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RESEARCH ARTICLE

GAME OF LAXITY BETWEEN FEMALE SEX HORMONES IN MENSTRUAL CYCLE & LIGAMENTOUS STRUCTURES: A MINI LITERATURE REVIEW

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ABSTRACT

Background: Incidence of joint laxity in the overall population is 5% to 20%, and its prevalence is higher in females. Increased joint laxity in females increases chances of frequent non-contact injuries. Women are at a greater risk for Anterior Cruciate Ligament (ACL) injuries and other knee joint related injuries than are men.
Purpose: The purpose of this review was to understand the effect of MC & associated hormonal fluctuations on changes in structural compositions and function of ligamentous structures.
Methods: A total of 15 references were included. A mini literature review was done by collecting data from MEDLINE/PubMed, ncbi, Research gate, and Semantic scholar databases from basic and clinical research studies examining hormone effects on collagen metabolism, tissue remodeling, ligament structural/mechanical properties, and knee joint laxity / ACL injuries to understand mechanisms through which hormones exert their influence on ligament laxity and consequent injury potentials. The clinical implications of these changes in ligamentous structures in the females' on-field injuries in sports, physical performance and lifestyle was studied.
Results: Estradiol, Progesterone, and Relaxin are the predominant hormones studied relating to ligamentous laxity. They have found to be directly acting on collagen metabolism, which alters the ligament property, explaining alteration in flexibility during MC & increase in the potential for ligament failure in physically active women. Mechanisms underlying Testosterone effect on ligament laxity is still unknown.
Conclusions: Hormonal fluctuations during MC affect structural composition of ligaments & consequently their laxity. Changes are evident when hormones are at a peak or near-peak concentrations. ACL injuries are commonly seen occurring due to knee joint laxity.

INTRODUCTION

Sex hormones are responsible for the sex differences in physical characteristics of an individual that emerge after puberty. [(1)] They also hold the potential to impact collagen metabolism, ligament remodeling, and the structural integrity of the ligamentous structures in our body, in a way that may increase the potential for ligament failure in physically active & healthy women. [(1)] Flexibility is the ability of a joint or series of joints to move through an unrestricted, pain free Range of motion. [(2)] The incidence of joint laxity in the overall population is approximately 5% to 20%, and its prevalence is higher in females. It is a natural phenomenon for women to have increased ligamentous laxity and flexibility compared to men. This excessive laxity is the reason that there is an increased incidence of patellar subluxations (knee joint issues), ligament sprains, and joint discomfort (especially hips, pelvis and lower back) seen in females, and especially female athletes.[(3)]

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Any alteration in the flexibility will hamper the performance of the individual. It has been found, that women and girls are at particularly high risk for ACL injuries, with rates 3 to 6 times greater than men, leading some to suggest a hormonal effect.[(4)] The menstrual cycle and sex steroid hormones have been implicated as risk factors for the greater occurrence of frequent non-contact injuries.[(5)] Estradiol, Progesterone, and Relaxin are the predominant hormones that have been studied in the menstrual cycle relating to ligamentous laxity. Women experience the double whammy of Estrogen and Relaxin, the latter of which negatively affects important Collagen Integrity at connective tissue and nerve rich bone surface areas (periosteum).[(3)] Estradiol and Progesterone are at their lowest levels during menses at the beginning of the menstrual cycle (days 1-6). [(4)] Estradiol reaches its peak concentration around the time of ovulation (days 12-14), with a second lower rise in the luteal phase (days 20-24). [(4)] Progesterone begins a gradual rise in the late follicular phase peaking in the mid-luteal phase (days 19-24). [(4)]

DISCUSSION

Overview of Menstrual Cycle (MC): According to Figure 1, the MC consists of a series of events that prepare the uterus for potential pregnancy. A MC that occurs regularly and lasts between 21 and 35 days is defined as eumenorrheic. [6]

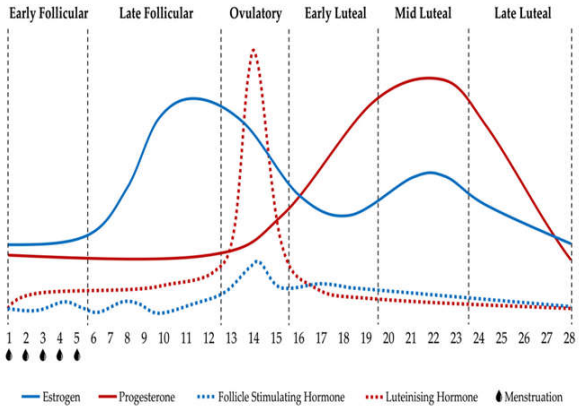

Figure1 : Overview of the Menstrual Cycle

A eumenorrheic MC is separated into two distinct main phases, follicular and luteal, which are established on the occurrence of menstruation, follicular maturation, ovulation and corpus luteum formation. [6] The MC is typically expressed in research using sub-phases, such as early follicular, late follicular, ovulatory, early luteal, mid luteal and late luteal. [6] The MC typically begins around 13 years of age and will continue regularly until perimenopause around the age of 45 years unless interrupted by pregnancy, hormonal contraceptive (HC) use or menstrual or ovulatory dysfunction. [6] The follicular phase is characterized by the maturation of the follicle containing an ovule and a retinue of follicular cells, which are responsible for transforming androstenedione into Estradiol, which in turn is released and, among many other actions, stimulates endometrial renewal.[7] The early follicular phase begins with menstruation when female sex hormonal concentration is relatively low , which usually takes 4 to 6 days to complete; during the late follicular phase, there is an increase in Estrogen as the ovarian follicles mature. The LH surge, in the late follicular phase, triggers ovulation. [6]

The luteal phase, is named so because the follicular cavity that was left after the ovule hatched, is transformed into a corpus luteum and continues to produce Estrogen, but it also releases important amounts of Progesterone. [7] The luteal phase is preceded by a significant increase in LH, and ovulation marks its onset; then, it lasts ±14 fairly constant days when comparing different women. The early luteal phase shows production of Progesterone and a small amount of Estrogen. [7] The mid-luteal phase contains the peak in Progesterone and the second, smaller peak in Estrogen, to prepare the endometrium for the implantation of a fertilized egg.[6] The luteal phase will end with pregnancy if a fertilised egg is implanted. If the egg remains unfertilised, the corpus luteum will degrade, causing a decline in Progesterone and Estrogen during the late luteal phase as the cycle prepares to restart, with the uterine lining eventually detaching & getting ready for menstruation to begin again. [6] Relaxin is secreted during the follicular and luteal phases, reaching its peak during the luteal phase. Lastly Testosterone fluctuates throughout the cycle and contributes to the formation of Estrogen. Changes in levels of the above hormones during menstrual cycle is the main reason for change in flexibility. It is also proposed that these hormones directly act on collagen metabolism, which in turn alters the ligament property & this explains some alteration in flexibility during the menstrual cycle motion. [2]

Association of ligament laxity and Menstrual Cycle Hormones: Wojtys et al conducted a survey reporting more injuries happening in the ovulatory phase, from days 0 to 14, than were expected and less injuries than expected occurred during the follicular phase, days 1-9. This is about the same time that Estrogens, LH, FSH and Estradiol reach peak levels and Progesterone and Testosterone levels begin to rise slightly. [8] The balance between the degradative and biosynthetic arms of the process of Tissue Remodeling is controlled by the relative activities of matrix metalloproteinases and tissue inhibitors of metalloproteinases. [9] The expression of some of these proteins is regulated by steroid hormones. Hence, it is hypothesized that the type of sex hormone or the nature of exposure to it could affect the remodeling capabilities and thereby alter mechanical properties of ligamentous structures.[9]

Numerous *in vitro* studies illustrate a direct effect of sex hormones on tissue properties. [10] Estrogens and Progesterone receptors have been reported as being present in normal connective tissue.[8] A study by Ned A. Heitz, was done with the purpose to investigate the prevalence of Anterior Cruciate Ligament laxity in females in conjunction with Estrogen and Progesterone surges during normal 28-30 days menstrual cycle. Serial Estrogen and Progesterone levels were measured via radioimmunoassay procedure to identify the follicular and luteal phases of the subject's menstrual cycle, and to determine periods of peak hormonal surges, ACL laxity was measured using knee arthrometer. A significant difference was noted in ACL laxity when comparing baseline Estrogen and Progesterone levels. Collagen is a protein that primarily functions to maintain strength and stiffness within the tissue and is found in muscles, tendons, and ligaments. Estradiol decreases collagen content in these tissues by inhibiting collagen synthesis (Fischer, 1973; Kwan, 1996; Liu, 1997). Yu *et al.* found that when the ligament is exposed to increased Estrogen levels, there is a dose dependent antagonist effect on fibroblast proliferation and procollagen synthesis. Additionally, Abubaker *et al.* (1996) demonstrated that Estrogen combined with Progesterone significantly decreased collagen content of ovariectomized female and orchiectomized male rats, which illustrated the importance for understanding the influence of combined sex hormones.

One of the primary functions of Estradiol and Relaxin is to increase the laxity of the pelvic ligaments during childbirth by decreasing collagen in these ligaments. Hence, Relaxin also downregulates collagen expression (Samuel, 1996; Unemori and Amento, 1990) by inhibiting the expression of procollagenase (Palejwala, 2002), an enzyme involved with the degradation of collagen. Due to the effects of sex hormones on collagen content, it is likely that, on a smaller scale, laxity of all ligaments increases during the menstrual phases of high Estradiol and Relaxin (the pre-ovulatory, and luteal phases) thereby causing cyclic changes in joint laxity. If joint laxity increases, the soft tissues may be at a higher risk for being injured (Myer, 2008; Skinner, 1986). The mechanisms underlying Testosterone effect on ligament laxity is unknown,

however a limited finding in the prostate gland indicated that Testosterone as opposed to Estrogen affects collagen metabolism via downregulating the expression of Estrogen Receptor (ER)-α. So far, no study has reported Testosterone effect on Relaxin receptor expression in the joints, although Relaxin has been shown to affect ligament laxity and its receptor was expressed in female knee joint of both humans and rodents.[11] Shultz *et al*. reported that Testosterone has a positive rather than a negative relationship with changes in knee laxity in the presence of Estrogen and Progesterone. On the other hand, Rozzi *et al*. reported that male athletes have greater knee joint laxity than female athletes, suggesting a negative influence of Testosterone on laxity. Hence, its exact role remains elusive.

Knee Joint specific changes due to hormonal fluctuations in menstrual cycle: Studies done so far, investigating the relationship between female sex hormones and joint laxity, mainly focused on the knee joint, more specifically ACL injuries. It is generally accepted that females have greater anterior knee joint laxity than males which has received attention as a potential risk factor for non-contact Anterior Cruciate Ligament (ACL) injury. [12] While hormone levels remain fairly constant in males, females are exposed to rhythmic fluctuations in endogenous hormones during the course of the menstrual cycle, with the absolute levels of Estrogen and Progesterone varying considerably during the course of a cycle.[13] In normal menstruating females, significant increases in knee laxity have been noted in the peri-ovulatory and mid-luteal phases of the menstrual cycle compared to menses, as defined by time periods that are thought to coincide with elevated levels of Estrogen and Estrogen & Progesterone respectively.[8][14] Comprehensive or quick fluctuations in serum Estrogens may result in structural or compositional changes in the ACL, causing decreased ligamentous strength and stability, which would predispose an individual to injury.[8] Progesterone begins a gradual rise in the late follicular phase just before ovulation, but its highest levels are reached in the mid-luteal phase (days 19-24). These periodic hormonal fluctuations in the menstrual cycle have been postulated to cause ligament laxity, increasing the risk for ACL injuries.[4]

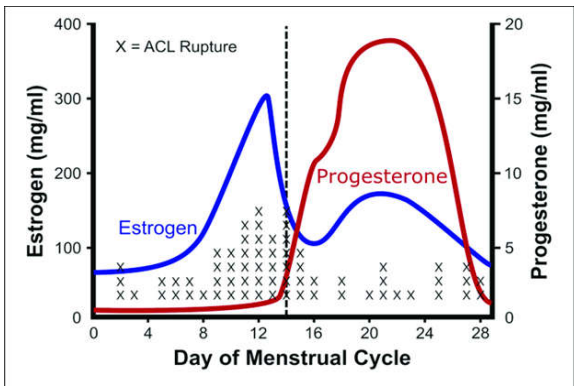

Figure 2. Occurrence of ACL injuries vs Days of Menstrual Cycle

As shown in Figure 2, Wojtys et al conducted a survey reporting on the occurrence of ACL injuries in correspondence with the phases of the menstrual cycle. They found further more injuries were reported as happening in the ovulatory phase, from days 10 to 14, than were expected and less injuries than expected occurred during the follicular phase, days 1-9. But, Heitz et al reported the greatest amount of ACL laxity was noted, and had a significant difference, during the luteal phase, between days 20 and 23, with an increased amount of Progesterone. However, other studies show that ACL tears occur with increasing frequency only during the follicular phase (Myklebust, 2003; Slauterbeck, 2002). These discrepancies might be because of the inconsistent methods used for identifying the relationship. A study done by S-K Park et al., reported that an increased knee laxity was observed during ovulation compared with the luteal phase, but no significant changes in knee mechanics corresponding to menstrual phases were found. [15] A positive correlation was thus found between changes in knee laxity and changes in knee joint loads from the follicular phase to ovulation, and from ovulation to the luteal phase. [15] Women in whom knee laxity increased showed increased knee loads, and those in whom knee laxity decreased showed decreased knee loads during the menstrual cycle. [15] Thus, knee laxity correlates positively with knee joint load, and an increased knee laxity during the menstrual cycle may be a potential risk factor for Anterior Cruciate Ligament injuries in certain women during sports activity. [15]

Conclusion

- Females show more hormonal fluctuations as compared to males
- Major changes in the ligamentous laxity are seen when the sex hormones are at a peak or near-peak concentrations.
- Females show ligamentous laxity changes mainly in pre-ovulatory & mid-luteal phases of menstrual cycle Hormone fluctuations are interdependent and a change in concentration of one hormone may cause variations in the concentration of another
- Females show ligamentous laxity changes mainly between follicular to ovulatory phases of menstrual cycle. These findings are dynamic and may vary.
- Females show more amount of ACL injuries occurring due to knee joint laxity due to hormonal fluctuations during various phases of the menstrual cycle.

Conflict of Interest: Authors state no conflict of interest. No author has any financial interest or received any financial benefit from this research.

Ethical clearance: Not applicable

Abbreviations

MC – Menstrual Cycle
ACL – Anterior Cruciate Ligament
LH – Leutinizing Hormone
FSH – Follicle Stimulating Hormone
ER – Estrogen Receptor

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