]. However, correlation with relaxin levels has not been demonstrated [12–14, 21, 73], possibly due to relaxin having more of a cumulative rather than an acute effect on joint laxity [21]. Unique to pregnancy, relaxin has been shown to have a role in remodeling connective tissue and reducing soft tissue tension in the pubic symphysis in preparation for parturition [26, 70, 74]. In several mammalian species (humans, guinea pigs, mice), elevated levels of estrogen and relaxin aid in the transformation of the pubic symphysis hyaline cartilage into fibrocartilage and eventually into the interpubic ligament during pregnancy [74]. In a study of ovariectomized mice, it was the interaction of progesterone, relaxin, and estrogen acting together that was necessary to cause structural changes in the pubic symphysis of the pregnant mouse typical of a normal pregnancy [75]. Additionally, some studies in humans have shown that estradiol levels correlate with increased laxity [70], but others have failed to demonstrate a clear relationship between maternal concentrations of estradiol, progesterone, or relaxin and joint laxity [71]. In a case study of a patient 5 weeks postpartum, she was found to have increased knee laxity on the knee that was status post ACL repair 2 months prior to conception [76]. She had minimal laxity at 7 months of gestation and her laxity normalized 3 months postpartum [76]. This case elucidates the likelihood that joint laxity and ligament stability change during pregnancy and postpartum, yet at this time we cannot attribute these changes to any one hormone nor do we know the exact origin of change.

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Myotendinous Unit

The most influential hormones for the myotendinous unit during pregnancy and lactation are likely estrogen, relaxin, testosterone, and IGF-1 with possible implications for prolactin. Both estrogen and testosterone receptors have been identified in skeletal muscle [77–81]. From studies of nonpregnant females, increased estrogen

levels during the menstrual cycle have been associated with decreased myotendinous stiffness [77, 82–85] and with diminished response of the rectus femoris muscle stretch reflex [86]. The mechanism is not entirely clear, but high levels of estrogen influence fibroblast proliferation, collagen synthesis, and collagen degradation likely via a cumulative effect [87] and possibly due to suppression of IGF-1 [85]. Decreased myotendinous stiffness may result in decreased joint stability [84] possibly leading to increased injury risk. However, other studies have noted no significant difference in tendon mechanical properties among the changing levels of estrogen with the phases of the menstrual cycle [88]. Furthermore, one study demonstrated inhibition of myofibrillar protein synthesis in tendons of women taking oral contraceptives compared to women not on contraceptives. This suggests that there may be a differential effect of endogenous and exogenous estrogen in regard to tendon stiffness and function [89]. Collectively, these findings may indicate that estrogen has more of a chronic rather than acute impact on tendon behavior [88]. Additionally, neuromuscular control, including fine motor activity and reaction time, has been reported to fluctuate over the menstrual cycle, and alterations of muscle activation patterns (gluteus maximus, semitendinous, and quadriceps) occur with peak estrogen levels [90]. It remains to be seen how the significantly elevated levels of estrogen during pregnancy affect myotendinous stiffness, but it is possible that joint stability might be compromised, especially in muscles spanning two joints and those with longer tendons.

Relaxin has been shown to modulate tendon growth and reduce myotendinous stiffness through activation of collagenase [13, 21, 64]. In young eumenorrheic women, elevated relaxin levels have been found to correlate with decreased patellar tendon stiffness, yet no changes of cross-sectional area were noted [91]. Relaxin has been shown to regulate normal skeletal muscle through the adenylate cyclase and nitric oxide pathways [13]. It has been found to have a role in the healing process by regulating inflammation, remodeling tissue, inhibiting fibrosis, and decreasing scar formation [13], which is crucial for the female body given the profound changes that occur to accommodate a growing fetus and prepare for parturition.

Testosterone is known to increase muscle mass and strength by inducing hypertrophy of type 1 and type 2 muscle fibers and increasing myonuclear and satellite cell number [92]. Additionally, in females, testosterone has been negatively associated with myotendinous stiffness [83], which may lead to decreased joint stability when testosterone levels are elevated as during the second and third trimesters. Similarly, IGF-1 enhances skeletal muscle hypertrophy by inducing protein synthesis and blocking muscle atrophy [38]. As IGF-1 and testosterone are elevated in the third trimester, this may be the most optimal time for pregnant women to strength train to enhance skeletal muscle hypertrophy. They may best benefit from strengthening exercises with minimal joint stress and perturbation due to the negative effects of elevated testosterone and elevated estrogen on myotendinous stiffness that can lead to decreased joint stability and possible increased injury risk [82, 83]. In addition to hormonal considerations, the third trimester may be less optimal for strength

training from a biomechanical perspective given changes such as increased lumbar lordosis and weight gain, which is further explained in other chapters.

Some studies have implicated prolactin in the etiology of DeQuervain's tenosynovitis in pregnant females, as observational studies have shown that DeQuervain's symptoms will resolve after women stop breastfeeding and their prolactin levels have normalized [25]. Similarly, prolactin has also been implicated in the etiology of carpal tunnel syndrome in pregnant and breastfeeding women [26]. The authors feel the role of prolactin is more correlative as these syndromes are associated with mechanical overuse of the wrists in the setting of pregnancy and breastfeeding. Please see additional chapters for more details regarding upper extremity pathology during pregnancy.

Nervous System

The predominant hormones influencing the nervous system in the pregnant female are likely estrogen, progesterone, and relaxin with potential influence from testosterone as well. Sex hormones have been shown to have effects on the excitability of neural structures in the peripheral and central nervous systems of nonpregnant individuals. While estrogen plays a stimulatory role enhancing nerve membrane excitability and synaptic transmission [93–95], progesterone plays an inhibitory and protective role [93, 94]. Exact mechanisms are unknown yet animal models suggest that estradiol and progesterone have an effect via direct receptors in the brain and spinal cord [94, 96–98], by modulating central neuronal excitability [44, 93, 94], altering the plasticity of axonal terminals and dendritic branches [1, 94], modulating motor behavior [1], and providing neuroprotective effects and stimulating myelination [98]. Relaxin specific receptors have been found in the central nervous system [99] and relaxin-3 is a neuropeptide that functions to modulate locomotor control, working memory, attentive state, and learning [99, 100]. Additionally, in animal models, testosterone has been shown to have neuroprotective and neurotherapeutic effects in injured nervous systems [101]. Although the influences of hormones on the central and peripheral nervous systems of the pregnant female are not clearly delineated, one can speculate that during the third trimester when progesterone and testosterone peak, their neuroprotective and neurotherapeutic effects are advantageous for the female in preparation for parturition.

Pain

The main hormones that seem to influence pain in the pregnant and postpartum female are likely estrogen and relaxin with possible influence from progesterone. In observational studies of women, estrogen has been implicated in back and upper

extremity pain [73]. Young menarche age has been associated with chronic upper extremity pain [73] while prior pregnancy, young maternal age at first birth, duration of oral contraceptive use, and use of estrogens during menopause have been associated with chronic low back pain [73]. For pregnant women, it has been theorized that estrogen causes increased joint and ligamentous laxity and that this laxity then leads to greater pregnancy-related low back pain [73]. However, studies have failed to show that increased joint laxity in pregnant women is associated with serum estradiol or relaxin levels [73].

The role of relaxin for women with pelvic girdle pain has received quite a bit of attention in the literature; however, there has yet to be a consensus regarding relaxin's effects [13]. Some studies have shown a correlation between higher levels of relaxin in the third trimester of pregnancy for those with pelvic girdle pain [19, 26, 72, 102, 103], while others have failed to show any correlation between relaxin levels and pelvic girdle [14, 104, 105] or low back pain [73]. Please see subsequent chapters for further discussion regarding pelvic girdle pain.

Lastly, estrogen, progesterone, and relaxin been implicated in the etiology of increased carpal tunnel syndrome and DeQuervain's tenosynovitis during pregnancy [26, 106]. Relaxin has been thought to modify areas of the carpal tunnel causing nerve compression [107]. However, the exact role of hormonal fluctuations and these musculoskeletal injuries have not been defined. Please see additional chapters for further details regarding upper limb issues in pregnancy.

Conclusion

In this chapter, we have reviewed hormonal influences on the neuromusculoskeletal system for the pregnant and postpartum female. Although dedicated literature on pregnant women is limited, we extrapolated from research on nonpregnant females and animal models to provide a framework for the clinician. The majority of the hormones we discussed do not act in isolation but instead act in concert with other hormones and various physiologic processes occurring during pregnancy (Table 2.1). When evaluating each aspect of the neuromusculoskeletal system, it is important for the clinician to consider which trimester patients are in and therefore which hormones may have the most profound influence. Continued dedicated research on the influences of hormones on the neuromusculoskeletal system will greatly benefit clinicians of various specialties caring for pregnant and postpartum females.

Table 2.1 Effect of key sex hormones on the neuromusculoskeletal system

	Bone	Cartilage	Ligament	Myotendious unit	CNS
Estrogen	Decreases bone resorption	Increased development and maintenance	Increased laxity	Decreased stiffness	Increased excitability
			Decreased stiffness		Increased synaptic transmission and formation
			Decreased load to failure		
Progesterone	Increases bone remodeling	Increased development and protection	Increased collagen production		Decreased excitability
					Neuroprotective
Testosterone	Stimulate bone formation	Protects against degradation	Increased ligament strength, contributes to increased laxity across menstrual cycle (with estrogen and progesterone)	Increases hypertrophic and hyperplastic response to resistance training	Neuroprotective
				Decreased stiffness	
Relaxin	Increases bone resorption	Decreased stiffness	Increased laxity	Decreased stiffness	Increased attentive state
			Decreased stiffness		

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