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THE RELATIONSHIP BETWEEN THE USE OF HORMONAL CONTRACEPTIVES AND LIGAMENTOUS KNEE INJURY IN THE FEMALE COLLEGIATE ATHLETE

by

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A Thesis

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Thesis Advisor: Leslie Spencer, Ph.D.

Dedication

I would like to dedicate this manuscript to the Rowan University Athletic Training Education Program (RUATEP).

Abstract

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THE RELATIONSHIP BETWEEN THE USE OF HORMONAL CONTRACEPTIVES
AND LIGAMENTOUS KNEE INJURY IN THE FEMALE COLLEGIATE ATHLETE
2019-2020
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Master of Science in Athletic Training

Female athletes are three to six times more likely than males to sustain a ligamentous knee injury due to hormonal risk factors. Hormones of the menstrual cycle have been shown to alter the physiological component of ligamentous structures during the three phases of the cycle. Use of hormonal contraceptives (HCs) may influence the incidence and severity of ligamentous knee injuries in female athletes. The objective of this cross-sectional study was to determine the relationship between HC use and the type and severity of ligamentous knee injuries sustained among female collegiate athletes using an online survey distributed to NCAA female athletes who experienced a ligamentous knee injury during the study time period (n=336). The electronic survey assessed demographic information, ligamentous knee injury and menstrual cycle characteristics, and HC use. Chi-Square analyses showed significant relationships between injury type and severity of injury, and injury type and menstrual cycle phase. The majority of respondents sustained ACL injuries, were in the luteal phase of the menstrual cycle, and HC users. Of the HC users, there were a greater number of respondents who were combined hormonal contraceptive users and oral contraceptive pill users. The type of ligamentous knee injury (ACL) impacted the severity of the injury. Female athletes were at the greatest risk for ligamentous knee injury in the luteal phase of the menstrual cycle. Future work should aim to identify injury prevention programs, protective equipment, and HC for decreasing the risk for ligamentous knee injury.

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Literature Review

  Background. With the passing of Title IX of the United States Educational Assistance Act in 1972, there has been a significant increase of female participation in athletics.[1,2] In 2004, there was a reported 80% increase in female and 20% increase in male participation in National Collegiate Athletic Association (NCAA) sports.[3] By 2018, these percentages increased to 43.8% and 56.2% of female and male student-athletes, respectively participating in NCAA sports.[4]

  In 2007, 182,000 collegiate athletes experienced injuries in the NCAA and this number has continued to rise with the increase in sport involvement and continual recognition of athletic injuries.[3,4] More than half of collegiate injuries occur to the lower extremity with the knee and ankle being the most common sites.[3] In the general U.S. population, there are approximately 250,000, or 1 in 3,000, ACL injuries that occur annually.[2] There are 60% more injuries that occur in women, with 16% being to the knee, compared to men in professional basketball.[5] Collegiate female athletes account for approximately 67% of all ACL injuries and 69% of non-contact ACL injuries compared to their male counterparts, making females 3-6 times more likely than males to sustain an ACL injury. [1,6,7,8,9,10] The sports in which females are more likely to suffer an ACL injury are basketball, gymnastics, lacrosse, and soccer.[11,12]

  There are various underlying risk factors that can predispose an athlete to a ligamentous knee injury.[9,13] The differences between males and females in ligamentous knee injury and laxity may be explained by biomechanical, neuromuscular, anatomical,

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and hormonal risk factors.[8,1] Hormonal risk factors that occur during the menstrual cycle can increase the susceptibility of non-contact knee injuries in female athletes. [6,8,9,12,14]

The Landing Error Scoring System (LESS) assesses the amount of errors an individual obtains from a jump-land movement, with a higher score indicating a greater risk for ACL injury.[15] Both before and after sport-specific exercise, female athletes have a significantly higher score on the LESS compared to males athletes, placing them in a high-risk category.[15] Compared to collegiate male athletes, female athletes have a 20% increase in rotary knee laxity while being assessed on the Lachman test, generalized ligamentous laxity, and knee hyperextension.[16] For every 1.3 mm increase in anterior knee displacement, or ligamentous laxity, the risk of ACL injury increased by a factor of four.[17]

Fifty-one percent of female athletes reported that their menstrual cycle had an effect on their training and athletic performance, with dysmenorrhea being the most common complaint in 60-90% of those who do not use hormonal contraceptives (HCs).[18] Primary dysmenorrhea involves a painful menstruation, nausea, headaches, fatigue, and diarrhea.[18] Other physical symptoms athletes may experience include stomach cramps, back pain, bloating, fatigue, vertigo, discomfort, hot flashes, increased appetite, breast soreness, dermatological changes, constipation, heavy bleeding, muscle aches, problems with exercising, sore throat, tight neck, and weakness.[18] Emotional symptoms may include mood changes, irritability, and being flustered.[18] All of these can be self-limiting factors of performance in female athletes.[18]

Females use HCs for their contraceptive effects and to eliminate negative symptoms of the menstrual cycle.[6,7] A majority (73.6%) of reproductive age women (17-

40 years of age) have manipulated their menstrual cycle in the previous year, with special events, holidays and convenience being the most common reasons.[19] Forty percent of competitive athletes have modified their menstrual cycle due to physical activity, exercise, or sport convience.[19] HCs work in favor for competitive female athletes by decreasing the likelihood of missing playing time.[19]

Ligamentous knee injury types. Ligamentous knee injuries account for approximately 40% of knee injuries. The ligaments of the knee are the primary static stabilizers of the knee.[20] Knee ligamentous structures most commonly injured are the anterior cruciate ligament (ACL), medial collateral ligament (MCL), lateral collateral ligament (LCL), and posterior cruciate ligament (PCL).[21]

Anterior cruciate ligament. The ACL originates on the anteromedial intercondylar eminence of the tibia and courses posteriorly and laterally to attach on the medial wall of the lateral femoral condyle.[2,22] Its function is to resist anterior translation and rotation of the tibia.[22] Injuries to the ACL may be the result of a direct contact or non-contact mechanism to the knee.[20] ACL injuries are the most common type of ligamentous knee injury with an occurrence of 46-68%.[21,23]

Medial collateral ligament. The MCL is comprised of three layers on the medial side of the knee and ascends from the distal pes anserine of medial tibia to the medial femoral condyle.[20,22] Its function is to resist valgus forces placed on the lateral aspect of the knee.[33] MCL injuries make up 26-29% of ligamentous knee injuries.[21,23]

Lateral collateral ligament. The LCL, also referred to as the fibulocollateral ligament, extends from the fibular head to the lateral femoral epicondyle to resist varus

forces placed on the medial aspect of the knee.[20,22] LCL injuries comprise 2-4% of all ligamentous knee injuries.[21,23]

Posterior cruciate ligament. The PCL originates on the posterior intercondylar eminence of the tibia and crosses the ACL in the opposite direction as it courses anteriorly and medially to insert on the lateral wall of the medial femoral condyle.[22] It counteracts the ACL to resist posterior, rotation of the tibia and hyperextension of the knee.[20,22] Injuries to the PCL are commonly caused by a direct blow to the anterior knee while the knee is flexed.[33] Similarly to the LCL, the PCL comprises approximately 2-4% of ligamentous knee injuries.[21,23]

Female endocrinology. The pituitary gland is responsible for the control of the menstrual cycle.[26] Typically, the cycle length lasts an average of 28 days and it is divided into three phases or stages, the follicular phase, ovulatory phase, and luteal phase.[25] Although, the phases may be referred to as alternate names, the timeline of the menstrual cycle stays consistent. Female sex hormones associated with the menstrual cycle may influence ligamentous knee injury and laxity in female athletes. [7,8,12,24,25,]

The menstrual cycle. The mean length of the menstrual cycle is 28 days but can vary from 23-35 days.[25] Slaughterbeck et al[8] and Heitz et al[12] defined the menstrual cycle as the menstrual phase (days 0-5), the follicular phase (days 6-14), and the luteal phase (days 15-28).[8,12] Wojtys et al[25] defined the menstrual cycle as the follicular phase (days 1-9), the ovulatory phase (days 10-14), and the luteal phase (days 15-28).[25] Herzberg et al[7] defined the menstrual phase as the menstrual phase (days 1-6), the ovulatory phase (days 12-14), and the luteal phase (days 20-24).[7] For the purpose of this study the

menstrual cycle will be operationally defined as the follicular phase (days 1-9), the ovulatory phase (days 10-14), and the luteal phase (days 15-end of cycle).

Hormone levels throughout menstruation. There is a constant fluctuation of hormones through the menstrual cycle. Estradiol and progesterone are at their lowest (60 mg/day) level with the onset of menses in the follicular phase. [7,8,12,] During the ovulatory phase, estrogen rises to a secretion rate of 400-900 mg per day in conjunction with the increase in luteinizing hormone (LH) and the growth of a dominant follicle.[8,25,27,] Twenty-four hours before ovulation, or at the onset of the luteal phase, estradiol peaks and there is a surge in LH and gonadropins.[7,8,25] Estradiol then significantly drops off to 300 mg per day, but rises again during this phase of the menstrual cycle. In conjunction with estradiol, progesterone peaks in the middle of the luteal phase at a secretion rate of 25,000 mg per day in response to increasing levels of LH and the development of the corpus luteum.[7,8,25,27] If there is an absence in pregnancy following ovulation, the follicle ruptures or collapses creating a sudden drop, but then spike, in estrogen.[7,25,27] In the late-luteal phase, progesterone levels rise again, but then decreases, triggering menstruation.[7,25,27]

The menstrual cycle and ligamentous knee injury. Since the menstrual cycle is one of the most distinct differences between males and females, it seems logical to consider that the increased prevalence of ACL ruptures in females over males could be due to this process. Wojtys et al[25] assessed which phase of the menstrual cycle was associated with female ACL injury over a two-year period.[25] Sixty-five women who sustained an acute non-contact ACL injury were included in this study. Subjects were excluded if they were pregnant, or nonpregnant with a history of irregular or missed

menstrual cycles. There were 51 oral contraceptive nonusers and 14 oral contraceptive

users. Subjects were recruited within the first 24 hours of sustaining their ACL injury.

Each subject completed a questionnaire inquiring about the date and mechanism of

injury, the frequency of their athletic participation in the past month, and a detailed

history of their menstrual cycle including, frequency and regularity, date of the last

menstrual period, average length of the cycle, and oral contraceptive or hormone

replacement use. Each subject gave a urine sample within 24 hours of sustaining the

injury, and within 24 hours of the first day of the onset of their next menstrual cycle. The

mean of the two urine measurements of estrogen, progesterone, luteinizing hormone

metabolites and creatinine were recorded for analysis to determine cycle phase when

sustaining the injury.[25]

The results showed that 15 participants injured their ACL in the follicular phase,

28 in the ovulatory phase, and 22 in the luteal phase. The oral contraceptive nonuser

group was more likely to tear their ACL during the ovulatory phase (phase II) over the

follicular or luteal phases. The oral contraceptive user group was also more likely to

rupture their ACL during the ovulatory phase, but at a lower expectancy than the oral

contraceptive nonuser group.

All three hormone metabolite levels measured by the urine assays were within

normal clinical ranges during the menstrual cycle. However, these were significantly

higher on the day of injury in comparison to day-one of the menstrual cycles, although

the results for each group were not indicated. The significant increase in hormone

metabolite levels on the day of injury suggests that hormone metabolites may influence

the susceptibility to ACL injury. The authors concluded that when there is a surge in LH

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and estrogen during the ovulatory phase, there is an increased risk of ACL injury compared to the follicular or luteal phase.[25]

Heitz et al[12] studied ACL laxity over the course of the menstrual cycle in active females.[12] All seven subjects reported a normal menstrual cycle, at least one healthy knee, and not taking HCs. Subjects were excluded from the study if they had a Q-angle of 10° in order to eliminate excessive genu valgum effects on results. The subjects reported to the appropriate centers on the day their menses began. Blood draws were taken to determine estrogen and progesterone levels, and the KT-2000 knee arthrometer was used to assess ACL laxity with 67, 89, and 133 N of force applied. These procedures were repeated on days 10, 11, 12, 13, 20, 21, 22, and 23 of the menstrual cycle.[12]

The results showed that there was a significant increase in ACL laxity when comparing the follicular phase (phase I) and ovulatory phase (phase II) of the menstrual cycle. It is suggested that this change may be due to the peak in estrogen during the ovulatory phase. There was also a significant difference in ACL laxity when comparing the follicular phase (phase I) and luteal phase (phase III) of the menstrual cycle. This change may be due to the peak of progesterone levels during the luteal phase, thereby causing the greatest amount of ACL laxity during the luteal phase.[25] Although the number of study subjects was low (n=7), this evidence suggests that the change of hormonal levels throughout the menstrual cycle may cause an increase in the laxity to the ACL.

In a systematic review on the menstrual cycle and contraceptives on ACL injuries and laxity, Herzberg et al[7] found that female athletes were at the lowest risk for ACL injury during the luteal phase (days 20-24) of the menstrual cycle and highest risk for

ACL injury and laxity during the ovulatory phase (days 12-14) of the menstrual cycle.[7] It was suggested that the use of HCs may reduce this risk due to their effects on suppressing follicular development and ovulation.[7] Depending on their hormonal concentrations, HCs may play a role in suppressing ovulation, thus, altering female sex hormonal output, and decreasing risk for ligamentous knee laxity and injury.

Hormones and ligamentous physiology. With increasing levels of estrogen, there is a significant decrease in collagen synthesis (40%) and fibroblast proliferation to the ACL.[28] Additionally, estrogen is a vasodilator, which increases the permeability of the blood vessels, thus increasing the water content to the ACL.[29] This creates a circulatory disruption in the ACL that can has been show to increase laxity, thereby predisposing an athlete to injury. [29]

Estrogen also has a role in controlling the receptors of relaxin on the ACL, meaning that when there is an increase in estrogen, there is an increase in relaxin sensitivity on the ACL.[14,29] When there is an upregulation in progesterone, there is an increase is secretion of relaxin which causes a softening in soft tissue structures in the female body.[30] Altogether, the sex hormones, estrogen and progesterone, may have an effect on the hormone relaxin, thus, altering the physiological structure of the ACL and predisposing a female athlete to ligamentous knee injury.[12,14,29,30]

Estrogen and progesterone. Evidence suggests that female sex hormones influence soft tissue structures of the body. Liu et al[29] studied the primary immunolocalization of estrogen and progesterone target cells in the human ACL in 13 women and four men ranging 18-79 years of age.[29] Knee ligament specimens were taken from each subject and studied under a microscope. Their results showed the presence of

estrogen and progesterone receptors in the cells of the ACL. Specifically, the estrogen and progesterone receptors were found in the cell walls of the blood vessels in the ACL, which have been shown to directly affect the metabolism of the cells in the blood vessel walls. [29]

The presence of these sex hormone receptors in the ACL suggest that with their fluctuations, in both males and females, may influence the risk of ACL injury. [29] However, since estrogen and progesterone are present in both males and females, the explanation for the increased prevalence of ligamentous injuries and laxity in females cannot be concluded. [9,29,31] These findings suggest that estrogen and progesterone may have a role in increasing the secretion of other hormonal components of the endocrine system.

Relaxin. Relaxin is a peptide hormone in the insulin superfamily that is regulated by progesterone and glucocorticoids.[4,7,9,14,15] If there is an increase of progesterone or glucocorticoids, there is an effect on relaxin levels, creating a physiologic effect throughout the body.[15] There is a fluctuation of hormones that occur in both pregnant women and non-pregnant women during their menstrual cycle.

During pregnancy the placenta and decidua secrete relaxin,[9,11,14,30,31] which softens the ligaments of the pelvic joints and the pubic symphysis to allow the expansion of the pubic symphysis, up to 10 mm, during labor to expand the birth canal for delivery.[11,14,31] During the luteal phase of the menstrual cycle, the corpus luteum secretes relaxin-2 mimicking its effect of pregnancy on the body.[11,14,31] Although, its effect is to mainly soften the pelvic structures to aid in labor and delivery, relaxin has been shown to have an effect on other musculoskeletal structures of the body.[11,14,31]

Relaxin has collagenolytic effects in its upregulation of collagenases, matric metalloproteinases, and tissue plasminogen activator (tPA).[9,14,30,31] It has an effect on ligamentous structures as it reduces the density and organization of collagen bundles leading to changes and a decrease in total collagen synthesis and content.[9,29,31] This creates an effect on the soft tissue structures of the body, such as the ACL, which can predispose an athlete to a non-contact ligamentous injury.[9] Because relaxin has only been detected in female's, it may explain the significant increase in ACL injuries in females during menstruation, as opposed to males.[9]

The relaxin receptors on the ACL are controlled by estrogen.[14,29] When there is an upregulation of estrogen, there is an increase in sensitivity of target organs, such as the ACL, in its response to relaxin.[14,29] However, relaxin levels are also shown to have a relationship with progesterone.[12] Heitz et al[12] found an increase in ACL laxity with an increase in estrogen and progesterone throughout the menstrual cycle.[12] Nose-Ogura et al[11] found that there was an increase in relaxin levels during the menstrual cycle's luteal phase (phase III) in 63.2% of female athletes.[11] During this phase, there is also an increase in both estrogen and progesterone, suggesting that progesterone and/or estrogen may have an effect on relaxin output. [11]

Relaxin and the female ACL. Dragoo et al[31] studied relaxin receptors in the human ACL.[31] Five females and five males underwent ACL reconstruction surgery where the ACL was harvested arthroscopically. The females answered questionnaires pertaining to their age, history of pregnancy, and their use of oral contraceptives and were given a pregnancy test. If the females were previously or currently pregnant or using oral contraceptives they were excluded from the study. The harvested ACL's were stored and

examined for relaxin levels with results indicating no binding of relaxin on the male ACL's but binding in the female ACL's. It was suggested that, although both males and females have estrogen and progesterone in their bodies, only females have relaxin within their ACL's which may explain the prevalence for higher injury rates in females over males.[31]

Dragoo et al[14] continued this work by examining the effect of relaxin on the female ACL in the animal model.[14] They randomly assigned 12 female guinea pigs into three groups, relaxin (RLX), relaxin plus estrogen (R+E), and normal ACL negative control and positive transected ACL control. Guinea pigs were chosen because of their response to relaxin and having an ACL large enough for biomechanical analysis. Over a 21-day period, the guinea pigs were administered hormonal dosages to reach a pregnancy level. The laxity of the ACL was tested on day 0 and day 21 by implanting radio-opaque markers in the femur and tibia of each leg and applying 22 N of force. The guinea pigs ACL's were tested to determine the ultimate load before failure. After the 21 days of hormone treatment, the guinea pigs treated with RLX, R+E, and controls showed a mean of 40.4 N, 32.7 N and 64.1 N of maximal load to failure, respectively, however there was no statistical difference between the RLX and R+E groups.[14]

This study suggests that anterior displacement of the tibia increased after hormonal treatment from pre-test to post-test, but not between groups.[14] Whether the guinea pigs were treated with RLX or R+E, the results indicate increased laxity to the ACL over the three weeks of treatment, suggesting the hormonal treatment altered the structural integrity of the female ACL. The data also showed the synergistic effect of R+E in that with the increase in estrogen there was an increase in relaxin. However, the

R+E group results were not significant compared to the RLX. This lack of significance

confirms that the presence of relaxin is responsible for a majority of the biomechanical

effect with ACL injury.[14]

Dragoo et al[9] furthered their investigation by studying the correlation between

relaxin and ACL tears among elite collegiate female athletes over a four year period.[9]

The purpose was to study if elite female collegiate athletes with elevated serum relaxin

concentrations (SRC) were at an increased risk of ACL injuries compared to those with

lower SRC. National Collegiate Athletic Association (NCAA) Division I female athletes

participating in basketball, lacrosse, field hockey, soccer, gymnastics and volleyball were

included in this study. Participants were excluded if they were currently pregnant. All

128 participants completed a questionnaire of their demographic information, menstrual

history, pregnancy history, HC use, and ACL injury history. Urine tests were taken to

determine the date of their LH surge. Blood tests revealed high levels of relaxin

indicating subjects were in the mid-luteal phase of their menstrual cycle at the time of

injury.[9]

The results showed that 21.9% of the participants suffered ACL ruptures over the

course of the four-year study. The mean SRC of those who tore their ACL was 6.0 ± 8.1

pg/mL, and the mean SRC of those who did not tear their ACL was 1.8 ± 3.4 pg/mL.

Those with a SRC greater than 6.0 pg/mL were four times as likely to injure their ACL

than those with numbers below 6.0 pg/mL. However, since SRC peaks at the mid-luteal

phase of the menstrual cycle, it is uncertain that the ACL collagen remodeling keeps up

with this hormonal surge. It may be that exposure to high SRC's over long time periods

increases the activation of relaxin receptors and is the possible cause of a decrease in ligament integrity during the menstrual cycle.[9]

Dragoo et al[30] examined the effect of HCs on SRC levels throughout the menstrual cycle in Division I female athletes.[30] The 169 participants that participated in this study recorded their demographic information, menstrual history, pregnancy history, and HC use. Similar to their previous study[4], urine tests were taken to determine the surge in LH and blood draws were taken in the mid-luteal phase so that the levels of SRC could be compared to menstrual history and HC use. It was reported that females taking HCs had lower levels of relaxin and progesterone than those not taking them. This can be described by the mechanism of action in that HCs have been reported to suppress of ovulation and sex hormones during the menstrual cycle. This study also suggests that progesterone may determine the levels of relaxin that are present during the menstrual cycle.[30]

Hormonal contraception. HCs are hormones that can be taken orally, injected, implanted, inserted, or secreted into the female body.[15,32] Females choose to use HCs for various reasons as they alter female sex hormones to manipulate the menstrual cycle.[18,27,32,33] Because evidence suggests that female hormones create a physiological imbalance of the ACL and increases the risk for injury, HCs have been studied to determine their impact on ACL injury risk.

When comparing HC users to HC non-users, a study suggests that there is an association between the use of HCs and ACL injury.[7] There have been significant findings that HCs decrease the risk of ACL injury and knee laxity in female athletes.[6.7] The majority of this literature examines the use of commonly-used oral contraceptive

pills (OCP) compared to alternative HC methods. In one study, OCP use decreased the risk of ACL injury by 20% in female athletes, but it is unclear which type of OCPs were studied.[7] There is limited evidence comparing the two classifications of HCs, progestin-only versus estrogen+progesterone HC, and the different delivery modes of HCs.

Classification. HCs can be classified into two categories, combined hormonal contraceptives (CHCs) of estrogen and progesterone, or progesterone-only contraceptives (POCs), all of which prevent ovulation using different mechanisms.[18,27,32,33] Sixty-eight point five percent of female athletes use CHCs and 30% use POCs.[18] Individually, both estrogen and progestin (progesterone) are able to inhibit follicle-stimulating hormone (FSH) and LH to suppress ovulation.[32,33] Progestin blocks the midcycle rise in LH secretion causing it to inhibit ovulation.[32,33] Ethinyl estradiol (estrogen) creates an increase in effectiveness of progestin to prevent irregular shedding of the endometrium.[32,33] Together, CHCs (estrogen and progesterone combined) create a highly viscous cervical mucosa which causes an unsuitable environment for transportation and implantation of sperm.[32,33]

In progestin-only contraceptives (POC), progestin creates a disruption in the hypothalamic-pituitary function, creating the suppression in ovulation. However, since the doses are lower in POCs contraceptives compared to CHCs there is higher chance of ovulation occuring.[32]

Modes of delivery. There are subcategories of modes of delivery for both CHCs and POCs. HCs are determined for each individual female and their intended mechanism of use. The modes of delivery of HCs are oral pills, injections, transdermal patches, subdermal implants, intravaginal rings, and intrauterine devices.[18,27] Oral contraceptives

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are used the most by 78.4% of female athletes, followed by 13.1% implants, 3.8% injections, 2.8% IUDs, and 0.5% intravaginal rings.[18] Oral contraceptive pills (OCP) have a first pass effect on the liver, meaning that it gets metabolized by the liver, and requires a greater dose of hormones.[33] Other HCs bypass the liver, and require less doses of hormones.[33]

Oral contraceptive pills. Combined OCPs inhibit FSH and LH to prevent ovulation in the cervical mucosa and create changes in the endometrium to avoid implantation of sperm.[6,27,32] Combined OCPs generally consist of 21 active tablets and seven inactive tablets that are taken on a daily basis.[27] However, this ratio can vary depending on the OCP being taken.[27] The active tablets can consist of monophasic, biphasic, or triphasic formulas.[27] The monophasic tablets consist of varying levels of estrogen and progesterone within each pill.[27] The biphasic consist of two tablets of combinations of other hormones.[27] Triphasic tablets are similar as they consist of combinations of other hormones, but in three tablets.[27] These types of OCPs mimic the hormonal changes during the menstrual cycle.[27] There is about 20-50 mg of estrogen and variations of the progesterone in the active tablets.[27] POC pills, also known as "minipills", are like OCPs, but contain low doses of progesterone only.[27,32]

Contraceptive injections. Contraceptive injections are a single 150 mg dose of medroxyprogesterone acetate (DMPA), a derivative of progesterone.[27,32] DMPA's mechanism of action is to suppress ovulation with the effects of the POCs.[27,32] It is administered once every three months but has side effects which can include irregular bleeding at the onset of use, weight gain, and delay of fertility after cessation of injections.[27]

Transdermal patches. Transdermal patches consists of 150 mg of norelgesteromin (progestin) and 35 mg of ethinyl estradiol (estrogen).[27] The patch is applied for the first three weeks of the menstrual cycle, then taken off for the last week of the menstrual cycle.[27] Typically, it is placed on the abdomen, back, buttocks, or upper outer arm and can maintain itself through daily activities.[27] Side effects can include headache, dysmenorrhea, breast discomfort, and local irritation at the application site.[27]

Subdermal implants. Subdermal implants consist of a 4 cm by 2 mm rod implanted into the body. Its mechanism of action is to partially suppress ovulation using the effects of the POCs.[27,32] The rod has an inner ethylene vinyl acetate core surrounded by crystals containing etonogestrel, the active ingredient in progestin.[27,32] Upon implantation, the implant releases 60-70 mg per day of progestin.[27] That number is modified to 35-40 mg per day at the end of the first year, 30 mg per day at the end of the second year, and 40 mg per day at the end of the third year.[27] The rod is surgically implanted and recommended to be removed at the end of three years of use.[27] The most common side effect is irregular bleeding with the onset of use, however, there can also be changes in sex drive, weight gain, discoloration, or scarring of the skin over the implant, and pain or infection at the insertion site.[27]

Intravaginal rings. The intravaginal ring is a non-biodegradable, flexible, transparent device that is inserted into the vagina.[27] It is similar to the transdermal patch as it is inserted for the first three weeks of the menstrual cycle and removed for the last week of the menstrual cycle.[27] The intravaginal ring releases etonogestrel and ethinyl estradiol at a rate of 0.120 mg and 0.015 mg per day, respectively.[27]

Intrauterine devices. Intrauterine devices (IUDs) are a POC method consisting of a T-shaped polyethylene frame with a steroid reservoir, containing a combination of levonorgestrel (progestin) and silicon, around the vertical stem.[27] The device can hold either 13.5 mg or 52 mg of levonorgestrel that provides contraception for three or five years, respectively.[27]

Hormonal contraception and ligamentous knee injury. The regulation of hormones throughout the menstrual cycle has shown to create an effect on the integrity of the ACL.[6] It has been suggested that these hormones are creating a risk factor for female athletes. However, HCs can potentially decrease this risk with its direct effect on the menstrual cycle with the hormones that it secretes into the body.[6] CHCs, specifically, OCPs, contain set levels of estrogen and progesterone.[6] These inhibit pituitary FSH and LH to prevent ovulation.[6] Hence, it may have an effect on ligamentous structure and laxity.

Hormonal contraceptive users versus hormonal contraception nonusers. Martineau et al[6] studied ligamentous laxity in users of the OCP as compared to nonusers of the OCP.[6] Female varsity athletes at an institution underwent a KT-1000 passive anterior translation measurement during their preseason physical examination. A screening questionnaire was completed to identify exclusion criteria. It asked about the use of OCP, and if so, the type of OCP, pregnancy history, and previous or present use of hormone-containing or hormone-altering products. Passive anterior translation of the tibia was measured with the KT-2000 Arthrometer at 67 N and 89 N.[6]

There were 78 participants in this study. Forty-two were OCP users and 36 were non OCP users. The results showed that the mean anterior translation of the tibia on the

non-dominant leg at 67 N of force was 3.00 ± 1.04 mm in OCP users and 3.86 ± 1.72 mm in non OCP users. The mean anterior translation of the tibia on the non-dominant leg at 89 N of force was 3.98 ± 1.13 mm in OCP users and 4.83 ± 1.82 mm in non OCP users. These results were statistically significant, indicating that the OCP users had reduced knee laxity compared to non OCP users.[6] This suggests that OCP use may not increase knee laxity in female athletes, thus, decreasing their risk of ligamentous knee injury.

Rahr-Wagner et al[26] investigated women who underwent ACL reconstruction and their use of oral contraceptives (OC) over a six-year period.[26] Included were 4,497 cases and the researchers matched each with at least one control. The OC use among women in both groups was investigated and the women were identified as either "never users," (those who had no OC prescriptions throughout the study period) and "ever users" (those who had greater than or equal to one OC prescription throughout the study period).[34] OC use was further examined by exploring how many years each case and control used it, with each subject rated as using it 1, 2 ,3, 4, or >4 years. They found that the "ever users" had a 11-20% decrease in risk of suffering an ACL injury that required surgery when compared to "never users". However, the length of OC use did not have an effect on ACL injury risk.[26] This means that those women who suffered an ACL injury that required operative treatment and were on an OC, despite the amount of time on it, were at a decreased risk for ACL injury compared to those not on an OC.

Ruedl et al[34] studied menstrual cycle phase and OC use in recreational skiers who suffered non-contact ACL injuries.[34] Over two winter seasons, subjects were recruited from a ski clinic where they underwent magnetic resonance imaging (MRI) for diagnosis of an ACL tear. Ninety-three subjects were included and were matched with 93 controls.

The subjects were given a questionnaire that recorded demographic information, history of knee injuries, menstrual cycle information, and the use of OC. The researchers found that OC use did not have an effect on decreasing the risk for ACL injury.[34]

Hicks-Little et al[2] also used the KT-100 knee arthrometer to assess anterior tibial displacement throughout the menstrual cycle stages and those who were using and not using HCs at the time of the study.[2] Fifty-three female athletes with at least one healthy knee and a normal menstrual cycle were included. The average of two anterior tibial displacement measurements were taken on day 1, 13, and 23 of the menstrual cycle in conjunction with the three phases. The results showed that the subjects using HCs had increased laxity of the knee compared to subjects not using HCs.[2] The researchers did not assess or indicate which types or modes of delivery of HCs were being used. These results suggest that HC use for the decrease in knee laxity is inconsistent throughout the literature.

Conclusion. Female athletes have been shown to have greater amount of ligamentous knee laxity and greater risk for ligamentous knee injury compared to males. There are various risk factors that contribute to this with hormonal risk factors being one of them. Hormonal fluctuations that occur during the menstrual cycle may contribute to an increased risk of sustaining a ligamentous knee injury and hormonal contraceptive may reduce this risk, however, further research is needed on these matters.

Statement of the Problem

There is evidence suggesting that hormonal changes present during the menstrual cycle have an association with ligamentous knee injury. However, the data on the relationship between hormonal contraceptive use and ligamentous knee injuries among

female athletes is inconsistent. Also, there is limited evidence on the relationship between the types and modes of delivery of hormonal contraceptives and the risk of ligamentous knee injury.

Aims and Hypotheses

The purpose of this study is to determine the relationship between hormonal contraceptive (HC) use, and the type and severity of the injury sustained among female collegiate athletes who experience a ligamentous knee injury. It is hypothesized that there will be a relationship between the use of hormonal contraceptives and type and severity of ligamentous knee injury among female collegiate athletes who experience them.

Specific hypotheses. Specific objective 1 is to identify the types of ligamentous knee injuries that are sustained by female collegiate athletes.

Specific hypothesis 1 is that there will be a greater number of anterior cruciate ligament injuries (ACL) compared to lateral collateral ligament (LCL), medial collateral ligament (MCL), and posterior cruciate ligament (PCL) injuries in female collegiate athletes who sustain a ligamentous knee injury.

Specific objective 2 is to identify in which phase of the menstrual cycle female collegiate athletes are at most risk for a ligamentous knee injury.

Specific hypothesis 2 is that female collegiate athletes in the luteal phase of the menstrual cycle will have the greatest number of ligamentous knee injuries compared to those in the follicular phase and ovulatory phase of the menstrual cycle.

Specific objective 3 is that among female athletes who sustain ligamentous knee injuries, determine the number who use combined-hormonal contraceptives (CHCs) versus progestin-only contraceptives (POCs).

Specific hypothesis 3 is that **a**mong female collegiate athletes who sustain a ligamentous knee injury, a greater number will report using progestin-only contraceptives versus combined hormonal contraceptives (CHCs).

Specific objective 4 is that among female collegiate athletes who sustain a ligamentous knee injury, determine the number who use hormonal contraceptives versus those who do not.

Specific hypothesis 4 is that among female collegiate athletes who sustain a ligamentous knee injury, there will be a greater number who are hormonal-contraceptive users compared to hormonal contraceptive non-users.

Specific objective 5 is to identify the types of hormonal contraceptives that female collegiate athletes are using when sustaining a ligamentous knee injury.

Specific hypothesis 5 is that there will be a greater number of female collegiate athletes who sustain a ligamentous knee injury who are users of oral contraceptive pills (OCP) compared to those who use intravaginal rings, transdermal patches, subdermal implants, and injections.

Specific objective 6 is that among female collegiate athletes who have had a ligamentous knee injury, determine the relationship between hormonal contraceptive use and type of ligamentous knee injury sustained.

Specific hypothesis 6 is that the use versus non-use of hormonal contraceptives among female athletes who sustain a ligamentous knee injury will not be associated with the type of injury sustained.

Specific objective 7 is that among female collegiate athletes who have had a ligamentous knee injury, determine the relationship between hormonal contraceptive use and severity of the ligamentous knee injury.

Specific hypothesis 7 is that the use of hormonal contraceptives among female athletes who sustain a ligamentous knee injury will be associated with a less severe injury.

Manuscript

Abstract

Context: Female athletes are three to six times more likely than males to sustain a ligamentous knee injury due to hormonal risk factors. Hormones of the menstrual cycle have been shown to alter the physiological component of ligamentous structures during the three phases of the cycle. Use of hormonal contraceptives (HCs) may influence the incidence and severity of ligamentous knee injuries in female athletes.

Objective: To determine the relationship between HC use and the type and severity of knee ligament injuries sustained among female collegiate athletes.

Design: Cross-sectional study.

Setting: Online survey.

Patients or Other Participants: Female National Collegiate Athletic Association (NCAA) athletes at least 18 years of age or older who experienced a ligamentous knee injury during the study time period (n=336).

Data Collection and Analysis: Electronic survey assessed the type and severity of the ligamentous knee injury, body mass index, variables related to the menstrual cycle, and variables related to HC use. Chi-Square analyses were performed using SPSS version 26.

Results: There were significant relationships between injury type and severity of injury (measured by days lost of participation) X^2 (2, n=170)=40.9, $p = 0.000$, injury type and severity of injury X^2 (8, n=170)=47.4, p=0.000, and injury type and menstrual cycle phase X^2 (10, n=192)=43.397, p=0.000. A majority of respondents were using HCs. Most (37.9%) of the injuries occurred in the luteal phase of the menstrual cycle, where athletes

were more likely to sustain multiple ligament injuries. The type of ligamentous knee injury impacted the severity of the injury.

Conclusions: Female athletes were at the greatest risk for ligamentous knee injury in the luteal phase of the menstrual cycle. Future work should aim to identify injury prevention programs, protective equipment, and HC for decreasing the risk for ligamentous knee injury.

Key words: Female athletes, ligamentous knee injury, menstrual cycle, hormonal contraceptives.

Introduction

Since the passing of Title IX of the United States Education Assistance Act in 1972, there has been a significant increase of female participation in athletics.[1,2] In professional basketball, 60% more injuries occur in women as compared to men, with 16% of these injuries being to the knee.[5] Compared to male athletes, female athletes have a 20% increase in rotary knee laxity and a significantly higher score on the Landing Error Scoring System (LESS), placing them in a high-risk category.[15] Collegiate female athletes account for approximately 67% of all anterior cruciate ligament (ACL) injuries and 69% of non-contact ACL injuries compared to their male counterparts, making females 3-6 times more likely than males to sustain an ACL injury.[6,7,8,9,10]

Hormonal risk factors are one of the various underlying risk factors that can predispose an athlete to a ligamentous knee injury.[9,13] Specifically, the menstrual cycle can increase the susceptibility of non-contact knee injuries in female athletes because of its constant fluctuation of hormones throughout the phases. [6,8,9,12,14] Wojtys et al[25] found that the time frame females sustained ACL injuries was more likely to occur in the

ovulatory phase (phase II, days 10-14) of the menstrual cycle compared to the other phases.[25] Heitz et al[12] found the greatest amount of laxity in the luteal phase (phase III, days 15-28) of the menstrual cycle.[12] Hertzberg et al[7] found that there was an increased risk of ACL injury during the ovulatory phase (phase II, days 12-14) of the menstrual cycle.[7]

Estrogen and progesterone have been shown to have receptors on the ACL in both males and females.[29] However, only females are reported to produce relaxin. This hormone which is controlled by estrogen and progesterone alters collagen synthesis to soften soft tissue structures during pregnancy and phase III of the menstrual cycle.[9,11,14,29,30] This physiological alteration can predispose a female athlete to a ligamentous knee injury. Dragoo et al[14] found an increase in anterior tibial displacement after the treatment of estrogen and relaxin in an animal model.[14] In a different study, Dragoo et al[9] found that female athletes with elevated serum relaxin concentrations (SRC) were four times as likely to tear an ACL than those with lower SRC.[9]

The literature assessing the use of hormonal contraceptives (HCs) in decreasing the risk of ligamentous knee injury in females is inconsistent. Martineau et al[6] studied oral contraceptive pill (OCP) use in female athletes and found a greater decrease in knee laxity in OCP users compared to OCP non-users.[6] Rahr-Wagner et al[26] found a 11-20% decrease in risk of sustaining an ACL injury in HC users compared to non-users.[26] Ruedl et al[34] reported that OCP use has no effect on decreasing ACL injury risk.[34] Hicks-Little et al[2] concluded that users of HC have an increase in laxity compared to HC non-users.[2] Also, there is no published evidence on the relationship between the types and modes of delivery of HCs and the risk of ligamentous knee injury.

The purpose of this study is to determine the relationship between hormonal contraceptive use and the type and severity of the injury sustained among female collegiate athletes who sustain ligamentous knee injuries. We hypothesize that there will be a relationship between the use of hormonal contraceptives and both type and severity of ligamentous knee injury in female collegiate athletes who have these injuries.

Methods

Participants. We emailed NCAA athletic trainers from Division I, II and III institutions with a link to an electronic survey to share with female athletes at their institutions who were competing during the fall 2019/winter 2019 season and sustained a ligamentous knee injury.

Inclusion criteria. Female collegiate athletes participating in athletics at NCAA institutions were included in this study. They were at least 18 years of age, sustained a ligamentous knee injury (ACL, MCL, PCL, LCL) in their fall 2019/winter 2019 sport season (August 1, 2019 – December 31, 2019), had at least one day's loss of athletic participation, and were evaluated by an athletic trainer or diagnosed by physician as having a ligamentous knee injury.

Exclusion criteria. Eligible participants were excluded if one or more of the following criteria were present: currently pregnant, had a previous procedure of a hysterectomy or tubal ligation, used an IUD at time of injury, used a hormonal treatment that is not considered hormonal contraception (example: testosterone) at the time of injury, and/or did not identify as a female.

Pregnant female collegiate athletes were excluded because their hormonal levels are different from those of non-pregnant athletes throughout the monthly cycle. Female

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collegiate athletes who have had a hysterectomy (removal of the uterus) or tubal ligation (blockage of the fallopian tubes) were also excluded because they do not menstruate and may be on a hormonal treatment other than hormonal contraceptives (HCs). Females who use IUDs were also excluded, as they are typically women who already have children. They are likely to have hormonal levels that are unlike the traditional-aged, childless female collegiate athletes. In addition, most IUDs do not contain any hormones. Since the purpose of this study was to investigate the potential impact of hormonal contraception, it was not appropriate to include the IUD user in the group of participants.

Procedures. We created an electronic survey using the Qualtrics Survey Software system (Provo, UT). Consent was obtained from the eligible participants electronically before starting the survey (Appendix A). We utilized the National Athletic Trainers' Association's (NATA) Research and Education Foundation's resources to distribute the surveys to NCAA athletic trainers nationally, reaching 4,389 athletic trainers. Data were collected between August 20, 2019 and December 31, 2019. Additional materials (i.e: personal letter and flyers) were used to recruit participants (Appendix B). This study was reviewed and approved by the researcher's University Institutional Review Board (IRB), Study ID: Pro2019000511.

Survey. The online survey consisted of a total of 26 questions related to exclusion criteria (stated above), demographic information (age, sex, height, weight, division, and sport), ligamentous knee injury characteristics (date the injury was sustained, type of injury, mechanism, and playing surface), menstrual cycle characteristics (on menstrual cycle at time of sustaining the injury and dates of last 3 menstrual cycles), and HC use

(use at the time of injury, mode of delivery, name, milligram contents, and menstruation frequency) (Appendix A).

Menstrual cycle phase calculation. We calculated the menstrual cycle phase for each participant by counting the number of days between the date that the participant's ligamentous knee injury occurred and the date of her most recent menstrual cycle. For the 15 participants who did not list both dates, we made an assumption that their menstrual cycles were 28 days long and calculated the date of the start of their menstrual cycle after their knee injury. We excluded 21 participants who did not indicate that they menstruated monthly.

For the 168 participants who provided usable data, the menstrual cycle phase was categorized as either "Follicular", "Ovulatory", "Luteal" or "Over 35 days" (Table 1).

Table 1

Menstrual Cycle Phases

Menstrual Cycle Phase	Number of Days into the Menstrual Cycle
Follicular	0-9
Ovulatory	10-14
Luteal	15-35
Over 35 days	Greater than 35

Data analysis. All data analyses were completed using SPSS v.26 (IBM SPSS, Inc. Chicago, IL). Descriptive statistics were calculated for each variable. Means and standard deviations were identified for age, height, weight, and body mass index. Next, we conducted a series of Chi-Square analyses to determine the significance of the

relationships between key variables. First, we explored the relationship between HC use (users vs. non-users) and type of ligamentous injury sustained (single vs. multiple ligament injury). Second, we analyzed the relationship between HC use and the severity of the ligamentous knee injury sustained (as reflected by the number of days' participation lost due to the injury). Third, we examined the relationship between the type of ligamentous knee injury and the severity, as measured by days of participation loss. Fourth, we examined the relationship between menstrual cycle phase and injury type.

We ran t-tests to compare the means of BMI for athletes with single versus multiple ligament injuries. We explored the relationships between BMI and injury type using both t-tests and a one-way ANOVA.

Results

Response rate. A total of 336 of these athletes completed the survey. We could not calculate the response rate because we did not know how many female athletes sustained a ligamentous knee injury and how many of them were asked by their athletic trainer to complete the survey. After exclusion criteria were applied to the data, a total of 212 responses were eligible for use in analyses.

Demographic and injury characteristics. We identified the demographic and injury characteristics of the 212 respondents (Table 2). The mean age of the respondents was 20 ± 1.193 years. Division III collegiate female athletes sustained more ligamentous knee injuries than any other division (39.6%). Injuries were also highest among women's soccer players (60.9%), through a non-contact mechanism (65.6%), and on an artificial grass (turf) playing surface (41.4%). The majority of respondents (74.5%) lost 29 days or more of athletic participation time loss (Table 2).

Of the 192 ligamentous knee injuries sustained by the respondents, more than half (61.5%) of the injuries were characterized as an ACL tear alone and 23.4% ACL injuries occurred in conjunction with an injury to another ligamentous structure of the knee (Table 2). There were 142 (74%) respondents who had a single ligament involvement, compared to 47 (24.5%) respondents who had multiple ligament involvement. The remaining 3 respondents were unsure what their injury was, and we characterized them as "unknown". Approximately, 75% of the respondents lost 29 or more days of athletic participation (Table 2).

Table 2

Demographic and Injury Characteristics of Respondents

Variable (out of N respondents of each variable)	n (%)
Age in years (N = 212)	
18	41 (19.3)
19	40 (18.9)
20	60 (28.3)
21	58 (27.4)
22	11 (5.2)
Greater than 22	2 (0.9)
Division (N = 192)	
Division I	67 (34.9)
Division II	49 (25.5)
Division III	76 (39.6)
Sport (N = 192)	
Women's soccer	117 (60.9)
Women's basketball	28 (14.6)
Women's indoor volleyball	16 (8.3)
Women's lacrosse	11 (5.7)
Other	20 (10.4)
Mechanism (N = 192)	
Contact	66 (34.4)
Non-contact	126 (65.6)
Playing surface (N = 192)	

Table 2 (continued)

Variable (out of N respondents of each variable)	n (%)
Artificial grass	79 (41.4)
Grass	56 (29.2)
Gymnasium floor	49 (25.5)
Other	8 (4.2)
Type of ligamentous knee injury (N = 192)	
ACL	118 (61.5)
ACL + LCL	4 (2.1)
ACL + LCL + MCL	4 (2.1)
ACL + MCL	31 (16.1)
ACL + PCL	1 (0.5)
ACL + PCL + MCL	3 (1.6)
ACL + PCL + MCL + LCL	1 (0.5)
LCL	1 (0.5)
LCL + MCL	2 (1)
MCL	21 (10.9)
PCL	2 (1)
PCL + MCL	1 (0.5)
Unknown	3 (1.6)
Type of ligamentous knee injury (N = 192)	
Single ligament	142 (73.9)
Multiple ligaments	47 (24.5)
Unknown	3 (1.6)
Days loss of athletic participation (N = 212)	
Up to 7	13 (6.1)
Up to 14	15 (6.6)
Up to 21	14 (6.1)
Up to 28	12 (5.7)
29 or more	158 (74.5)

Menstrual cycle and hormonal contraceptive use characteristics. We report

the data on menstrual cycle and HC use in Table 3. Approximately 70% of the

participants did not recall being on the menstrual cycle when sustaining their ligamentous

knee injury. The majority (37.9%) of the participants were in the luteal phase of the

menstrual cycle at the time of injury.

More than half (60.4%) of the respondents were using a HC at the time of injury while the rest were not on a HC (39.6%). Of the HC users, 87.7% were using a combined hormonal contraceptive (CHC) vs. 12.5% using a progestin-only contraceptive (POC). 87.7% of respondents that were using an OCP at the time of sustaining their ligamentous knee injury. More than half of the respondents did not answer the questions pertaining to the classification of their HC, which may limit these findings.

Table 3

Menstrual Cycle and Hormonal Contraceptive Usage Characteristics

Variable (out of N respondents of each variable)	n (%)
On menstrual cycle at time of injury (N = 192)	
Yes	41 (21.4)
No	132 (68.8)
I don't remember	19 (9.9)
Menstrual Cycle Phase (N = 190)	
Follicular	56 (29.5)
Ovulatory	25 (13.2)
Luteal	72 (37.9)
Over 35 days	15 (7.9)
Unknown	22 (11.6)
Hormonal Contraceptive Use (N = 192)	
Yes	116 (60.4)
No	76 (39.6)
Hormonal Contraceptive Mode of Delivery (N = 114)	
Oral Pill	100 (87.7)
Subdermal implant	9 (7.9)
Injection	3 (2.6)
Intravaginal ring	2 (1.8)
Transdermal patch	0 (0)
Hormonal Contraceptive Classification (N = 104)	
Combined hormonal contraceptive (CHC)	91 (87.5)
Progestin-only contraceptive (POC)	13 (12.5)
Menstruation Frequency (N = 98)	
Every month	75 (76.5)
Every 2 months	2 (2)

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Table 3 (continued)

Variable (out of N respondents of each variable)	n (%)
Every 3 months	6 (6.1)
Never	10 (10.2)
Other	5 (5.1)

Results of Chi-Square analyses. Chi-Square analyses showed no significance between ligamentous knee injury type and any of the following variables: HC use, playing surface, type of sport played, BMI or menstrual cycle phase (Table 4).

Injury type when characterized as the top three injuries. There was a statistically significant relationship between ligamentous knee injury type (when categorized as the top three injuries: ACL, ACL+MCL, and MCL) and the severity of the ligamentous knee injury (as measured by days' participation loss) X^2 (2, N = 170) = 40.9, p = 0.000 (Table 4). Injuries involving the ACL (ACL alone or ACL+MCL) were significantly more likely to result in a loss of 29 days or more when compared to injuries of the MCL alone. This was further demonstrated when we collapsed the severity categories to just two (less than 29 days or greater than or equal to 29 days) X^2 (8, N = 170) = 47.4, p = 0.000 (Table 4).

Table 4

Injury Type Chi-Square Analyses (when categorized as top three injuries: ACL, ACL+MCL, and MCL)

Variables	Df	Value	p
Hormonal contraceptive use	2	0.751	0.687
Playing surface			
All categories	6	2.337	0.886
Artificial grass/turf, grass, gymnasium floor, other	18	12.917	0.796

Table 4 (continued)

Variables	Df	Value	p
Sport			
All sports	2	1.268	0.530
Women's soccer vs. other	16	13.919	0.605
Menstrual cycle phase	10	9.586	0.478
Severity			
5 categories	2	40.9	*0.000
2 categories	8	47.4	*0.000

*statistical significance ($p < 0.05$)

Injury type as single versus multiple ligament injuries. Chi-Square analyses

showed no significant relationships between the amount of ligament involvement (single

versus multiple) and the following variables: severity, type of sport played, HC users vs.

non-users, division, HC type, BMI, and playing surface (Table 5). There was a

statistically significant relationship between the amount of ligament involvement and

menstrual cycle phase X^2 (10, $N = 192$) = 43.397, $p = 0.000$ (Table 5). For both single and

multiple ligament injuries, athletes were most likely to be in the luteal phase of the

menstrual cycle. This was especially true for athletes with multiple ligament injuries.

Table 5

Injury Type Chi-Square Analyses (when categorized as single versus multiple ligament injury)

Variables	Df	Value	p
Hormonal contraceptive use	1	0.363	0.547
Playing surface			
All categories	9	5.960	0.744
Artificial grass/turf, grass, gymnasium floor, other	3	4.013	0.874

Table 5 (continued)

Variables	Df	Value	p
Sport			
All sports	8	5.429	0.711
Women's soccer vs. other	1	0.025	0.874
Severity			
5 categories	4	3.960	0.411
2 categories	1	0.901	0.342
Division	2	0.088	0.957
Hormonal contraceptive type	2	0.578	0.749
Mode of delivery	5	1.481	0.915
Menstrual cycle phase (5 categories, see table 3)	10	43.397	*0.000

   *statistical significance ($p < 0.05$)

Results of t-test and one-way ANOVA. We ran an independent samples t-test to explore the relationship between BMI and the two levels of injury, single versus multiple. The results did not show significance between the means [t (186) = -0.165, $p = 0.869$)]. We also ran a one-way ANOVA to explore the relationship between BMI and three levels of injury type. This result was also non-significant [F (2,166) = 0.051, $p = 0.950$].

Discussion

The purpose of this study was to determine the relationship between hormonal contraceptive use and the type and severity of the injury sustained among female collegiate athletes who sustain a ligamentous knee injury. We hypothesized that there would be a relationship between the use of hormonal contraceptives and type and severity of ligamentous knee injury among female collegiate athletes who experience them. Our specific hypotheses examined the type of ligamentous knee injuries sustained, which phase of the menstrual cycle the injury was sustained, the types of hormonal contraceptives that were used, the number of respondents who were hormonal

contraceptive users vs. non-users, modes of delivery of the hormonal contraceptives, and severity of the ligamentous knee injuries.

Type of injury sustained. Anterior cruciate ligament (ACL) injuries were the most commonly injured ligament structure of the knee (84.4%), regardless if it was isolated or combined with another ligamentous injury, thus supporting our first hypothesis. It commonly occurred in isolation (61.5%) rather than combined with another ligamentous structure of the knee (22.9%). Previous research by Anderson et al[10] has reported a 67% occurrence rate of ACL injuries among female athletes, although it is unknown how many structures were involved in these cases.[10]

Medial collateral ligament (MCL) were the second most frequent injury type in this study, at 10.9% for isolated and 21.9% for combined ligament injury, resulting in a total occurrence prevalence of 32.8%. This is slightly higher than the reported 26-29% occurrence rate of MCL injuries in other studies.[21,23]

Both lateral collateral ligament (LCL) and posterior cruciate ligament (PCL) occurred in 6.25% and 4.16% of the cases in this study, respectively. Both were slightly higher than previously reported occurrences of 2-4% in other studies.[21,23] They both were most commonly associated with another knee ligament injury.

Severity of injury sustained. Respondents who had an ACL or ACL+MCL ligamentous knee injury were more likely to have 29 or more days of athletic participation loss compared to an MCL alone ligament injury. Therefore, if the ACL is involved in the ligamentous knee injury, there is a greater chance of missing more playing time as compared to other ligamentous structures of the knee. The ACL plays a large role in stabilizing the knee by preventing anterior translation and rotation of the

tibia and the MCL stabilizes the medial knee by preventing valgus motion.[22] Surgical

intervention is often determined for MCL injuries dependent on the grade of the injury.[36]

Grades I and II typically heal with conservative treatment, while grade III may need

surgical intervention depending on its response to non-operative treatment or if it is

combined with another ligamentous structure, such as the ACL, that requires operative

treatment.[36] Since the ACL has a large role in stabilizing the knee[22], when it is damaged it

may needs surgical intervention to be repaired to allow for normal gait.

Menstrual cycle phase. Ligamentous knee injuries occurred most often during

the luteal phase of the menstrual cycle at 37.9%, supporting our second hypothesis. Our

results confirm the prior findings of Heitz et al[12], who found that the greatest amount of

ACL laxity occurred in the luteal phase of the menstrual cycle.[12] However, there were

only seven subjects included in their study and ACL laxity was measured, not ACL

injury risk or surveillance of ACL injury. Wojtys et a[25] found that 15 women suffered a

non-contact ACL injury in the follicular phase, 28 in the ovulatory phase, and 22 in the

luteal phase of the menstrual cycle.[25] Also, Hertzberg et al[7] found that females were at

the lowest risk of ACL injury in the luteal phase of the menstrual cycle and the highest

risk of ACL injury in the ovulatory phase of the menstrual cycle.[7] Although our results

showed that the greatest amount of ligamentous knee injury occurred in the luteal phase

of the menstrual cycle, there was less than a 10% difference between injuries that

occurred in the luteal phase and injuries that occurred in the follicular phase of the

menstrual cycle.

This study hypothesized an increase in ACL injury rates due to the reported

increase in hormone levels during the menstrual cycle's luteal phase. During this phase,

both estrogen and progesterone spike and fluctuate throughout.[7,8,15,25,27] Also, relaxin

levels increase and peak during this phase in 63.2% of female athletes.[9,11] This may cause

a hormonal imbalance and predispose the knee to ligamentous injury. It is important to

note that each menstrual cycle phase is different in length of days, and that the luteal

phase may be associated with more injuries simply because it is longer than the others

and not because of hormonal differences. While we cannot change the time length for

each phase, we interpret our statistical analyses using the variable menstrual cycle phase

with this confounder in mind.

The second greatest occurrence of ligamentous knee injury was in the follicular

phase of the menstrual cycle, which could be for two reasons. One being that the

follicular phase is the second largest time frame of the three menstrual cycle phases

following the luteal phase and more injuries would occur during this compared to the

ovulatory phase. Second, this could be explained by the theory that ACL collagen

remodeling may not keep up with the hormonal surges that occur during the luteal phase

of the menstrual cycle and may not present with the ligamentous knee injury until a later

time.[9]. It may be that exposure to high serum relaxin concentrations over long periods of

time increases the activation of relaxin receptors and is the possible cause in ligament

integrity during the menstrual cycle.[9]

Single vs. multiple ligament involvement. We found the highest number of

multiple and single ligament injuries occurring in the luteal phase of the menstrual cycle,

especially multiple ligament injuries. This coincides with our second hypothesis that

there would be a greater number of ligamentous knee injuries in the luteal phase of the

menstrual cycle compared to the follicular and ovulatory phases. While there was not a

large difference between the number of ligamentous knee injuries that occurred within each menstrual cycle phase, our findings of a greater occurrence of multiple ligament injuries during the luteal phase makes our hypothesis and findings especially true. Not only were the respondents more likely to sustain a ligamentous knee injury during the luteal phase, they were also more likely to sustain multiple ligament knee injuries. However, further research is needed to strengthen the literature on this topic.

Hormonal contraceptive use.

Types of HC used. Over 80% of our respondents were using a CHC compared to a POC. This does not support our third hypothesis that among female collegiate athletes who sustain a ligamentous knee injury, a greater number will report using POCs versus CHCs. We based our hypothesis off the literature that CHCs contain doses of both estrogen and progestin and in return can control both of these sex hormone fluctuations (estrogen and progesterone) that occur during the menstrual cycle. Therefore, POCs only control for progestin and we believed that with estrogen not being controlled in the POC users there would be a greater amount of injuries. However, CHCs tend to be more commonly used because they are better tolerated than POCs due to fewer negative side effects.[13] In our study, 87.5% of female athletes reported using CHCs, which is higher than the prevalence reported by Martin[18] (68.5%) of CHCs used by female athletes.[13] We determined the type of HC used by determining the milligram contents of the HCs reported by respondents in the survey, which may have resulted in some inaccuracy due to the nature of self-reported data.

Hormonal contraceptive users versus non-users. Our fourth hypothesis was also supported by the data, which showed a greater number of HC users (60.4%) than non-

users (39.6%) among this population. This is greater than what Martin[18] previously reported (49.5%).[18] These results may be due to the multiple mechanisms of action of HCs, such as the contraceptive effect and decreasing the symptoms associated with dysmenorrhea.[6,7] This can work in favor of competitive female athletes by decreasing the likelihood of missing playing time.[19] It is worth noting that the reason for HC use was not assessed in the participants of our study.

Type of injury sustained. We did not find any significant associations between the HC users and non-users and the type of injury sustained, which supports our sixth hypothesis. There is limited evidence on this because most of the literature assessed either the ACL only or other structures of the body, such as the patellar tendon and achilles tendon.[35] As for ACL injury assessment, Ruedl et al[19] concluded that HC use, specifically OCPs, had no effect on decreasing the risk for ACL injury.[19] Further research is needed on assessing injuries of all ligamentous structures of the knee and their association with the use vs. non-use of HCs.

Severity of injury sustained. Last, we did not find any significant associations between the use of hormonal contraceptive and a less severe injury, which does not support our seventh hypothesis. Although, we did find that those who had the ACL involved in their ligamentous knee injury had a greater severity or time loss from participation, this was not associated with the use or non-use of hormonal contraceptives and more literature is needed on this matter.

Modes of delivery. The most common HC mode of delivery in HC users was the OCP at 87.7% compared to alternative modes of delivery at 12.3%, which supports our third hypothesis. This is greater than what was previously reported at 78.4% by Alentorn-

Geli et al.[13] Competitive female athletes favor OCPs compared to other modes of delivery because of their ability to manipulate menstruation.[11] Schaumberg et al[11] reported a significant difference in menstruation manipulation planning in competitive athletes compared to sub-elite recreationally active women.[11] Alternative modes of delivery (subdermal implants, injections, intravaginal rings, and transdermal patches) may be used less often than OCPs because they are administered/ implanted by either a doctor or have a preset number of hormones to secrete dependent on the menstrual cycle and in return cannot be used to manipulate the menstrual cycle.[27] This can also cause inconvenient in-house doctor visits causing more frequent co-pays.

Chapter 3

Conclusions, Future Work, and Limitations

Conclusions

Overall, we found that there were significant relationships between injury type and severity, and between injury type and stage of the menstrual cycle for ligamentous knee injuries sustained in NCAA female collegiate athletes. There were a greater number of respondents who were HC users compared to HC non-users. Of the HC users, the majority of the respondents were using CHCs and OCPs. The results suggest that ligamentous knee injuries sustained by the respondents occurred in the luteal phase (phase III) of the menstrual cycle. Likewise, respondents were more likely to sustain multiple ligament injuries compared to single ligament injuries during this phase. Additionally, the type of ligamentous knee injury, specifically injuries involving the ACL (ACL and ACL+MCL), resulted in a more severe injury (greater amount of days loss of athletic participation).

It would be unrealistic and problematic to instruct female athletes to reduce the intensity of their activity during certain stages of the menstrual cycle. Although, it was not assessed in this study, future work could aim to research prevention programs and compare different types of equipment/bracing for the prevention of ligamentous knee injuries in female athletes.

Future Work

The present study only included female athletes who sustained a ligamentous knee injury. Future research should prospectively monitor a large sample of female athletes, including those who do and do not sustain a ligamentous knee injury, to

determine potential differences between the two groups and identify HC use factors associated with sustaining a ligamentous knee injury.

Additionally, future research should recruit subjects who use CHCs and POCs in equal numbers, allowing for meaningful comparisons of ligamentous knee injury factors between the two groups. Also, future research should aim to compare female athletes who use various types of HCs to female athletes who do not use any form of HCs to determine if HCs decrease the risk of ligamentous knee injury.

Limitations

A limitation of our study was that the responses of the survey were self-reported from the participants. Self-reported data carries the risk of inaccuracy of the responses due to the challenge of accurately recalling details pertaining to the time of injury, misunderstanding questions, or intentionally misrepresenting the responses to questions. This may have skewed the results as respondents may have estimated the dates of their menstrual cycle and injury, had to remember if they were on their menstrual cycle or not at the time of injury, and may have misinterpreted directions given when providing HC information. This could be avoided if non-injured female athletes were recruited before the start of their sport season and given directions on keeping a record of their menstrual cycle dates, date of injury if they sustain one during the study time period, and HC use information.

We shared the survey with athletic trainers to administer to appropriate participants and is considered a strength because the athletic trainer may know and understand better than the injured athletes the details of the injury, however, a second limitation was that we could not calculate the response rate. We do not know how many

athletic trainers shared the survey with their injured female athletes and then how many of those female athletes actually completed the survey. Knowing a response rate would strengthen our study but may not skew the study or our results in a direction if the respondents answered truthfully.

A third limitation to our study is that the time period was consistent with the fall and partial winter seasons but did not extend to the remaining winter and spring seasons. An extension of the time period may provide more respondent characteristics that could be used for analyses.

Last, menstrual cycle phase is defined in days, with each of the three phases lasting a different number of days. It is possible that the statistical analyses performed with this variable were affected by the varying time frame of each phase. This is a limitation of the present study. In future studies, a more sophisticated statistical analysis could potentially correct for this confounder.

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Consent

Welcome to the research study!

TITLE OF STUDY: The relationship between the use of hormonal contraceptives and ligamentous knee injury in the female collegiate athlete
Principal Investigator: Dr. Leslie Spencer

*You are being asked to take part in a research study. This consent form is part of an informed consent process for a research study and it will provide key information that will help you decide whether you wish to volunteer for this research study.
*Please carefully read the introductory information provided below. They will provide clear information about the purpose of the study, study specific information about what will happen during the study, what are the anticipated risks and benefits, and what alternatives are available to you if you do not wish to participate in this research study.
*The study team will explain the study to you, and they will answer any question you might have before volunteering to take part in this study. It is important that you take your time to make your decision. *You may take this consent form with you to ask a family member or anyone else before agreeing to participate in the study.
*If you have questions at any time during the research study, you should feel free to ask the study team and should expect to be given answers that you completely understand.
*After all your questions have been answered, if you still wish to take part in the study, you will be asked to give your informed consent at the bottom of this form.
*You are not giving up any of your legal rights by volunteering for this research study or by signing this consent form.

1. **What is the purpose of the study?**
   The purpose of this study is to determine the relationship that hormonal contraceptives have with ligamentous knee injury in female collegiate athletes.

2. **Why have you been asked to take part in this study?**
   You have been asked to take part in this study because you are at least 18 years of age, a female, a NCAA student-athlete, have sustained at least one ligamentous knee injury recently, and have lost at least one day of athletic participation.

3. **What will you be asked to do if you take part in this research study?**
   If you decide to take part in this research study, you will be asked to complete a series of questions on an electronic survey. Questions included in the survey will be related to your demographic information, menstrual cycle, ligamentous knee injury, and hormonal contraceptive use, if applicable.

4. **Who may take part in this research study? And who may not?**

Participants may be included if they are at least 18 years of age, or older, female, NCAA student-athletes, have sustained at least one ligamentous knee injury between the period of August 1st, 2019 – December 31st, 2019, and have at least one day's loss of athletic participation due to their ligamentous knee injury. Participants will be excluded if they are males, under the age of 18 years, non-NCAA athletes, have not sustained a ligamentous knee injury, have no day's loss of athletic participation, are currently pregnant, have undergone a hysterectomy (previous removal of the uterus), have undergone a tubal ligation (tying of the fallopian tubes), are on a hormonal treatment of testosterone, or have an intrauterine device (IUD) inserted in them.

5. **How long will the study take and where will the research study be conducted?**
   The study will take approximately 5-15 minutes to complete. It may be done from an electronic device, such as, but not limited to, a laptop/computer, tablet, or smartphone.

6. **How many visits may take to complete the study?**
   This study can be completed in one sitting.

7. **What are the risks and/or discomforts you might experience if you take part in this study?**
   There is absolutely no physical risk of harm for you in this study. There may be mild psychological/ emotional risk when asking you to recall factors that relate to possible mild, moderate, and severe ligamentous knee injuries.

8. **Are there any benefits for you if you choose to take part in this research study?**
   There may not be any direct benefit. However, there may be mild benefits for the participants in this study as the study may suggest hormonal risk factors that relate to previous ligamentous knee injury. There may be benefits to female collegiate athletes in the future on how to reduce the risk of ligamentous knee injuries.

9. **What are the alternatives if you do not wish to participate in the study?**
   Your alternative is not to participate in this study.

10. **How many subjects will be enrolled in the study?**
    We anticipate approximately 200 responses

11. **How will you know if new information is learned that may affect whether you are willing to stay in this research study?**
    Given that this is a one-time survey and you do not provide your identity and contact information, it will not be possible to follow-up with you individually. If new information about the topic is learned during the course of the study, an

email will be sent to all of the Athletic Trainers who received the initial invitation to participate.

12. **Will there be any cost to you to take part in this study?**
    There is not cost for you to take part in this study.

13. **Will you be paid to take part in this study?**
    You will not be paid for your participation in this research study.

14. **Are you providing any identifiable private information as part of this research study?**
    No. This a completely anonymous survey.

15. **How will information about you be kept private or confidential?**
    The information you provide will never be associated with your personal identity. The survey is anonymous.
    Data will be stored electronically in a password protected program on a computer and backed up to a flash drive. The principle investigator, associate investigator, and committee members will be the only personnel with access to the data. The data will be kept and stored electronically on the hard drive of the Principal Investigator for three years, after which, the data will be permanently deleted.

16. **What will happen if you do not wish to take part in the study or if you later decide not to stay in the study?**
    Participation in this study is voluntary. You may choose not to participate, or you may change your mind at any time.
    If you do not want to enter the study or decide to stop participating, your relationship with the study staff will not change, and you may do so without penalty and without loss of benefits to which you are otherwise entitled.

17. **Who can you call if you have any questions?**
    If you have any questions about taking part in this study or if you feel you may have suffered a research related injury, you can call the Principal Investigator:
    Dr. Leslie Spencer
    School of Health Professions | Health and Exercise Science Department
    856-256-4500 ext. 53761 | spencer@rowan.edu

    If you have any questions about your rights as a research subject, you can call:
    Office of Research Compliance
    (856) 256-4078– Glassboro/CMSRU

18. **What are your rights if you decide to take part in this research study?**
    You have the right to ask questions about any part of the study at any time. You should not sign this form unless you have had a chance to ask questions and have been given answers to all your questions.

AGREEMENT TO PARTICIPATE
I have read the entire information about the research study, research risks, benefits and the alternatives, or it has been read to me, and I believe that I understand what has been discussed.
All my questions about this form or this study have been answered and I agree to volunteer to participate in the study.

○ I consent, begin the study

○ I do not consent, I do not wish to participate

Agreement of Age

I am at least 18 years of age or older

○ Yes

○ No

Survey

Q1 Are you currently pregnant?

○ Yes

○ No

Q2 Have you ever had a hysterectomy (removal of the uterus)?

○ Yes

○ No

Q3 Have you ever had a tubal ligation (fallopian tubes tied)?

○ Yes

○ No

Q4 Do you currently use an intrauterine device (IUD)?

○ Yes

○ No

Q5 Are you currently on a hormonal treatment that is not considered hormonal contraception (for example: testosterone)?

○ Yes

○ No

Q6 How old are you?

○ less than 18

○ 18

○ 19

○ 20

○ 21

○ 22

○ greater than 22

Q7 Do you identify as female?

○ Yes

○ No

Skip To: End of Survey If Q7 = No

Q8 Are you currently an NCAA athlete?

○ Yes

○ No

Skip To: End of Survey If Q8 = No

Q9 Have you recently sustained a ligamentous knee injury?

○ Yes

○ No

Skip To: End of Survey If Q9 = No

Q10 How many days of athletic participation have you lost due to your ligamentous knee injury?
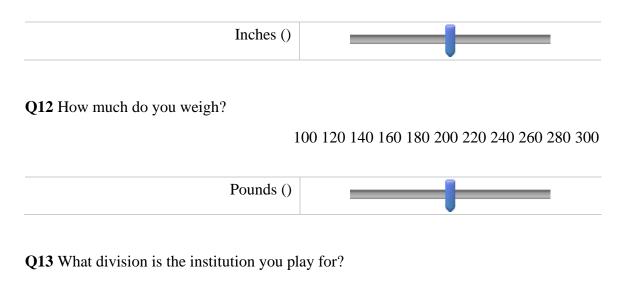
○ 0 days

○ 1-7 days

○ 1-14 days

○ 1-21 days

○ 1-28 days

○ 29+ days

Skip To: End of Survey If Q10 = 0 days

Q11 How tall are you?

30 37 44 51 58 65 72 79 86 93 100

Inches ()	

Q12 How much do you weigh?

100 120 140 160 180 200 220 240 260 280 300

Pounds ()	

Q13 What division is the institution you play for?

○ Division I

○ Division II

○ Division III

Q14 What sport do you currently play?

▼ Women's basketball (1) ... Women's indoor volleyball (21)

Q15 When did you sustain your ligamentous knee injury?

○ Date (mm/dd/yyyy) _____

Q16 What is the name of the ligamentous knee injury you recently sustained? (check all that apply)

☐　　　　Anterior cruciate ligament (ACL) sprain/tear

☐　　　　Posterior cruciate ligament (PCL) sprain/tear

☐　　　　Grade I lateral collateral ligament (LCL) sprain

☐　　　　Grade II lateral collateral ligament (LCL) sprain

☐　　　　Grade III+ lateral collateral ligament (LCL) sprain

☐　　　　Grade I medial collateral ligament (MCL) sprain

☐　　　　Grade II medial collateral ligament (MCL) sprain

☐　　　　Grade III+ medial collateral ligament (MCL) sprain

☐　　　　I do not know

☐　　　　Other _____

Q17 Was the cause of your ligamentous knee injury a contact or non-contact mechanism?

Contact- another person or object causing a direct blow to your knee
Non-contact- no other outside forces caused your knee to injure

○ Contact

○ Non-contact

Q18 What playing surface were you playing on when sustaining your ligamentous knee injury?

○ Artificial grass / turf

○ Grass

○ Gymnasium floor

○ Track

○ Sand

○ Concrete / road

○ Wooden bowling ally

○ Synthetic bowling ally

○ Other   _____

Q19 Were you having your menstrual period at same time you sustained your ligamentous knee injury?

○ Yes

○ No

○ I don't remember

Q20 What are the dates of the start of your last three menstrual cycles? Please take your best guess if you are not certain.

○ Last menstrual cycle date (mm/dd/yyyy)

_____

○ Second to last menstrual cycle date (mm/dd/yyyy)

_____

○ Third to last menstrual cycle date (mm/dd/yyyy)

_____

Q21 Were you taking a hormonal contraceptive (hormonal birth control) at the time you sustained your ligamentous knee injury?

○ Yes

○ No

Skip To: End of Survey If Q21 = No

Q22 What is the mode of delivery of your hormonal contraceptive?

○ Oral pill

○ Intravaginal ring

○ Transdermal patch

○ Subdermal implant

○ Injection

○ Other _____

Q23 What is the name of your hormonal contraceptive?

○ Alesse-28

○ Apri

○ Aviane

○ Brevicon

○ Crysella

○ Demulen 1/35-21

○ Demulen 1/35-28

○ Demulen 1/50-21

○ Demulen 1/50-28

○ Desogen

○ Estrostep 21

○ Estrostep FE

○ Genora 1/35

○ Genora 1/50

○ Jenest 28

○ Junel Fe 20

○ Kariva

○ Levlite 28

○ Levlen 21

○ Levlen 28

○ Levora 0.15/30-21

○ Levora 0.15/30-28

○ Lo Estrin 24-4

○ Loestrin 21 1/20

○ Loestrin 21 1.5/30

○ Loestrin fe 1/20

○ Loestrin fe 1.5/30

○ Lo-Ovral 28

○ Low-Ogestrel 28

○ Lutera

○ Microgestin 1/20

○ Microgestin 1.5/30

○ Microgestin fe 1/20

○ Microgestin fe 1/5/30

○ Micronor

○ Mircette

○ Modicon

○ Mononesessa

○ Necon 0.5/35-21

○ Necon 0.5/35-28

○ Necon 1/50-21

○ Necon 1/50-28

○ Necon 1/35-21

○ Necon 1/35-28

○ Necon 10/11-21

○ Necon 10/11-28

○ Nor-QD

○ Nordette 28

○ Norinyl 1/50

○ Norinyl 1/35

○ Nortrel 0.5/35

○ Nortrel 1/35

○ Ogestrel 0.5/50-28

○ Ortho-cept

○ Ortho-Novum 1/35

○ Ortho-Novum 1/50

○ Ortho-Novum 10/11

○ Ortho-Novum 7/7/7

○ Ortho-cyclen

○ Ortho Tri-Cyclen

○ Ortho Tri-Cyclen LO

○ Ovcon 50

○ Ovcon 35

○ Ovral 28

○ Ovrette

○ Seasonale

○ Seasonique

○ Sprintec

○ Tri-Levlen 21

○ Tri-Levlen 28

○ Tri-Norinyl 28

○ Trinessa

○ Triphasil 28

○ Tri-Sprintec

○ Trivora 28

○ Yasmin 28

○ Yaz

○ Zovia 1/50E

○ Zovia 1/35E

○ NuvaRing

○ Kyleena

○ Liletta

○ Mirena

○ Skyla

○ Ortho Evra

○ Xulane

○ Implanon

○ Nexplanon

○ Norplant

○ Depo Provera

○ Other _____

Q24 If you selected "other", please provide the name of your hormonal contraceptive below:

_____

Q25 What are the milligram levels in your hormonal contraceptive? Please reference the examples below of where to find this on your hormonal contraceptive packaging. The first set of images are examples of where to find the values for estrogen. The second set images are examples of where to find values for progesterone. If there is only **ONE** number provided, please insert "0" for "Estrogen" and that provided number for "Progesterone".

ORAL CONTRACEPTIVE PILL   INTRAVAGINAL RING   TRANSDERMAL PATCH

*Note: Estrogen may be referred to as Ethinyl Estradiol or others.

ORAL CONTRACEPTIVE PILL   SUBDERMAL IMPLANT   INJECTION

*Note: Progesterone may be referred to as Norelgestromin, Norethidrone acetate, etonogestrel, etc.

○ Estrogen _____

○ Progesterone _____

Q26 How often do you menstruate when taking your hormonal contraceptive?

○ Every month

○ Every 2 months

○ Every 3 months

○ Every 6 months

○ Other _____

Appendix B

Subject Recruitment

Cover Letter

You are invited to participate in a survey titled "The relationship between the use of hormonal contraceptives and ligamentous knee injury in the female collegiate athlete." The study is being conducted by Leslie Spencer, Ph.D., Shari Willis, Ph.D., Robert Weaver, Ph.D., and Nicole Thompson, Athletic Training student, of Rowan University, School of Health Professions, Health and Exercise Science Department, 201 Mullica Hill Road, Glassboro, New Jersey 08028.

The purpose of this study is to determine the relationship that the use of hormonal contraceptives have with ligamentous knee injury in female collegiate athletes. The estimated time it will take to complete this survey is 5-15 minutes.

There is absolutely no physical risk of harm to participants in this study. There may be mild psychological / emotional risk in asking you, the participant, to recall factors that relate to a mild, moderate, or severe ligamentous knee injury.

There may not be benefits to the individual participants in this study. There may be benefits to female collegiate athletes in the future on how to reduce the risk of ligamentous knee injuries.

We are collecting private information in this research study. Your identifiable information will not be used in any of the future research projects or disclosed to anyone outside of the research team. Data will be stored electronically in a password protected program on the hard drive of the University-issued computer of the Principal Investigator and backed up to a flash drive. The Principal Investigator, student investigator, and two thesis committee members will be the only personnel with access to the data. Your privacy and confidentiality will be protected. There will be no use of names with data being stored electronically. The data will be kept and stored confidentially on the hard drive of the Principal Investigator for three years after the conclusion of the study. At that point, the electronic data will be completely erased. Hard copies of the data will not be kept.

Your participation in this study is voluntary. You may withdraw from the study at any point of time. If you have any questions or concerns related to this study, you may contact the investigators listed.

Nicole Thompson
Athletic Training student,
Rowan University

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856-812-1689

Leslie Spencer, Ph.D.
Professor of Health and Exercise Science
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This study has been reviewed and approved by the Rowan University Institutional Review Board. If you have any questions about your rights as a participant or are dissatisfied at any time with any aspect of this study, you may contact the Office of Research Compliance at (856) 256-4078.

IRB Approval Number: Pro2019000511

If you agree to participate, please follow the link below and take the survey. Otherwise, you may exit out of the survey.

Thank you.

To complete the survey, click on link below:
_____

Flyer

CALLING ALL <u>FEMALE ATHLETES</u> WITH A <u>KNEE INJURY</u> TO PARTICIPATE IN A RESEARCH STUDY!

Are you a female NCAA athlete that has recently sustained a ligamentous knee injury?

- If so, you may be eligible to participate in a research study
- This research survey will assess risk factors that have may have caused you to suffer your injury
- The study will take 5-15 minutes to complete and can be done on any electronic device
- By participating in this study, you are supporting a graduate athletic training student at Rowan University with their master's thesis project
- The survey is anonymous, and all information is kept confidential

If you agree to participate, please use the link or QR code below for access to the research survey.

https://rowan.co1.qualtrics.com/jfe/form/SV_8GLRd89HpHAL8vb

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Personal Letter

Hello,

My name is Nicole Thompson and am a fifth-year athletic training student at Rowan University in Glassboro, New Jersey. Currently, I am working toward obtaining my master's in athletic training and am studying female collegiate athletes and hormonal risk factors that may be associated with ligamentous knee injuries as my thesis project. Previously, a survey has been sent out to athletic trainers to share with their ligamentous knee injured female athletes to assess these factors. Unfortunately, the response rate has been low, and I would appreciate it if you could cooperate with the study team and I by distributing the link to this survey link below out to eligible participants with the following criteria:

- Female NCAA athlete
- At least 18 years of age, or older
- Prognosed (by you) or diagnosed (by a D.O. or M.D.) to have sustained a ligamentous knee injury (ACL, MCL, LCL, and/or PCL) in the 2019 fall or the 2019 winter season
- At least one day loss of athletic participation

Female collegiate athletes who have met the inclusion criteria above are eligible to complete this short survey. It will take approximately 5-15 minutes and can be completed on an electronic device. If possible, please assist me in sharing the survey to appropriate athletes at your institution.

If you or your athletes have any questions or concerns regarding this study, please do not hesitate to reach out to me or my faculty advisor. Our contact information is listed below. Thank you for your time.

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*Study has been approved by Rowan IRB, IRB# Pro2019000511