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Type of oral contraceptive pills in patients with complete ACL tears: A retrospective study

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Abstract

Purpose: Differences in sex hormones are one of the proposed mechanisms for the increased risk of anterior cruciate ligament (ACL) injury in female athletes. Oral contraceptive pills (OCPs) may reduce the risk of ACL injuries in females, but the effects of different types of OCPs have not been examined. This study aimed to investigate the type of OCPs used in women diagnosed with ACL tears. We hypothesized that a greater proportion of women with ACL tears will be exposed to OCPs containing high estrogen and less androgenic progestins than other types of OCPs. **Methods:** Medical records from Hospital for Special Surgery (New York, NY) for women ages 16-55 with diagnosis of an ACL tear while concurrently taking OCPs were reviewed from January 2016 to June 2018 for demographic data, documentation of ACL injury, type of OCP at time of injury, ethinyl estrogen dose, and progestin dose. OCP androgenicity was determined by multiplying the dose of progestin by the progestin's androgenicity. **Results:** A total of 223 patients sustained an ACL tear while taking OCPs. The most commonly used OCP was a high estrogen/low androgenicity progestin pill (107/223=48%).When each hormone was considered individually, the majority of women were exposed to OCPs with high estrogen (58.7% vs 41.3%, $p<0.0001$) and low androgenicity progestin (84.8% vs 15.3%, $p<0.0001$). **Conclusion:** A large portion of women who sustained ACL tears were taking a high estrogen/low androgenicity progestin OCP at the time of injury and this is different than population data where the majority of women are exposed to moderately high androgenicity progestins. Future studies should be conducted to determine if OCPs with high estrogen and low androgenicity progestin correlate with increased risk of ACL injury.

Background

Sex disparity in musculoskeletal injury is most apparent in injuries to the anterior cruciate ligament (ACL), for which female athletes have a 2- to 8-fold increased risk of injury compared to male athletes[1-5]. The increased risk in female athletes is a multifaceted problem attributable to sex differences in anatomy, neuromuscular control, and sex hormones, all of which have been shown to influence knee stability[6,7]. Interest in sex hormones stems from evidence demonstrating that sex differences in risk of ACL injury develop during puberty and persist throughout adulthood, coupled with evidence that risk of ACL injury and ligamentous laxity changes across the menstrual cycle[7, 8]. Furthermore, exposure to exogenous estrogen and progestins through oral contraceptive pills (OCPs) may reduce the risk of ACL injury, particularly in the adolescent population[8-10].

Despite the frequent use of OCPs amongst female athletes and their effect on musculoskeletal tissues[11,12], the mechanism by which OCPs reduce the risk of ACL injury is unknown. Within the current literature, limitations exist. Although studies have compared OCP versus non-OCP users in the context of ACL injury[8,11,13], no human studies have accounted for the variability within OCPs of differing concentrations of estrogen (low vs. high) and types of progestins (low androgenicity vs. high androgenicity)[14]. Studies have also been limited in the number of sports included, analyzing a single sport or only a few sports[4,13,15].

Additional studies are needed to determine the link between OCP usage and a potential decrease in ACL injury by considering the concentration and type of hormones in different OCPs and their impact on ACL injury frequency. Two animal studies have examined the potential effects of OCPs on ACL

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Table 1. Demographic Characteristics by Study Groups

Characteristic	Overall (N=223)	High E/Low A (n=107)	Low E/Low A (n=82)	High E/High A (n=24)	Low E/High A (n=10)
Age; years; mean (SD)	29 (9)	29 (10)	28 (9)	28 (10)	28 (7)
Body mass index; kg/m2; mean (SD)	24 (4)	24 (4)	23 (3)	23 (3)	23 (1)
Caucasian race; n (%)	177 (79)	87 (81)	61 (74)	21 (88)	8 (80)
Non-Hispanic/Latino ethnicity; n (%)	203 (91)	102 (95)	71 (87)	22 (92)	8 (80)

SD: standard deviation

material properties. In these studies, rats exposed to OCPs with high androgenicity progestins or with high progestin:estrogen ratios demonstrated greater ACL strength compared to rats with normal estrous cycles and those exposed to OCPs with low androgenicity progestins or low progestin:estrogen ratios[16,17]. These studies suggest that a differential effect of OCP type exists regarding ACL load-to-failure. A better understanding of this connection may allow for targeted use of specific OCPs with the aim of optimizing ACL stability and reducing injury risk in women. The purpose of this study is to investigate the type of OCPs used in women diagnosed with ACL tears. We hypothesize that a greater proportion of women with ACL tears will take OCPs with higher estrogen concentrations and less androgenic progestins.

Materials and Methods

Data Source and Study Design

A search of patients in the electronic medical record system from January 2016 through June 2018 was performed based on the following inclusion criteria: female, age 16–55 years, diagnosis of complete ACL tear according to International Classification of Diseases-10 (ICD-10) codes (S83.511a, S83.512a, S83.519s, S83.511d, S83.512d, T84.89xa, T84.89xd, S83.519a, S83.511a, S83.512a), and reporting use of OCP at the time of injury presentation and diagnosis. Patients were excluded if their chart did not document OCP use at time of ACL injury or chart review yielded an inaccurate diagnosis of ACL injury. Medical records were reviewed for demographic data, documentation of ACL injury, type of OCP at the time of injury, ethinyl estradiol (EE) dose, and progestin dose. Androgenicity is a measure of the progestin's affinity for and binding to the androgen receptor and is a product of the dose and androgenic activity of progestin ((progestin dose [mg]) × androgenic activity of progestin/mg). The threshold between high and low estrogen was 0.2 mg[18], and the threshold between high and low androgenicity was 1.0 mg[14].

This retrospective study was approved by the Institutional Review Board at Hospital for Special Surgery (New York, NY). A waiver of consent was obtained. All data were collected from electronic medical records at Hospital for Special Surgery, and there was no patient contact.

Statistical Analysis

The proportions of women using each type of OCP were calculated. Chi-squared testing was used to assess for significant differences between the groups of OCP-type and individual hormones. The proportions between high versus low estrogen and androgenicity were also tested using a *t*-test for statistically significant differences at an alpha level of 0.05.

Results

The initial search identified 315 potential patients. After screening for eligibility, 92 patients were excluded due to the lack of OCP use at the time of ACL injury (n=79) or the absence of ACL injury (n=13). A total of 223 patients who sustained an ACL tear while taking OCPs were included in the study. Demographic characteristics by study group are shown in **Table 1**. The mean age was 29 ± 9 years, and the mean BMI was 24 ± 4 kg/m^2. The majority of patients were of Caucasian race (n=177; 79%) and non-Hispanic/Latino ethnicity (n=203; 91%). Eighty-seven percent of patients tore their ACL during a sport- or exercise-related activity. The distribution of OCPs by progestin type, estrogen, and androgenicity are shown in **Table 2**.

The most commonly used OCP was a high estrogen/low androgenicity pill (n=107; 48%); this was a higher proportion than the other OCP combinations of low estrogen/low androgenicity (n=82; 37%), high estrogen/high androgenicity (n=24; 11%), and low estrogen/high androgenicity (n=10; 4%), but the difference was not statistically significant ($X^2(1)=2.32$, $p=0.13$) When estrogen dose was considered individually, the majority of women were taking OCPs with a high concentration of estrogen (58.7% vs. 41.3%, $p<0.0001$).

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Table 2. Characteristics of Oral Contraceptive Pills

Oral Contraceptive Pill	N (%)	Estrogen	Progestin	Androgenicity
High Estrogen/High Androgenicity				
Altavera, Cyclafem, Dasetta, Levora, Lillow, Nordette, Portia, Quasense, Seasonale	20 (8.9)	High	Levonorgestrel	High
Kelnor, Zovia	4 (1.8)	High	Ethynodiol diacetate	High
High Estrogen/Low Androgenicity				
Mono Linyah, Mononessa, Ortho Tri-cyclen, Previfem, Sprintec, Tri-Estarylla, Tri-Femynor, Tri-Linyah, Tri-Lo-Marzia, Trinessa, Tri-Previfem, Tri-Sprintec,Trinessa LO, Ortho Tri-cyclen LO	66 (29.6)	High	Norgestimate	Low
Apri, Desogen, Emoquette, Enskyce, Reclipsen	17 (7.6)	High	Desogestrel	Low
Ocella, Yasmin	10 (4.5)	High	Drospirenone	Low
Cryselle, Low-Ogestrel	8 (3.6)	High	Norgestrel	Low
Balziva, Ortho-Novum	4 (1.8)	High	Norethindrone	Low
Microgestin 1.5/30	1 (0.4)	High	Norethindrone acetate	Low
Enpressese	1 (0.4)	High	Levonorgestrel	Low
Low Estrogen/High Androgenicity				
Junel 1.5/30	9 (4.0)	Low	Norethindrone acetate	High
Zenchent	1 (0.4)	Low	Norethindrone	High
Low Estrogen/Low Androgenicity				
Junel, Larin, LO Loestrin, Microgestin	29 (12.4)	Low	Norethindrone acetate	Low
Aviane, Alesse, Aubra, Falmina, Lessina, Lutera, Orsythia, Sronyx, Vienva	29 (12.4)	Low	Levonorgestrel	Low
Gianvi, Loryna, Nikki, Vestura, Yaz	24 (10.8)	Low	Drospirenone	Low

For progestin, the majority of women were exposed to low androgenicity progestins (84.8% vs. 15.3%, $p<0.0001$).

Discussion

Differences in sex hormones are one of the proposed reasons for the increased risk of ACL injuries in female athletes[6]. Historically, sex hormones have been considered non-modifiable risk factors for ACL injury. Recent work suggests that exposure to OCPs confers a protective effect on ACL tears, especially in 15–19-year-old females[8-10,19]. Therefore, OCPs might offer a way to modify the hormonal milieu and reduce risk of injury. OCPs contain different concentrations of estrogen and progestin with different levels of androgenicity (affinity for androgen receptors). However, to our knowledge, none of the prior studies investigating the role of OCPs in reducing ACL have examined OCP type. The purpose of this study was to investigate the type of OCPs used in women diagnosed with complete ACL tears, specifically assessing the dose of estrogen and the androgenicity for each OCP.

Female athletes exposed to OCPs have also been shown to have decreased anterior tibial translation[20] and increased knee stability[21], suggesting that exogenous estrogen or progestins might alter ligament and joint laxity. The underlying mechanism for how OCPs modify ACL material properties has not yet been established. However, it is known that the ACL contains receptors for estrogen, progesterone, testosterone, and relaxin[22-25]. In vitro exposure of the ACL to estrogen and relaxin results in increased laxity and reduced load to failure, whereas progesterone and testosterone appear to increase ACL load to failure[25-28].

The most frequently utilized OCP in our cohort of women with ACL tears contained high estrogen

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and low androgenicity progestins. Based on animal studies, this type of OCP may result in compromised ACL biomechanics. Woodhouse et al. demonstrated that ACLs from rats exposed to an OCP with a high androgenicity progestin had increased elongation and energy absorbed prior to failure, compared to those from control rats with normal physiologic estrous cycles[16]. Additionally, Konopka et al. found that rats exposed to OCPs containing high androgenicity progestin (high progesterone:estrogen ratio) had increased ACL load-to-failure compared to control rats and those exposed to OCPs with low androgenic progestin (low progesterone:estrogen ratio)[17]. While the authors recognize the differences in estrous cycles between rats and humans, these animal studies are important in the context of analyzing the role of exogenous hormones in the form of OCPs and ACL material properties.

It is important to note that other animal studies have not found a change in ACL material properties and exogenous estrogen. For example, Strickland et al. found no change in knee ligament material properties in sheep exposed to exogenous estrogen[29]. Collectively these studies suggest that the type of exogenous progestin might be more important than exogenous estrogen when considering the effect of OCPs on the ACL. The type of OCPs most frequently used by subjects in our cohort is similar to other populations in regard to estrogen dose, as population data show that the majority (67%) of 15–44-year-old women take OCPs with high estrogen. This same population data, as well as a review article from 2014, suggests that the majority of women are exposed to moderately high androgenicity progestin[30,31]. In contrast, our cohort of women with ACL tears were more commonly using OCPs with low androgenicity progestin. The difference in type of progestin exposure in our study cohort compared to population data warrants further investigation to determine whether a relationship between OCP progestin type and ACL injury exists. The two previously discussed animal studies support this idea, since they demonstrated that high androgenicity progestin exposure resulted in superior ACL biomechanics over low androgenicity progestin or no OCP exposure. Our study, combined with the animal data, shows that further investigation is warranted to explore this relationship.

In addition to altering ligament material properties, exogenous hormones in OCPs could alter aspects of neuromuscular control, another known risk factor for ACL injury. Previous literature has presented conflicting results regarding neuromuscular control changes across the natural menstrual cycle (endogenous serum estrogen fluctuations)[21,32-40]. Sarwar et al. demonstrated increases in quadriceps strength and handgrip strength at mid-cycle[32], and Davies et al. found increased grip strength and standing long jump performance during the early follicular phase[34]. Higher estrogen levels during the ovulatory phase also resulted in significantly lower active stiffness in the lower extremity musculature when compared to other phases within the menstrual cycle[38]. In terms of knee joint laxity, previous literature demonstrates that anterior tibial translation, a proxy for ACL and knee joint laxity, fluctuates across the menstrual cycle with increased laxity around ovulation and possibly a second peak in the luteal phase[21,35,36, 41,42]. Additionally, muscle stretch reflex of the rectus femoris is modulated across the menstrual cycle, being significantly lower in the peri-ovulatory phase compared to the luteal phase[40]. However, other studies have demonstrated no change in the parameters of neuromuscular control when measured across the natural menstrual cycle[38, 43-46]. Gur et al. measured the effects of endogenous estradiol on isokinetic measurement of knee muscles and did not find statistical significance in change across the menstrual cycle for measurements of torque, power, work, and endurance[44].

Limitations

It is important to consider our results in the context of the limitations of our study. First, as this was a retrospective study, we were limited by the information found in the electronic medical records. We reviewed each chart to confirm that the patient was taking the OCP at the time of injury, but documentation may not be truly indicative regarding timing of OCP use. Second, we had no true comparative group within the study. Ideally, our results should be compared to prescribing data for an age-matched population cohort. However, we did not have access to comprehensive population data and had to rely on a few studies that reported prescribing data.

Conclusion

Prior work suggests that use of OCPs might reduce the risk of ACL injury, but a differential effect of the type of OCP as it relates to risk of ACL injury has not been explored. This study demonstrates that the most commonly used OCP in our cohort of women who sustained ACL tears were taking a high estrogen/low androgenicity progestin OCP at the time of injury. In regards to the progestin specifically, the majority of women with ACL tears were taking OCPs with low androgenicity, and this is different than population

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data where the majority of women are exposed to moderately high androgenicity progestins.

Future studies should be conducted to determine if OCPs with high estrogen and low androgenicity progestin correlate with increased risk of ACL injury. If so, specific types of OCPs might offer a way to modify the hormonal milieu and reduce risk of injury. Future directions should also include animal studies comparing the most commonly used types of hormonal contraception to look for a differential effect on ligament material properties, human studies looking at in vivo measures in women taking different OCPs, and prospective studies using OCP type as a way to reduce risk of ACL injury.

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