The Polypeptide Hormone Relaxin:

Relationship to Pelvic Pain during Pregnancy and Anterior Cruciate Ligament Injury?

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**I. Introduction**

 Relaxin, a polypeptide, mammalian hormone, functions as a powerful, chemical messenger affecting many essential, biological processes including metabolism, growth and reproduction.1 Known to resemble insulin and insulin growth like factor in structure,1-3 relaxin has seven known peptide forms that circulate in the female bloodstream, each of which has an affinity for effecting different bodily tissues and processes.1 Two of the seven relaxin peptide variations play an integral role in remodeling musculoskeletal tissue1 and have gained attention in research literature most notably for their function during pregnancy.2,4 Relaxin’s collagenolytic effect, or ability to remodel collagen,1-5 in musculoskeletal tissue such as ligaments, is responsible for the pelvis’ ability to widen in preparation for childbirth.6 Relaxin, however, is also present at varying levels during the female reproductive cycle in non-pregnant women, and its effect on ligament structure and function is not specific to the pelvis.1,3 Recently, relaxin hormone receptors have been identified on the human female anterior cruciate ligament (ACL).7 Both the ligaments of the pelvis and the ACL are known target areas for relaxin to bind to and are subject to the effect of this hormone; although beneficial in many cases, several researchers propose elevated levels of relaxin may be a detriment.

 Serum relaxin concentration (SRC) fluctuates during pregnancy and different stages of a women’s menstrual cycle,8 and consequences of elevated SRC are reported and highly debated in the literature. It has been proposed that elevated SRC results in increased joint laxity secondary to collagen metabolism in connective tissue, both in the pelvis during pregnancy and knee, which may lead to pain and injury.9 Joint laxity in the pelvis during pregnancy, considered critical for childbirth,1 has been identified at times when SRC is at its highest, and researchers suspect elevated SRC may have a relationship to disabling, pelvic girdle pain that many women experience during pregnancy.2 Additionally, the high incidence of non-contact ACL injuries in female athletes compared to their male counterparts is being investigated; high SRC causing ACL weakness is one culprit under scrutiny.10

 The purpose of this paper is to evaluate how SRC fluctuates throughout a women’s menstrual cycle and during pregnancy and the role of relaxin in the body, specifically on musculoskeletal tissue. Additionally, a review of the literature regarding the proposed relationship between high serum relaxin concentration and pelvic girdle pain during pregnancy, as well as ACL injury in female athletes will be explored.

**II. Phases of the Menstrual Cycle & Relaxin Concentration Fluctuations**

 When reviewing and discussing the literature regarding relaxin hormone, it is beneficial to have a basic understanding of the female menstrual cycle and terminology used in the literature. A women’s menstrual cycle on average last 28 days and consists of two phases: follicular and luteal.8 The follicular phase (or pre-ovulation) spans days 1–14 and begins when the uterine lining begins to shed, or menses.8 Menses continues on average for the first 5-7 days of the follicular phase.8 The second phase of the menstrual cycle is referred to as the luteal phase (or post-ovulation), spans days 15-28 and ends at the first day of menstruation.8 Although it is one point in time, ovulation is often referred to in the research as a phase; authors commonly report that the “ovulation phase” lasts between days 10-14 and is triggered by a surge of luteinizing hormone.5 Literature regarding the female reproductive cycle deserves careful review; often there are inconsistencies in terminology and reports of timeframes of each cycle vary.

 During pregnancy, relaxin is produced by the placenta.2,4,8 Relaxin rises considerably within the first trimester until it peaks at gestational week 10-12.2,4 Following this peak, SRC begins a slow decline to week 17, after which is remains steady into late pregnancy at 50% of the peak recorded level.4 Serologic testing postpartum reveals that relaxin is undetectable.2

 In non-pregnant women, the source of relaxin hormone is the corpus luteum, the remains of the follicle that released the egg during ovulation.2,4,5,8 Following ovulation, this body remains in the ovary and functions to produce the sex hormone progesterone, as well as relaxin.4 Seven to ten days after ovulation during mid-luteal phase, relaxin levels surge; at this point relaxin is at its highest concentration levels.4,5

**III. Role of Relaxin & the Musculoskeletal System**

Mediated by various signaling pathways, relaxin travels through the bloodstream, binding to target receptor sites on various musculoskeletal tissues in order to perform its essential regulatory effect.1 Researchers have identified numerous ways that relaxin effects multiple connective tissues including: bone, synovium, muscle, ligament, tendon, and cartilage. Alongside other hormones, and through a complex, multi-step process, relaxin supports bone remodeling by acting as an osteoclast-activating factor to promote bone resorption.1 On the other hand, a different form of relaxin regulates bone metabolism and osteoblast proliferation.1 It has been determined that relaxin affects both osteoclast and osteoblast activity in bone, giving it a dynamic and important role. Some researchers even suggest that a particular form of relaxin may be a potentially useful treatment in osteoporosis.1

 By altering the function of neutrophils and leukocytes, relaxin in combination with other hormones has anti-inflammatory proprieties which have been considered to play an important role in chronic inflammatory conditions such as rheumatoid arthritis (RA).1 The synovium, or lining of a joint, often hypertrophies in individuals with RA, leading to bone damage.1 It is reported that during pregnancy when SRC is at its highest, individuals with inflammatory conditions like RA are less symptomatic.1 This relationship presents insight into potential treatment ideas for diseases in which inflammation of synovial tissue is present.1

 Through many critical steps and involvement in the three stages of healing (inflammation, remodeling and fibrosis), researchers suggest that relaxin plays an important role in skeletal muscle healing and regeneration.1 Most notably, after immature granulation tissue fills in a muscle wound, begins to mature, and then moves through the last stage of healing (fibrosis) relaxin works as an antifibrotic agent to inhibit the formation of dense scar tissue formation.1 If dense scar tissue is able to form it would impair the recovery potential of the muscle.1 Instead, relaxin promotes desired muscle cell regeneration across the wound in order to support functional, healthy muscle tissue formation. 1

 Lastly, relaxin appears to have a collagenolytic effect which reduces the overall stiffness of ligaments, tendons and cartilage.1 Collagen, an important fibrous protein, is responsible for providing structure to various connective tissues and helping joints of the body maintain integrity when a load is applied.5 Mediated by matrix metalloproteinase, collagenase, and tissue plasminogen activator,1 relaxin appears to reduce the density and organization of collagen bundlesand therefore, alter the mechanics of tissues containing collagen.5 Although controversial, researchers suggest that this alteration in mechanics may contribute to increased joint laxity.1,5 This is a positive attribute in pregnancy, when pelvic laxity and separation on the pubic symphysis is essential for childbirth.2 Conversely, researchers are suspicious that increased laxity occurring secondary to collagen remodeling, may put women at risk of injury when demonstrating increased SRC.

**IV. Clinical Significance of Elevated Relaxin during Pregnancy**

 Pain in the lumbar spine and pelvic girdle region is one of the most commonly reported complaints among pregnant women.4,11 It is estimated that 50-80% of women experience lumbopelvic pain at some point during pregnancy,4,12 and symptoms interfere with everyday activities such as walking, housework, exercise, leisure, sexual life, personal relationships, and caring for other children.11,13 Women with lumbopelvic pain report a decrease in job performance,14 and up to 52% of women take sick leave during pregnancy.13 Lumbopelvic pain often has considerable consequences on a women’s physical functioning and is correlated with a significantly lower health-related quality of life13 and depressive symptoms post-partum.2

 The exact etiology and pathogenesis of pregnancy-related lumbopelvic pain is not clearly understood,14 and is believed to constitute a combination of hormonal, circulatory and biomechanical factors.15 Of particular interest to researchers is the effect that the reproductive hormones such as relaxin have on anatomical structures.4 As research develops about the role of relaxin on musculoskeletal tissue, specifically to increase laxity during pregnancy, investigators are eager to determine if there is a relationship between elevated relaxin levels, connective tissue changes, and disabling, pelvic pain during pregnancy. Making a correlation between these components is difficult because there are few studies, and of the ones performed, evidence is weak and controversial.

 In a systematic review, including 6 studies, Aldabe et al compiled research that addressed the relationship between pelvic pain during pregnancy and elevated SRC.2 The hypothesis behind the investigations assessed was that relaxin’s collagenolytic effect on connective tissue would increase joint laxity and mobility, leading to instability and pain.2 One important aim for the Adalbe et al study was to determine the level of evidence quality.2 The literature review demonstrated controversial results and poor evidence quality, highlighting a need for critical evaluation and further investigation.

 Of the 6 studies included, only 2 (33%) demonstrated a relationship between high SRC and prevalence of pelvic girdle pain.2 Conversely, the four others (66%) did not find a positive association. One of the studies reporting no positive association demonstrated high risk of bias when assessing pelvic pain because neither pain location, nor psychometric properties of validity and reliability of outcome measures were discussed.2 Adable highlights that, according to the 2009 Guidelines for Systematic Reviews, “high quality evidence can be considered when at least 75% of the studies have consistent findings with none having a risk of bias.”2 The overall level of quality of the studies that reported no association between elevated SRC and pelvic girdle pain was low. Aldabe et al suggests that when assessing pelvic girdle pain, a clear demonstration of pain location, and valid, reliable measures are critical.2 Evident by the low quality research and inconsistent results, determining a relationship between elevated SRC and pelvic girdle pain is equivocal.

 Two useful findings were reported by Kristiansson et al in a prospective clinical cohort study involving 187 pregnant women addressing the relationship between SRC and pelvic and back pain.4 First, the author’s reported that each woman has a “relaxin track” throughout pregnancy meaning that some women have uniformly higher levels of relaxin when tested throughout pregnancy while others have uniformly lower values.4 The authors were able to make an association between high relaxin levels and pelvic pain that started during pregnancy, specifically at the pubic symphysis and greater trochanter; however were unable to foster a relationship with pain intensity and or level of disability experienced by the participants.4 Second, relying on results from previous animal studies may be disadvantageous. The authors conclude that relaxin does certainly have a role in the necessary structural changes that take place within a women’s pelvis during pregnancy, but recognize that the extent at which it influences structural pelvic changes pain may be less when compared to many of the previous animal studies.4 Reasons for this include other mammalian species have overall higher levels of SRC compared to human studies and their peak levels of relaxin are identified in late pregnancy rather than at the 12 gestational week as identified in humans.4 In light of these factors, critical analysis is essential when reviewing animal studies. Additionally, investigating the effect of a higher “relaxin track” may provide more insight into who is at risk and help researchers form more homogenous participant samples.

**V. Clinical Significance of Elevated Relaxin in Female Athletes**

 Female athletes experience a high incidence of ACL injuries, approximately one in 10 female athletes yearly.3 Several theories have been proposed to explain this inequality; the effect of gender-related hormonal differences is one popular supposition. Compared to their male counterparts, it is reported that female athletes injure their ACL during sporting events 2 to 8 times more frequently than men.9,10 Suggested theories that will not be discussed in this review, but are important considerations include differences among females and males in anatomical structure, patterns of movement, joint-loading patterns, muscle strength, and neuromuscular control.9,10 Other researches have hypothesized that the fluctuations in female sex hormones, such as relaxin, that occur throughout the female menstrual cycle may form direct connection between menstrual cycle and ACL passive laxity.9,10 Furthermore, it is suggested that this connection can be expanded to relate increased ACL laxity to injury as a result of challenges in determining position in space and providing effective muscle contraction secondary to joint laxity.9

 Although relaxin has an established role in pregnancy and reproductive tissues, the effect it has on non-reproductive tissues, like the ACL, is less understood. Relaxin receptors have been identified on the ACL in females,7 and researchers acknowledge that the ACL is susceptible to the collagenolytic effects produced by relaxin which may reduce its integrity. A review of the literature is inconclusive due to scarcity of quality evidence applicable to human subjects and assessing effect of relaxin alone.

 In a controlled laboratory study on guinea pig models, Dragoo et al investigated the effect that administration of relaxin only and relaxin plus estrogen had on the integrity of the ACL compared with a control group.5 Tibial displacement was tested my radiography; although increased laxity was detected in all hormone groups, it was not significant.5 It was clearly determined, however, that after 3 weeks of treatment with either relaxin only or relaxin plus estrogen subjects demonstrated significant ACL weakness compared to controls when a load was applied to failure and that no difference existed between the relaxin group with the relaxin plus estrogen group.5 This lack of statistical difference in load to failure between the two hormone groups suggest that relaxin is the hormone responsible for these integrity changes.5 Even though this study demonstrates adequate power, it used a very small sample size and is not necessarily generalizable due to use of an animal model. Dragoo et al suggest that elevated SRC has an effect on the mechanical properties of the ACL in guinea pigs, but it is unclear how this applies to humans and further investigation is warranted.5

 In a more recent study performed by Dragoo et al, including 169 female elite athletes, the relationship between SRC and oral contraceptives use was under investigation.3 Oral contraceptives are known to suppress ovulation and therefore prevent the formation of the corpus luteum, the body responsible for releasing relaxin in the luteal or post-ovulation phase.8 The results of this investigation identified a significantly lower SRC among oral contraceptive users compared to non-contraceptive users.3 If a conclusive relationship between elevated SRC and ACL injury can be more firmly established, Dragoo et al suggest that oral contraceptive use may decrease prevalence of ACL injury in female athletes secondary to the inhibition of relaxin production and collagen remodeling.3 For athletes that participate in sports that involve jumping and cutting, this could as a preventative measure and perhaps decrease risk of injury.

 An important consideration when reviewing the literature regarding relaxin levels and ACL integrity is that no one hormone works exclusively on its own. Relaxin is just one of several female sex hormones that regulate reproduction and influence the cells and organs in which they bind to. Although not included in detail within this review, there are many studies that investigate the role these other hormones (estrogen and progesterone) have on ACL injury. These studies are inconclusive and demonstrate poor methodological quality.

 In a systematic review including seven articles related to menstrual cycle and ACL injury risk, Hewett et al determined that non-contact ACL injury is more common during the late pre-ovulatory phase of the menstrual cycle.10 On the other hand, Park et al, reports that increased laxity is more common during ovulation9 and Shultz et al suggests knee laxity has a more transient relationship with the menstrual cycle and typically is evident around ovulation and early luteal phase as well as late luteal phase.16 The results of these studies demonstrate inconsistencies present in the literature regarding knee laxity, ACL injury and sex hormones.

 There are several factors that may explain such variations. First, the female reproductive cycle is variable among women and methods used to determine what phase of the menstrual cycle a women is in may be unreliable. Self-report questionnaires and basal temperature reports are not accurate and may lead to serum collection at inappropriate time.17 Second, many studies use uncontrolled subject populations which weakens the results. If participants are not identified as non-oral contraceptive user or oral contraceptive users, results will be inaccurate and misleading. Third, several studies used more than one examiner which increases likelihood of interrater variability. Lastly, many of the investigations use small sample size and lack adequate power. Although none of these studies evaluated relaxin specifically, they provide insight about other potential contributors to knee laxity and identify challenges present in the literature.

**VI. Conclusion**

 The female reproductive cycle and pregnancy are complex, intricate processes that rely on the precise interaction and involvement of many powerful hormones including relaxin. Relaxin is present at different concentrations in each woman, circulates at different times, interacts with other hormones, and each women’s individual response to this hormone varies. Researchers interested in this topic are faced with many challenges due the complex nature of hormones and the endocrine system.

 Investigating the relationship between relaxin and pelvic pain during pregnancy may give clues about which women are more susceptible to experiencing lumbopelvic pain during pregnancy and after delivery. Unfortunately, the women that express a higher “relaxin track” as discussed by Kristiansson et al, may be the unlucky ones. Determining factors that contribute to some women expressing higher or lower relaxin levels has not been investigated. If high levels of relaxin are responsible for increased pain in the lumbopelvic region during pregnancy, hindering its uptake by the use of relaxin-receptor blockers might seem beneficial. The challenge is that relaxin plays an important role in many biological processes and therefore inhibiting its release is futile. This highlights a need for effective pain reduction interventions and perhaps serum testing in early pregnancy would provide information about who is susceptible and will need to work harder to prevent discomfort, disability and reduced quality of life.

 Since collagen is the main loadbearing component of the ACL, it is possible that relaxin's collagenolytic effects may impact the mechanical properties of the ACL; however, determining a relationship between elevated SRC and ACL injury has not been firmly established. Further research is warranted, and improved study design is necessary in order to produce high quality evidence. Besides gender-related hormonal differences, there are a considerable number of theories proposed to explain the high incidence of ACL injury in female athletes. Until a relationship is definitively established between elevated SRC and ACL weakness, intervention strategies targeted on well-established risk factors for ACL injury are more valuable.

 If a direct link does exist between elevated SRC and joint laxity and/or weakness which may lead to pain and injury, it is advantageous for healthcare providers, such as physical therapists, to fully understand this correlation in order to identify women at risk. Additionally, developing intervention strategies for pain and injury prevention during times of increased SRC and educating female patients will ensure that optimal, comprehensive care is given.

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