

Review Article

Effects of Hormonal Contraceptives on Non-Bone Related Injury Risk and Athletic Performance in Female Athletes: A Systematic Review of the Literature

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Abstract

Hormonal fluctuations during the menstrual cycle have been reported to affect athletic performance and injury risk. Altering hormonal levels through contraceptives may impact performance and injury risk in women. The aim of this study is to review the literature on the relationship between hormonal contraceptives (HC), and performance and injury. A literature search resulted in 2267 articles that were screened to 61 articles included in this review. The studies examined showed no consistently significant difference between women athletes taking HC and those who were not in regards to athletic performance and injury risk. HC does not appear to have a significant impact on aerobic performance, anaerobic performance, heat acclimatization or cognition. HC containing antiandrogenic components have been shown to decrease strength gains, but HC not containing antiandrogens do not appear to have this same effect. Similarly, the current literature does not support the use of HC to reduce risk or injury, nor does it seem to increase the risk of injury in the majority of women athletes. One potential subgroup of athletes that may benefit from HC as a prophylactic means of injury prevention are female athletes in the 15-19 year old age group where there is evidence to suggest a protective effect against ACL tear. Overall, hormonal contraceptives do not appear to have a direct effect on athletic performance or injury prevention in women athletes. Clinicians should not use performance or injury risk as an indication for prescription of hormonal contraception.

ABBREVIATIONS

HC: Hormonal Contraception; OCPs: Oral Contraceptive Pills; OC: Oral Contraception, LARC: Long-acting Reversible Contraception; ACL: Anterior Cruciate Ligament; VO2max: Maximal Oxygen Uptake

INTRODUCTION

Female participation in sport continues to grow, especially at a highly competitive collegiate level. As of 2005, more than 2.9 million girls were participating in high school sports in the United States, equating to a 13% increase from the late 1990s. Meanwhile, collegiate participation had grown by 51% as increased opportunities were provided for these athletes to continue competing after high school [1]. Alongside this trend of increased participation is the ever evolving use of contraception, especially hormonal contraceptives (HC), that may contain derivatives of estrogen and/or progesterone. Statistics provided

through the National Survey for Family Growth and the Center for Disease Control and Prevention state that 12.6% of women ages 15-49 used oral contraceptive pills (OCPs), 10.3% used long-acting reversible contraception (LARC), and 2.1% used injectable medroxyprogesterone (Depo-Provera). Overall, this age range of women used contraception at a rate of 65% with 25% using a form of HC [2]. Compared to a sample population of elite female athletes, approximately half were using HC [3].

Hormonal fluctuations during the menstrual cycle and athletic performance that have been explored in previous research studies. Several studies report a higher cardiovascular strain during moderate exercise in the mid-luteal phase, when levels progesterone and estrogen are increased [4]. A decrease in time to exhaustion in hot conditions during prolonged exercise has also been shown to occur during the mid-luteal phase, when core temperatures are elevated [5]. Altering hormonal levels in

athletes through the use of HC therefore may impact performance in female athletes.

It is also known that female athletes have a higher incidence of certain types of injuries when compared to male athletes [6]. Anterior cruciate ligament (ACL), injuries, for example, are reported as occurring two to nine times more often in female athletes than their male counterparts with teenage female athletes being especially affected [7]. Female soccer players were found to be approximately twice as likely to sustain an ACL injury than their male counterparts [6,7]. There are anatomical and biomechanical differences among the different sexes that contribute to this disparity, but hormonal influence is less well established [8].

Our goal is to review any and all relevant studies completed so that health care providers can have a comprehensive, yet concise reference in providing their patients with evidence based recommendations when counseling women athletes on their options for contraception.

METHODS

A search was performed for clinically relevant studies examining the relationship between hormonal contraceptives and injury risk and performance in women athletes. PubMed and Cochrane Library databases were searched using the inclusion criteria of "hormonal contraceptives", "injury", "performance" and "female athletes". Exclusion criteria were articles in non-English language, non-hormonal contraception/not distinguished and studies on the effect on bone. Covidence software was used as the primary screening and data extraction tool. After primary screening, two independent reviewers assessed the results and further screened the literature by performing a title and abstract review. After this process was complete, any remaining studies were then further screened by the two independent reviewers by performing full text reviews. Data extraction was summarized in a table outlining a description of the participants, specific exposures, outcomes and key findings of the various studies. Any discrepancies between reviewers regarding decisions on including individual studies were flagged for further review by a third reviewer for final decision. At least two reviewers were required to be in agreement regarding meeting inclusion criteria for a study to move onto the next round of review. Quality assessment of the individual articles was assessed using the Cochrane Risk of Bias Comparison.

2267 articles were selected on initial search and imported into Covidence. 197 duplicate articles were then removed, leaving 2070 articles for initial screening. 1841 studies were deemed to be irrelevant for the scope of this review based on title and abstract screening. This left 229 studies for full text screening of eligibility, of which 110 were excluded on further evaluation. This left 119 studies from the initial pool of 2070 studies from literature search. From there, critical review was performed and which led to a total of 60 articles qualifying for data extraction. Prior to submission for publication, we searched for any recently published and updated articles, leading to 1 additional article being included in final data extraction for a total of 61 articles (Figure 1).

RESULTS AND DISCUSSION

Injury

It is well established that female athletes have a higher incidence of certain types of injuries and different risk factors than their male counterparts [6-8]. Hormonal status has been identified as a potential contributor to this disparity [8]. A total of 29 studies were included in this area of review (Table 1).

Tendons/Ligaments/Joints

Physical changes to tendons and ligaments are observed throughout the female menstrual cycle. Increased levels of the peptide hormone Relaxin-2 were found to correlate to increased ACL laxity. These levels were measured as being highest during the luteal phase of the menstrual cycle in women not taking any form of hormonal contraception. However, when taking HC, these elevated levels were significantly reduced during this time period. These findings seem to propose a potential mechanism in how HC could possibly have a protective role against injuries to the ACL [8].

The relationship between the female sex hormones and connective structures of the MSK system has not been extensively researched. Hansen et al. found that there can be lower rates of tendon collagen synthesis in young HC users. In addition, these users have also been found to have reduced knee joint laxity and a decrease in varying degrees of laxity across the menstrual cycle [9]. It has been found that the high levels of estrogen that occur at the end of the follicular phase and during the ovulatory phase are associated with increased laxity and elevated risk of ACL tear [9]. However, similar structural or mechanical properties with menstrual changes do not appear to affect non-ligamentous connective tissue like the patellar tendon [9]. Additionally, Pokorny et al. reported findings of no significant differences in joint laxity measurements of the knee or the hand between OC users and non-users, although it is notable that their original hypothesis was that OC users would have increased joint laxity compared to the non-users. Additionally, these subjects were tested at one point in time each when determined to be in the non-menstrual phase of their cycle [10].

ACL Injury

Regarding HC and injury risk in female athletes, there has been the most research done surrounding ACL injuries. These injuries have been found to be two to nine times more likely to occur in female athletes than males [6,7]. Additionally, these injuries account for significant time lost from training and competition along with a median total health care utilization cost of \$13,403.38 [11].

While not taking a more in depth look into physiologic changes, alteration of other injury risk factors, or temporality, Agel et al. and Liederbach et al., mainly found that there was no difference in rates of ACL injury between OC users and non-users [12,13]. There were some reports of decreased injury rates in these athletes, however, some of this data has not been published for peer review.

ACL laxity and anterior tibial translation are intimately related to ACL injury. Lee et al., and Martineau et al., both

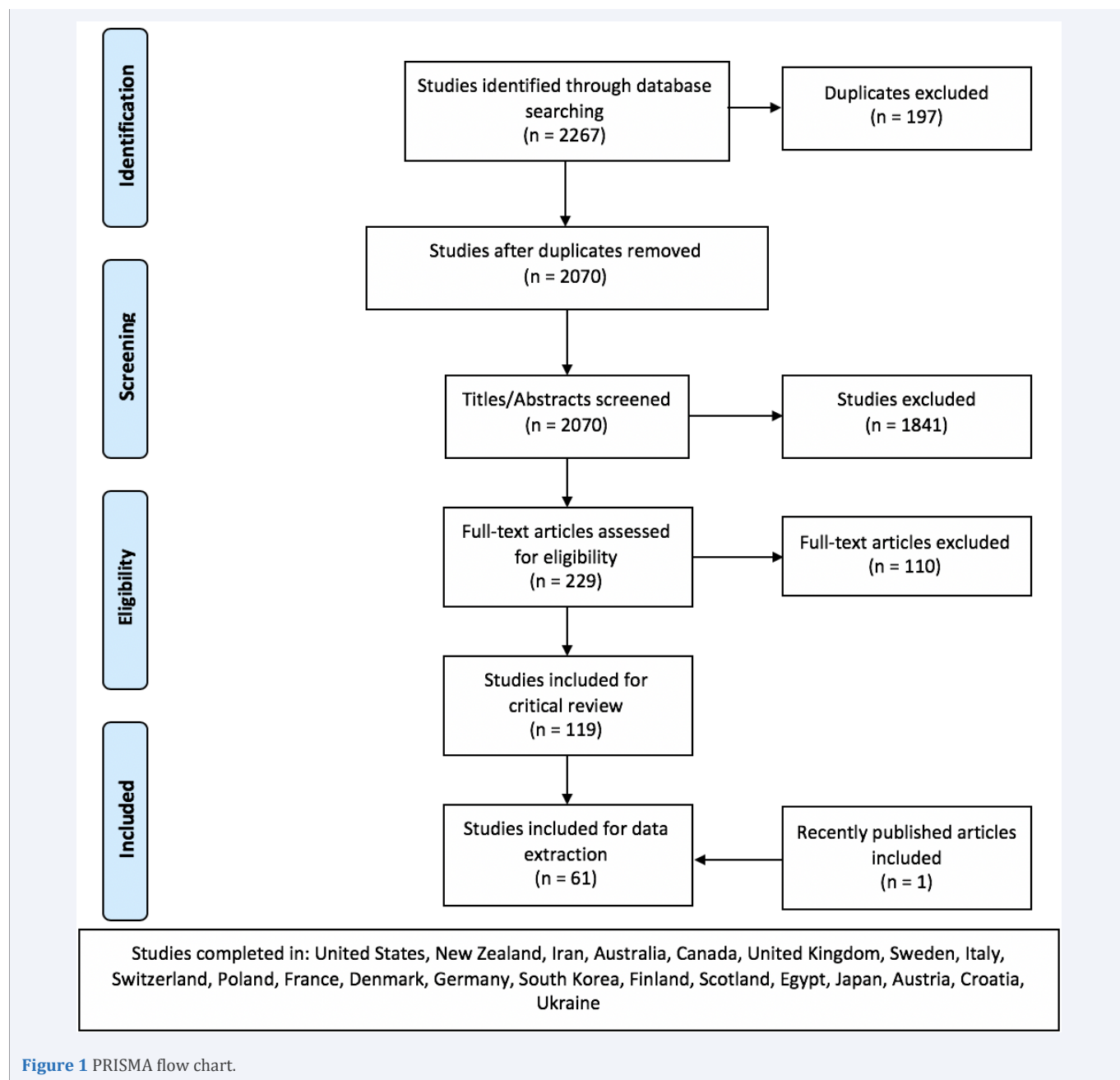


Figure 1 PRISMA flow chart.

reported a decrease in ACL laxity and a corresponding decrease in anterior tibial translation for HC users [14,15]. Martineau et al. went on to suggest the possibility of using HC as prophylaxis for ACL injury based on their findings. Lee et al., on the other hand, reported an increased risk of injury with this reduction in laxity for HC users, a finding that was unique to their study. It is also important to note that Hicks-Little et al. reported HC users having increased anterior tibial translation from increased ACL laxity, leading to increased risk of injury in this group compared to the non-HC user group [16]. This study, along with an additional publication noted the increased laxity and tibial translation being significantly greater during the follicular +/- ovulatory phase of the cycle compared to the luteal phase [17].

There does appear to be a consensus amongst researchers that risk of ACL tear in the female athlete fluctuates throughout

the menstrual cycle, whether on OCPs or not. The time of risk appears to increase and peak as the follicular phase culminates in ovulation, which also happens to correspond with peaking levels of estrogen as mentioned previously, and the time of least risk is during the luteal phase when estrogen levels are at their lowest [16,18-24]. Trojian et al., also made mention of the fact that anterior tibial translation was its greatest during the follicular phase connecting increased ACL laxity, increased translation, peaking levels of estrogen, and the highest risk for ACL tear. Wojtys et al., found that while there was an overall significantly greater than expected occurrence of ACL tears in the ovulatory phase compared to luteal phase for all female athletes, HC use could mitigate this association of the ovulatory phase with increased ACL tear risk [24].

Use of HC may make the time of most risk more predictable

Table 1: Data Extraction Table summarizing the key findings in the individual studies examined.

Injury:	Reference	Participants	Exposure	Outcome	Key Findings	Comments
Tendons/ Ligaments/ Joints:						
	Nose-Ogura 2017	106 elite female athletes: 77 eumenorrheic athletes, 13 athletes with amenorrhea and 16 athletes taking OC.	Observational study to investigate changes in relaxin-2 levels in athletes taking OC.	Measured relaxin-2 levels in follicular and luteal phases and in those taking OC. Levels of relaxin-2, estradiol, progesterone, luteinizing hormone and follicle-stimulating hormone were measured in serum samples (n= 183).	Serum relaxin-2 concentrations were significantly higher during the luteal phase (n= 57) than in the follicular phase (n= 72), or in athletes on OC therapy (n=10) (P<0.001, P<0.001 and P<0.05, respectively). In the luteal phase, 36.8% (21/57) of the athletes had relaxin levels>6 pg/mL. During the second cycle of OC therapy, relaxin-2 concentrations decreased dramatically to below the detection limit (0.26 pg/mL).	High serum relaxin-2 concentrations were only detected during the luteal phase. In athletes with high relaxin-2 concentrations during the luteal phase, OC therapy decreased serum relaxin-2 levels.
	Hansen 2016	This is a chapter from a greater body of work.	Chapter analyzing the relationship between sex hormones and tendon.	"Influence of Oral Contraceptives on Tendon and Ligaments."	Lower tendon collagen synthesis in young OC users. OC use reduces knee joint laxity in young athletes and laxity does not vary across cycles like in non-OC users. One study reports more than 2x lower rates of traumatic knee and ankle injuries in OC users.	Few studies were evaluated for the OC portion of this chapter and the authors note the availability of research on the topic is "sparse."
	Hansen 2013	30 females from sub-elite Copenhagen handball clubs. 15 long term users (7.0 ± 0.6 yr) of different OCs (age 23.1±1 yr) and 15 eumenorrheic non-OC users for at least 5 years (age 22±1).	Patellar tendon force and elongation measurements were obtained along with cross-sectional area and length of tendon. Tendon biopsies were recovered as well.	Results were analyzed to determine the relationship between OC use and patellar tendon characteristics.	There was an inverse relationship between estradiol levels and tendon stiffness for all subjects (r=-0.49, P=0.02). OC users and non-users with no significant difference for patellar tendon force, elongation, cross-sectional area, length, tendon fibrils and collagen cross-linking. P>0.005.	Data to support other findings that high estrogen exposure is associated with increased knee laxity and elevated ACL tear risk. Long term OC use or menstrual phase do not influence structure or mechanical properties of patellar tendon for these athletes.
	Pokorny 2000	55 females age 20-25 (30 OC users and 25 non-OC users).	Masked, single factor, posttest only control group designed study looking at the relationship between reported oral contraceptive use and peripheral joint laxity.	Subjectively measured passive anterior tibial translation, passive abduction/adduction of the PIP and DIP of 5th digit of nondominant hand, passive joint motion of 2nd PIP in OCP users vs non-users.	No significant differences in laxity measurements at the knee or hand were found between the 2 groups. Average knee laxity varied between 5.7-7.9 mm of anterior displacement for both groups. Average PIP abduction and adduction varied between 6.5-6.7' for both groups and DIP hyperextension was 28.6-29.9'.	Indicate that self-reported oral contraceptive use was not associated with peripheral joint laxity.
ACL Injury:						
	Agel 2006	Data from 209 NCAA schools on ACL injuries and ankle sprains from the 2000-2001 basketball season and the 2001-2002 basketball and soccer seasons.	Retrospective analysis of participating NCAA schools' noncontact ACL injury and ankle sprain data from their 2000-2001 basketball seasons and 2001-2002 basketball and soccer seasons.	Analysis of data regarding hormonal therapy's relationship to injury.	No difference in injury rates between those who used or did not use hormonal therapy.	Possible protective effect of hormonal therapy. This conclusion can be drawn from calculating that these injuries were twice as likely to occur in basketball players, and that only 42% of basketball players reported hormonal therapy use while 70% of soccer athletes used hormonal therapies.

Liederbach 2008	298 dancers from New York ballet companies, a modern dance company, and a university-level conservatory of dance (men and women ages 18-41yrs).	This prospective epidemiologic study captured data from a variety of dancers over 5 years. Dance exposure was any participation where the subject was exposed to the possibility of dance injury.	Compared ACL injury rates and rate ratios in OCP users vs non-users.	No difference in injured vs non injured with regards to OC use. (P=0.13). Incidence of ACL injury was reported at 0.009/1000 exposures.	No conflicts of interest.
Lee 2015	40 women from Loma Linda University and the surrounding community. 15 OC users (age 25.1±2.8 yrs) and 25 eumenorrheic non-users (25.2±1.6yrs).	Subjects underwent ACL laxity testing and used a visual analog pain scale to measure baseline results as well as results 1, 2 and 3 days after completing extensive squatting exercises.	Results were analyzed with the purpose of examining the difference in ACL laxity after exercise between young OC users vs non-users.	OC users experienced more pain post exercise (P<0.001). Both OC users and non-users showed reduction in laxity 2 days after exercise (P<0.05).	Financial support from the pain division of Pfizer pharmaceutical. The author notes less laxity is associated with injury and that his athletes should be more cautious on the 2nd day after exercise.
Martineau 2004	N = 78 female athletes from varsity sports teams at McGill University. 42 OC users aged 20.4±1.4yrs; 36 non-users aged 20.4±1.4yrs.	This was a blinded, single-factor, posttest-only control group design in which participants were evaluated with questionnaires and KT-1000 measurements to determine tibial translation effect.	2-tailed t tests were performed on nondominant knee data of OC users and non-users to determine the effect of OC use on ligament laxity.	OC users had significantly less average anterior tibial translation. Mean anterior translations at 67N: OC users: 2.95 ± 0.93mm. Non-users: 3.86 ± 1.72mm (P = 0.008). Mean anterior translations at 89N: OC users: 3.88 ± 1.06mm. Non-users: 4.83 ± 1.82mm (P = 0.011).	This data suggests a protective effect of OC use on ACL injury. OC users had statistically significant decrease in knee laxity, may be the reason for protective effect against ACL tear. The author suggests potential prophylactic use to prevent injury.
Hicks-Little 2007	53 female collegiate student athletes (25 OC users and 28 non using controls) with no history of knee injury.	This research laboratory design had a 2x3 factorial design with 2 independent variables: (i) group (control, OC use) (ii) cycle phase (follicular, ovulation, luteal). The dependent variable was anterior tibial displacement.	Results were analyzed with the intent to establish if differences in tibial displacement exist during different phases of the menstrual/OC cycle.	OC users had increased anterior tibial laxity in the ovulatory and luteal phases (F=4.49; df=52.1; P<0.05). Suggests that there is an increased laxity in those takings OCPs with potential for increased injury risk.	To confirm validity of these measurements, a pilot study was performed in men and results were consistent (intersession reliability coefficient of r=0.9±0.08. Findings are unique and contradictory to other studies.
Trojian 2011	Eighteen females (18-30 years of age), taking OCP's for at least 3 months.	Observational study of OCP users. Used KT2000 measurements biweekly for 4 weeks to determine anterior tibial translation.	Looking to determine if there is a presence of differing anterior translation between the initial week and the last week of an OCP cycle.	Week 1 = 5.28 mm, Week 2 =4.72, Week 3 = 4.87, Week 4 = 4.64; Week 1 versus Week 3, P<0.01	Cited that women on OCPs were more likely to tear ACL at the start of their menstrual cycle.
Arendt 2002	83 female student athletes from NCAA schools. 25 were taking oral contraceptives, 58 were not.	This is a retrospective analysis of noncontact ACL injury data that athletic trainers collected from these athletes.	Results from linear and nonlinear regression models analyze noncontact ACL injury data for OCP users vs. non-users. There is a focus on identifying periodicity of injury.	28-day periodicity in both groups. High and low risk times for injury identified as the follicular (peaking at day 8) and luteal (peaking at 25) phases respectively. OC use correlated with a larger gap between high and low risk time frames.	Small sample size may create artificially high and low points of injury.
Herzberg 2017	This is a systematic review with a level of evidence at 4. Twenty-one studies were included.	Search terms included: athletic injuries, knee injuries, ligaments, joint instability, menstrual cycle, ovulation, hormones, and contraceptives. Strength of evidence was assessed with the GRADE approach.	Systematic review investigating potential effects of OCPs on ACL injuries.	Current quality of evidence is very low (contrasting findings of and contradicting conclusions of laxity cannot allow for a definitive statement on the relationship between OC use and laxity/ACL injury).	The authors report that electronic studies miss up to half of potential studies. This was an electronic study and so need for further assessment is essential. They do report that current evidence shows up to 20% reduction in ACL injury risk with OC use.
Hewett 2007	A literature search for articles relating to ACL injury and the menstrual cycle was conducted. 7 articles from the years 1998 to 2003 were reviewed.	A PubMed database search was conducted with subject terms "menstrual cycle, anterior cruciate ligament, and injury". It was supplemented with searching for relevant journals and unpublished studies.	Results were organized by paper reviewed. 6 compared OC users to non-users.	OC and non-OC users showed increase rate of injury during the 1st half of OC/menstrual cycle. "The use of OC in combination with neuromuscular training may increase the dynamic stability of the knee joint and may decrease injury risk in female athletes."	The authors have a high rate of exclusion with each potential study examined which could have led to significant selection bias.

Lee 2014	19 nonathletic, healthy females divided into 9 OC users (age 25.1±3.3 yrs) and 10 non-OC users (age 24.7±2.0 yrs).	Participants underwent testing for ACL elasticity, force of knee flexors, and knee flexion-extension hysteresis at 22°C and 38°C. Tests were conducted during menstruation (1-3 days after onset of menstruation), the follicular phase (9-11 days after onset menstruation), ovulation (13-16 days after onset menstruation), and the luteal phase (21-24 days after onset menstruation).	Statistical analyses of results were used to determine the relationship between OCP users and ACL elasticity, force of knee flexors (FFK), and knee flexion-extension hysteresis (KFEH) at varying temperatures.	Non-OC users showed fluctuations in ACL elasticity, force of knee flexors, and knee flexion-extension hysteresis across menstrual cycle. OC users did not. At 22°C, ACL elasticity significantly lower and FFK and KFEH were significantly higher in OC users (P<0.05). No between group differences at 38°C (all P>0.05).	These results suggest a protective effect of OC use. The decrease in variability from OC use should correlate to decrease risk of injury.
Lefevre 2013	172 women who sustained an ACL tear during the 2010-2011 ski season (age 34±8.7 yrs). 53 were using oral contraceptives.	This prospective study, observational, non-interventional study involved a questionnaire to gather accident information, sport level and menstrual cycle information.	Results were analyzed with a focus on OCP use and/or menstrual cycle phase at time of injury.	ACL injuries by phase of cycle: 33.72% follicular, 36.63 % ovulatory, 29.65% luteal. ACL tear was 2.4x more likely in pre-ovulatory than post-ovulatory phases in non-OC and OC users (71.4% vs 67.9%; P=0.64). No differences between OC users and non-users (P>0.05).	No conflicts of interest. No protective effects seen as exhibited by OCs.
Ruedl 2009	93 female recreational alpine skiers in the 2006/2007 and 2007/2008 winter seasons in a ski resort in the western part of Austria that sustained an MRI-confirmed non-contact ACL injury and 93 randomly matched controls based on age.	Case-control study of female recreational alpine skiers to assess for risk factors for ACL injury. used self-reporting survey to identify presence of prior OC use, phase of menstrual cycle (preovulatory vs postovulatory).	Looked to determine if OCP use was related to ACL injury risk.	OR = 1.92 (CI 1.07-3.44) for pre-ovulatory phase at time of ACL injury for both groups combined. No significant differences between subjects and controls regarding OC use.	Changes in weight and fat mass did not appear to affect performance. OCPs may serve to increase BMD in those athletes that have chronic amenorrhea and corresponding estrogen deficiency.
Wojtys 2002	65 female athletes (mean age 28±10 years, range 15-46) who sustained an acute ACL injury. 14 OCP users and 51 non-users.	Looked at mechanism of injury, menstrual cycle details, use of oral contraceptives, and history of previous injury.	Retrospective study looking at confirmed ACL tears in females and potential factors from their histories that affect their likelihood of ACL tear.	Significantly greater than expected percentage of anterior cruciate ligament injuries during midcycle (ovulatory phase), and a less than expected percentage of those injuries during the luteal phase of the menstrual cycle (chi-square=27.7, p<0.001). Oral contraceptive use diminished the significant association between anterior cruciate ligament tear distribution and the ovulatory phase (chi-square=29.8, p<0.001).	Supports possible protective effects of OCPs against ACL tears.
Gray 2016	15-39-year-old women. Cases = those receiving surgical reconstruction of ACL. Controls were matched 3 to 1 with cases. OC use was defined as those with any prescription fill for OCs.	Subjects participated in this case control study analyzing insurance claims from 2002-2012 for ACL injury and OC use.	Odds ratios were calculated to identify relationships between OC use and ACL injury.	Women 15-19 years old undergoing ACL reconstruction were 18 % less likely to use OCs than matched controls (adjusted odds ratio, 0.82; 95% CI, 0.75-0.91; P < 0.0001). 25-29 and 30-34-year-olds were more likely to use OCs than controls. Adjusted odds ratios of 1.15 (95% CI, 1.02-1.30; P < 0.05) and 1.16 (95% CI, 1.04-1.31; P < 0.05) respectively.	These differences in behaviors by age group are worth investigating with RCTs and prospective studies to create predictive solutions. Need for further research into the possible protective benefits of OCPs.

	Martineau 2004	N = 78 female athletes from varsity sports teams at McGill University. 42 OC users aged 20.4±1.4yrs; 36 non-users aged 20.4±1.4yrs.	This was a blinded, single-factor, posttest-only control group design in which participants were evaluated with questionnaires and KT-1000 measurements to determine tibial translation effect.	2-tailed t tests were performed on nondominant knee data of OC users and non-users to determine the effect of OC use on ligament laxity.	OC users had significantly less average anterior tibial translation. Mean anterior translations at 67N. OC users: 2.95 ± 0.93mm. Non-users: 3.86 ± 1.72mm (P = 0.008); Mean anterior translations at 89N. OC users: 3.88 ± 1.06mm. Non-users: 4.83 ± 1.82mm (P = 0.011).	This data suggests a protective effect of OC use on ACL injury. OC users had statistically significant decrease in knee laxity, may be the reason for protective effect against ACL tear. The author suggests potential prophylactic use to prevent injury.
	DeFroda 2019	165,748 female patients users 15-49 years old: total 82,874 patients in both the OCP and non-OCP groups.	Retrospective observational study reviewing <i>PearlDiver</i> database for OCP users 15-49 years old and matched with non-users.	Chi-square testing to compare the rate of OCP users undergoing ACL reconstruction to non-OCP users.	OCP group patients aged 15-19 had 63% lower odds of ACL reconstruction than non-OCP group (OR 0.37 ($\chi^2 < 0.001$, 95% CI 0.27-0.50)). Among all age groups, OR = 0.82 for experiencing an ACL reconstruction while on OCP ($\chi^2 = 0.001$, 95% CI 0.72-0.92) compared to not using OCP. NNT = 6 for 15-19-year old.	OCPs may have protective effects on ACL tears, especially in the 15-19 age group. Consideration prescribing OCPs to these younger athletes with proper risk assessment.
Non-ACL MSK Injury:						
	Brynhildsen 1997	Female elite athletes in volleyball (n=205), basketball (n= 150), and soccer (n=361) as well as age-matched controls (n= 113).	A questionnaire was administered in Sweden by coaches to players to gather information on the players' lower back pain as well as contraceptive methods. Case control study.	The questionnaire was administered with the intent identifying if women who use oral contraceptives have a higher prevalence of lower back pain than those who do not use oral contraceptives.	No significant differences between athletes currently experiencing lower back pain and using OCs (51%) or those currently experiencing lower back pain who don't use OCs (49%). No significant difference between athletes with previous lower back pain who used OCs (31%) or did not use OCs (29%).	Grants to fund this project were partially given by the Research Council of the Swedish Sports Federation, 'Förenade Livs Mutual Group Life Insurance Company', Stockholm; Lions Foundation and Östergötlands Läns Landsting.
	Brynhildsen 1997	28 female soccer players with back pain (ages 15-26 with median 21) and 22 female soccer players without lower back pain (ages 17-28 with median age 21). Each group had an average menstrual cycle length of 28 days. 46% of those with back pain used OCs, 45% of those without back pain did not use OCs.	Case control study with participants selected from 12 soccer clubs in Sweden based on their responses to a questionnaire regarding lower back pain and menarche. Selected participants were physically evaluated to identify and exclude those with physical injuries. Screened participants were asked to keep a diary of menstrual periods, OC use, physical activity, and subjective measurements of back pain during their 5-8 months of the active soccer season.	Results from the diaries were categorized by menstrual/OC cycle phase and evaluated for differences in lower back pain severity and frequency.	OC users and non-users showed no differences in days with lower back pain per cycle (no data provided for this point).	Several participants were excluded because of mid-study pregnancy or moving residences. Previously, there were recommendations to avoid OCPs if LBP was present, but this does not support the hypothesis that the two are linked.
	Gallagher 2018	90 collegiate student-athletes (40 male and 50 female). Females were divided into 24 HC users and 25 non-users at time of injury (1 excluded for IUD use). All participants sustained at least one concussion during their collegiate careers between January 2011 and December 2016 and did not have a history of neurological disorders.	Retrospective analysis of subjects' electronic treatment records. These included completed Sport Concussion Assessment Tools (SCATs) that reveal total symptom number (0-22) and symptom severity score (0-132).	Descriptive analyses were used to evaluate between group differences in length of recovery, peak symptom severity.	Non-HC users demonstrated higher symptom severity than HC users (F [1,47] = 5.142, P < 0.05, d = 0.70). Symptom severity was strongly related to LOR for males (r=0.513, p<0.01) but not females (r=-0.003, p>0.05). No significant differences in length of recovery between female HC users (24±30 days) and non-HC users (20±19 days) P>0.005.	No competing interests. Evidence for differing outcomes for concussion in OC vs non-OC using females and their male counterparts. Retrospective findings such as this can always benefit from being applied as predictive models in future prospective studies.

	Mihalik 2009	36 healthy college females aged 21.4±1.7 years (24 OC users, 12 eumenorrheic non-users aged). Participants had not had a concussion in the past 3 months.	This single-blinded prospective counterbalanced repeated measure design involved subjects completing a standard concussion test battery during 3-5 days after the onset of the menstrual phase and 4-6 days prior.	Results were compared to determine if changes in neurocognitive function, postural stability and self-reported symptoms across the menstrual/ OC.	Neither group showed differences in neurocognition, postural stability, or self-reported symptoms/severity between sessions (all P>0.05). OC users had less symptoms (P=0.001) and less symptoms severity (P<0.001).	No conflicts of interest. Differences in cognition and balance should not be suspected based on OC use. Baseline status holds true no matter the menstrual cycle phase.
	Chauhan 2014	N=421: 158 active symptomatic Achilles tendinopathy, 174 active asymptomatic, 89 inactive controls.	Observational cohort study conducted via a web-based questionnaire produced by combining literature identified risk factors with the VISA-A (0-100) questionnaire.	These researchers analyzed the relationship between associated factors and VISA-A scores across the 3 groups.	Those active and symptomatic for Achilles tendinopathy were more likely to have risk factors that included contraceptive use (P<0.01).	Abstract only, so there was a lack of detail in the methods, results and discussion sections.
VTE:						
	Cerquozzi 2012	35-year-old white, elite female triathlete with no personal or family history of thrombotic events.	3-year history of left hip and groin pain investigated by MRI revealed distension of left common and external iliac veins with associated deep vein thrombosis (DVT).	OC use discontinued and warfarin used for 6 months.	MR angiogram confirmed resolution of DVT. Lack of risk factors outside Factor V Leiden mutation suggest role of OC in symptoms.	Informed consent was obtained from the patient for this publication.
	Landesberg 2012	20-year-old female collegiate cross-country runner with acute pulmonary embolism.	Case report for pulmonary embolism in young and otherwise healthy individual. Potential relationship with OC use.	Discontinue OC and start anticoagulation therapy.	Resolution of symptoms.	Due to lack of risk factors, OC use was identified as the potential link between PE and this female athlete.
	Abbott 2013	19-year-old female Division 1 basketball player taking OCs for 6 months.	Case report for pulmonary embolism in young and otherwise healthy individual. Potential relationship with OC use.	Discontinue OC and initiate anticoagulation therapy.	Resolution of symptoms.	Heterozygous for Factor II prothrombin and V Leiden mutation.
	Dapul 2014	A Division II college softball pitcher with right upper extremity edema and pain taking OCs and no other medications for one year.	Spontaneous DVT in subclavian vein (Paget-Schroetter Syndrome).	Required acute anticoagulation and discontinuation of OC. Resection of first rib and scalene performed because venogram showed chronic stenosis from compression. Laboratory work up for genetic disease revealed positivity for Factor V Leiden.	Positive Factor V Leiden and OC use thought to be main contributors contributed to her spontaneous thrombus formation. High amount of activity with involved limb can accelerate this process in those predisposed.	This is a rare condition that can have serious complications.
	Aquino 1989	18-year-old female softball player using OCs for 4-5 months.	Case report for DVT of axillary and subclavian veins in young and otherwise healthy individual. Potential relationship with OC use.	Discontinue OC and initiate thrombolytic therapy.	Resolution of symptoms.	Diagnosed as "effort thrombosis" from trauma secondary to softball play but patient advised to abstain from OC use.
Perform- ance:						
	Reference	Participants	Exposure	Outcome	Key Findings	Comments:
Aerobic:						
	Perkins 1984	10 female college varsity athletes: 5 OCP users and 5 non-OCP users participating in the same pre-season conditioning program.	Observational study into the effects of OCPs on hemodynamic & cardiovascular parameters, serum lipid levels and max oxygen uptake.	Compared numerous parameters of hemodynamics and cardiovascular status in OCP users vs non-users (VO2 max, hematocrit and hemoglobin, resting BP, resting HR, max HR, %body fat, body weight, total cholesterol, triglycerides, HDL-C, LDL-C, VLDL-C, RQ).	Hemoglobin with only significant increase (p<0.005).	Main takeaway was no impact of OCPs on VO2 max (only direct performance marker). Very small sample size.

	Bryner 1996	15 men as controls. 10 women between 18-30yrs of age.	Randomized, double-blinded, placebo-controlled trial. The men were tested twice by maximal treadmill test and an endurance run 14 days apart to elucidate any performance variabilities that were not hormonal. Women did the same during their follicular and luteal phases. Women then randomly assigned to placebo or oral contraceptive groups for 21 days and tests were repeated.	The treadmill and endurance runs were conducted to evaluate changes in VO2 max that may occur with fluctuations in hormone levels in those taking OCPs vs those not taking OCPs.	No difference between the follicular and luteal phases for VO2 max [41.6 (SD 12.1) and 39.7 (SD 11.4) ml/kg*min] respectively. No difference in VO2 during the first and third weeks of treatment [37.3 (SD 7.4) and 41.0 (SD 12.4) ml/kg*min]. No difference during the endurance test between the follicular and luteal phase for VO2 either [37.5 (SD 9.4) and 32.9 (SD 8.1) ml/kg*min] respectively. No difference during the first and third weeks of treatment for VO2 33.9 (SD 10.1) and 35.2 (SD 8.6) ml/kg*min].	There seems to be a trend towards decreased VO2 max with OC use but because of the standard deviations it cannot be ruled significant. It could possibly be accounted for by the variation in conditioning of the athletes participating in this study.
	Ruzic 2003	50 women (age range, 18-30 years; mean±SD, 26±3) using hormonal contraception for at least 12 months before the beginning of the study. Divided into antiandrogen group (n=26) and estrogen-progestogen group (n=24).	Recorded quadriceps muscle strength via isometric dynamometry, fat-free mass via bioimpedance method, VO2 max.	Investigated the potential antiandrogen effects of hormonal contraception on muscle strength gain and fat-free mass gain during exercise in women.	Mean gain in muscle strength was significantly greater in estrogen-progestogen group vs antiandrogen group (128.9.9±17.06 N vs 101.86±18.54 N; p<0.001). mean increase of fat-free mass was significantly greater in the estrogen-progestogen group (1.4±0.2 kg vs 1.6±0.3 kg, p<0.001). No significant differences in VO2 max between the groups.	Advised for the avoidance of antiandrogens in OCPs for female athletes as it could minimize the effects of strength and conditioning training.
	Vaiksaar 2011	All participants were undergoing routine testing at the Tasmanian Institute of Sport or were participating in their state sporting organization representative squads.	Tests performed in Follicular phase (FP) and Luteal phase (LP): power output (Pa), HR, oxygen consumption (VO2), CO2 production (VC02), minute ventilation (Ve), mean RER, Ve/VO2, Ve/VC02 were all measured at max output and at aerobic-anaerobic transition points.	Investigating any differences in aerobic exercise testing performance at various points of menstrual cycle and in those on OCPs.	Higher values recorded at both intensities in LP vs FP for OCP users for Ve/CO2 (p<0.05). No other findings were significant for differences between groups or across phases.	Supported that those taking OCPs should not be worried about interference with performance and timing endurance performance with menstrual cycle phase was not needed.
	Gordon 2018	16 females physically active for 30 minutes or more at least 3 days per week. 10 did not use OCs (age 20.6±1.6 yr) and 6 used OCs containing 30ug synthetic estrogen and 150ug synthetic progesterone (age 21.7±2.16 yr).	Both groups participated in this laboratory experiment on five occasions to determine VO2 max and cardiovascular responses. The 5 trials correspond to 1 familiarization trial (FAM), and then one trial the menstruation (MEN), mid-follicular (mFOL), mid-luteal (mLUT) and pre-menstruation (pMEN) phases of the menstrual/OC cycle.	Statistical analysis performed to examine the effect of menstrual/OC cycle phase on VO2max and associated cardiodynamic responses.	OC users showed no VO2 plateaus and significant differences in VO2 plateau from non-OC users during mLUT (0.010), mFOL (P = 0.007), and pMEN (P<0.001)-phases during the last 60s of VO2 max trials. OC VO2 max did not differ from non-OC users (all P>0.05)	VO2 plateau affected by monophasic oral contraceptive use but VO2 max is not. Author states VO2 plateaus were "almost non-existent."
	Giacomoni 2000	10 female physical education students (age 23±3 yrs) using monophasic OC for at least 18 months.	This is a randomized cross-over trial in which subjects participated in a submaximal treadmill run at varying intensities lasting 4 minutes each. Tests occurred during days 2-4, 7-9, and 19-21 of their cycles. On each occasion subjects were tested at 08:00h, 13:00h, and 17:00h. These measurements were averaged for a single value per day tested.	Heart rate, ventilation, O2 uptake, CO2 uptake, respiratory exchange ratio and running economy were assessed for OCP users vs non-users.	Major finding was that there was a decrease in oxygen uptake during OC consumption for a given exercise intensity. O2 uptake (VO2) increased by 3%-5.8% on days 2-4 of cycle (F (2,18) = 6.3; P= 0.008). Running economy (ml O2/kg*km) significantly improved on days 19-21 (P<0.05)	OC users may expect lower VO2 and better running economy at different points in the OC cycle. Small sample size.

	Casazza 2002	6 moderately active, healthy, non-smoker female university students (not competitive athletes) from University of California, Berkeley, who were eumenorrheic (25.5±1.5 yr) and had not taken OCs for at least 6 months.	Subjects were administered the same triphasic OC once per day for 4 complete cycles (28 days each cycle). Peak and submaximal exercise during the follicular (days 4-8 after menses) and luteal (17-25 days after menses) phases before OC use and during the inactive (days 22-28 of cycle) and high-dose (days 8-14) phases after 4 months of OC use.	Looking at markers of exercise capacity and performance in OCP users.	OC use increased body weight (59.6±2.3 to 62.26kg, P<0.05) which is thought to decrease peak exercise capacity. OC use showed trend towards decreased VO ₂ peak (2.53±0.21 to 2.25±0.18 l/min).	Sample size of 6 may not allow results to be reproducible or broadly applicable.
	Lebrun 2003	14 women not using oral contraceptives for at least three months before the study who participated regularly in competitive aerobic activities (VO ₂ max > 50ml/kg/min)..	This is a double blind, placebo controlled RCT testing VO ₂ max, anaerobic capacity (via anaerobic speed test), aerobic endurance (via time to fatigue at 90% VO ₂ max), and isokinetic strength (from Cybex II dynamometer). All tests performed in both the follicular and mid-luteal phases while not taking OCs. Participants were then randomly assigned a tricyclic OC and were retested.	Results were analyzed to determine the effects of triphasic OC use on various athletic performance characteristics.	No significant differences in athletic performance characteristics between OC users and non-users (P>0.05). A notable trend of 4.7% decrease in average VO ₂ max occurred in OC users but individual variability was high.	The authors used an overwhelming amount of exclusion criteria. This suggests a narrow scope of generalizability for their results (14 subjects were chosen of 51). One of the few true RCT's available for study.
	Joyce 2013	16 healthy women (8 OC users aged 20±2 yrs and 8 non-users aged 22±3 yrs) who participated in formally scheduled team sports. (exercising 3 or more days per week for 30 minutes or more). No subjects participated in regular cycling. Each OC user was matched with a non-OC user for age of menarche, BMI, and weekly duration of physical activity.	Subjects participated in an Incremental Exercise Test to Exhaustion (determining VO ₂ peak and anaerobic threshold [AT]) as well as 4 Submaximal Exercise Tests (below and above AT to exhaustion) to determine Pulmonary gas exchange, heart rate, blood pressure, blood lactate concentration, and perceived levels of exertion.	Results were analyzed to evaluate the relationship between chronic OC use and endurance performance.	Time to exhaustion similar between groups (t=0.159, P=0.88). VO ₂ peak at AT were lower in OC users. (VO ₂ peak OC: 2.13±0.20L/min. VO ₂ peak Control: 2.58±0.50L/min) (VO ₂ at AT OC: 1.18± 0.15L/min. VO ₂ at AT Control: 1.47± 0.27L/min) (both P<0.05).	Results show that long-term OC use negatively affects peak VO ₂ and VO ₂ at AT but does not alter endurance exercise performance.
	Schaumburg 2017	Recreationally active women taking an OC (n=25) or experiencing natural regular menstrual cycles (MC; n= 16).	peak power output (PPO), VO ₂ peak and peak cardiac output (Qpeak). Testing was completed before, immediately after, and 4 weeks after 12 sessions of SIT.	aimed to examine the influence of OC use on peak performance and physiological adaptations after sprint interval training (SIT).	VO ₂ _{peak} increased in both groups after SIT (both p<0.001). MC group showed greater improvement in VO ₂ peak (OC, +8.5%; MC, +13.0%; P= 0.010). Q _{peak} increased in both groups, with greater improvement in the MC group (OC, +4.0%; MC, +16.1%; P= 0.013). OC group showed more sustained training effects in VO ₂ _{peak} (OC -4.0%; MC -7.7%; P=0.010).	OC use limited the improvements made in physiologic training adaptations from SIT.
Anaero-bic:						
	Lebrun 2003	14 women not using oral contraceptives for at least three months before the study who participated regularly in competitive aerobic activities (VO ₂ max > 50ml/kg/min).	This is a double blind, placebo controlled RCT testing VO ₂ max, anaerobic capacity (via anaerobic speed test), aerobic endurance (via time to fatigue at 90% VO ₂ max), and isokinetic strength (from Cybex II dynamometer).	Results were analyzed to determine the effects of triphasic OC use on various athletic performance characteristics.	No significant differences in athletic performance characteristics between OC users and non-users (P>0.05). A notable trend of 4.7% decrease in average VO ₂ max occurred in OC users but individual variability was high.	The authors used an overwhelming amount of exclusion criteria. This suggests a narrow scope of generalizability for their results (14 subjects were chosen of 51). One of the few true RCT's available for study.

			All tests performed in both the follicular and mid-luteal phases while not taking OCs. Participants were then randomly assigned a tricyclic OC and were retested.			
	Bushman 2006	24 moderately active women (17 OC users [15 multiphasic and 2 monophasic], 7 eumenorrheic non-users). Average age of users was 21.4±2.9 while non-users were 20.3±1.3.	3 days of performance testing were conducted within the same month. The first day was to familiarize subjects with the Margaria-Lalamen and Wingate performance tests. The next 2 days evaluated performance during menses and the luteal phase respectively.	Results from these performance tests were analyzed with the purpose of comparing the impact of the menstrual/OC cycle on short-term, high intensity performances.	OC users showed no difference in Peak power between menses and luteal phase (566.4±69.1 and 575.6±2.6 watts). OC users showed no difference in Anaerobic capacity between menses and luteal phase (401.7±70.4 and 405.7±67.7 watts).	Several menses and luteal measurements skewed by equipment failure. small sample size, OC users with multiple types of formulations. Further research on between group differences may elucidate differences between OC users and non-users.
	Giacomoni 2000	17 female physical education students (age 23±3 yrs.) 7 eumenorrheic and 10 using monophasic oral contraceptives. 6 OC using and 4 eumenorrheic subjects experienced perimenstrual symptoms (MS).	Anaerobic testing via force-velocity, multi-jump, and squatting jump tests were tested during menstruation (days 1-4), the mid-follicular phase (days 7-9), and the midluteal phase (days 19-21).	Statistical analysis to determine the differences between OC users and Non-OC users with regards to anaerobic performance.	OC users showed no significant differences in anaerobic performances compared to non-OC users. (all variables P>0.05). OC use was not correlated with presence of MS. MS maximum cycling power decreased by 8 in the mid-follicular phase compared to the follicular phase (P<0.05).	Cholesterol intake, running schedules were not controlled for and there was quite a large range amongst the subjects. Type and duration of OC use was different for each runner. Authors suggest that exercise may be protective against lipid alterations that.
	Redman 2004	5 elite and sub-elite female rowers taking Triphasil-28 or equivalent (hormonally similar to 50- to 125 microgram levonorgestrel and 30- to 40 microgram ethinyl estradiol).	Measured weight, total fat mass, total bone mineral density (BMD), total change in BMD.	Goal was to investigate the effects of OC use on body composition and physical performance in female athletes.	There was an increase in weight and fat mass only in athletes with oligo-/ amenorrhea (p<0.01). Little impact on physical performance was recorded. OC treatment also increased bone mineral density, with the largest increase in athletes with a low bone mineral density at baseline (p<0.05).	Changes in weight and fat mass did not appear to affect performance. OCPs may serve to increase BMD in those athletes that have chronic amenorrhea and corresponding estrogen deficiency.
	Bryant 2011	38 athletic women who regularly ran more than 20km per week for at least 2 years prior and had no history of serious lower extremity injury. 19 participants were not taking OCs (average age 28yr) and 19 were (average age 31.9yr).	Non-OC users tested on the first day and 24hrs before menstruation (predicted with body temperature changes). OC users tested at day 1 and 14.	Leg stiffness and foot center of pressure (COP) during hopping in OCP users and non-users were measured by a force plate with the intent of elucidating exogenous estrogen's effect on the neuro-mechanics of hopping.	Non-OC users saw a 30% higher COP path length at ovulation as well as a 25% increase in COP path velocity. These increases were not seen in OC users suggesting more stability and a correlation to the lower incidence of lower extremity musculoskeletal injury seen with OC use.	Postural differences could have contributed to differences in measurements. Due to qualities of the controls sample population, results may not be generalizable to all activity levels and ages.
Strength:						
	Drake 2005	14 physically active University of Southern Mississippi students with a mean age of 23±1 years. (8 were OC users with at least 6 months of use. 6 were non-OC eumenorrheic subjects). All subjects were involved in a strength training and aerobic program.	A prospective quasi-experimental cohort design comparing EMG and MMG between NOC and OC users at the follicular, ovulation, and luteal phases of one of their menstrual/ OC cycles. Maximum isotonic strength was also determined through maximum weight lifted on the dominant leg through a full range of motion.	The EMG and MMG results were compared with OC use and cycle phase to differentiate neuromuscular properties of the rectus femoris.	No significant differences in EMG or MMG results, isotonic strength, or fatigue during exercises between OC users and non-OC users. (All P>0.05). No evidence to support differences in muscle function between the groups.	Partially funded from the Committee on Services and Resources for Women (2001), University of Southern Mississippi, Hattiesburg, MS. Acknowledged by authors that it would be hard to apply results to the entire population due to small sample size.

Ekenros 2013	17 healthy, moderately active university students from Sweden. 8 used OCs (mean age 26.4±2.5) and 9 had not for at least 3 months (mean age 27±4.8).	This crossover design study measured maximum isokinetic muscle strength on knee flexors, isometric handgrip strength, and a 1-leg hop test distance. Measurements occurred during the early follicular phase, the ovulatory phase, and the luteal phase of the same cycle.	The goal was to compare hop performance, as well as muscle strength in upper and lower extremities for OC and non-OC users within 3 specific phases of the menstrual/OC cycle.	No differences in isokinetic muscle strength (P=0.78) handgrip muscle strength(P=0.76) and hop performance (P=0.78) between OC users and non-users.	Sample size was supposed to be 24 but 7 dropped out or did not comply with the study treatment. The remaining 17 are a small sample size that should be noted. Supports positions that OC use does not hinder performance.
Elliott 2005	21 female subjects (14 combined monophasic OC users and 7 eumenorrheic controls)	Maximum dynamic and isometric leg strength, maximum isometric strength of the first dorsal interosseous muscle were measured on days 7 and 14 of pill consumption and on day 5 of pill withdrawal. Controls were measured on days 2 and 21 of their menstrual cycle.	Results analyzed to determine if a relationship between maximum force production in OC users and non-users.	OC users were not stronger or weaker than eumenorrheic controls. All measured variables P > 0.05.	Large differences in hormone concentration were found in each subject but this did not appear to directly impact strength.
Gordon 2013	17 well trained females. 11 did not use OC (age 20.7±1.4 yrs) and 6 used OCs ((age 20.3 ± 0.5 yrs).	This laboratory-controlled experiment tested concentric strength of knee flexor and extensors at four different points in the menstrual/OC cycle: menstruation (days1-3), mid-follicular (days9-11), mid-luteal (days 19-20), and premenstrual (days 27-28).	Results of knee flexor/ extensor strength tests were examined with respect to OC use or non-use.	OC users showed no differences between phases (differences all P>0.05). Non-OC users saw decreases in peak torque production during menstruation for extensors at 120° (P=0.027) and flexors at 60° and 120° (both P<0.03). Skeletal muscle is sensitive to changes in estrogen concentration in terms of its ability to contract, velocity of contraction.	Seemingly protective effect of OC use because the variations in torque production seen in non-OC users provides more susceptibility for injury. OC users maintain consistent torque production vs. non-OC users. Small sample size.
Lebrun 2003	14 women not using oral contraceptives for at least three months before the study who participated regularly in competitive aerobic activities (VO2 max > 50ml/kg/min)..	This is a double blind, placebo controlled RCT testing VO2 max, anaerobic capacity (via anaerobic speed test), aerobic endurance (via time to fatigue at 90% VO2 max), and isokinetic strength (from Cybex II dynamometer). All tests performed in both the follicular and mid-luteal phases while not taking OCs. Participants were then randomly assigned a tricyclic OC and were retested.	Results were analyzed to determine the effects of triphasic OC use on various athletic performance characteristics.	No significant differences in athletic performance characteristics between OC users and non-users (P>0.05). A notable trend of 4.7% decrease in average VO2max occurred in OC users but individual variability was high.	The authors used an overwhelming amount of exclusion criteria. This suggests a narrow scope of generalizability for their results (14 subjects were chosen of 51). One of the few true RCT's available for study.
Myllyaho 2018	18 healthy, physically active women (age 24-41) with 9 using OC for at least 1 year (avg. age 28.2±3.1) and 9 having never used OC (avg. age 31.3±5.4).	observational study examining the effects of a 10-week program combining high intensity strength and endurance training.	Measures of performance (strength, endurance) were compared between OCP users and non-users.	Stress fractures reported in 22 athletes (34.4%). maximal bilateral isometric leg press (Isom), maximal bilateral dynamic leg press 1RM, countermovement jump (CMJ), 3k meter running test all with no significant differences between OC users and non-users.	Athlete's taking OC were not negatively impacted in any fashion in terms of their performance and response/adaptations to high intensity training. Same training protocols can be applied to both groups for equally as good results.
Nichols 2008	31 collegiate female softball and water polo athletes: 13 OCP users (mean age 20.0±1.2, mean BMI 25.0) vs 18 non-OCP users (mean age 18.7±1.1, BMI 24.8).	Double blinded design investigating the effects of combined OCPs on strength and torque production following a 12-week strength development plan compared with those not taking OCPs.	Measures of strength were compared between OCP users and non-users (1RM bench press (1RMBP), 10RM leg extension (10RMLE), isokinetic peak torque bench press (IKBP), isokinetic peak torque leg extension (IKLE).	Significant increases in 1RMBP, 10RMLE, IKLE regardless of group (p<0.05). No significant difference in IKBP from start to finish of 12-week program (p<0.05). No significant differences in any parameters between the groups.	Use of OCPs did not provide androgenic effect to increase strength metrics beyond that stimulated by the program itself and also did not inhibit strength gains. Study did not provide numerical data for increases in parameters of strength and torque production.

	Peters 2006	12 females taking monophasic pill w/ 30 micrograms ethinylestradiol PLUS either 150 micrograms levonorgestrel (LEV: mean age 19.8±0.3) or 250 micrograms norgestimate (NOR: mean age 20.6±0.2).	Investigating the androgenicity of progressions in OCPs and their effect on maximal leg strength.	Compared effects of OCP use on measures of strength/performance (peak extension/flexion torque).	No significant differences found between the two groups at any point of the study for peak extension torque (F=0.719, p=0.416) or peak flexion torque (F=0.291, p=0.601).	No association between progestins in OCP and leg strength. Study lacked a true control group.
	Ruzic 2003	50 women (age range, 18-30 years; mean±SD, 26±3) using hormonal contraception for at least 12 months before the beginning of the study. Divided into antiandrogen group (n=26) and estrogen-progestogen group (n=24).	Recorded quadriceps muscle strength via isometric dynamometry, fat-free mass via bioimpedance method, VO2 max.	Investigated the potential antiandrogen effects of hormonal contraception on muscle strength gain and fat-free mass gain during exercise in women.	Mean gain in muscle strength was significantly greater in estrogen-progestogen group vs antiandrogen group (128.9.9±17.06 N vs 101.86±18.54 N; p<0.001). mean increase of fat-free mass was significantly greater in the estrogen-progestogen group (1.4±0.2 kg vs 1.6±0.3 kg, p<0.001). No significant differences in VO2 max between the groups.	Advised for the avoidance of antiandrogens in OCPs for female athletes as it could minimize the effects of strength and conditioning training.
	Ali 2016	Ten healthy females (24 ± 4 years; 59.7 ± 3.5 kg; undertaking 2–6 training sessions per week. All taking low-dose monophasic oral contraceptives of the same hormonal composition.	Randomized, double-blind, placebo-controlled crossover-design trial. Ingestion of capsule containing 6 mg·kg ⁻¹ body mass caffeine anhydrous or artificial sweetener (placebo). 90-min intermittent treadmill running protocol.	Isometric strength performance, eccentric/concentric strength, power of knee flexors/extensors (using isokinetic dynamometer), countermovement jump (CMJ), was measured before, during and after the exercise protocol, as well as ~12 h post-exercise.	Caffeine supplementation significantly increased eccentric strength of the knee flexors (P< 0.05) and eccentric power of both the knee flexors (P< 0.05) and extensors (P< 0.05). However, there was no effect on isometric or concentric parameters, or CMJ performance.	Caffeine supplementation increased eccentric strength and power in female team-sport players taking OCS both during an intermittent running protocol and the following morning.
	Wikstrom-Frisen 2017	59 trained female athletes, n = 19 trained with high frequency in follicular phase, n = 19 trained with high frequency in luteal phase. Control group (n = 21).	Two groups performed high frequency leg resistance training for two weeks of each menstrual/oral contraceptive cycle for four months and trained 1x/week for the rest of the cycle. High frequency was training 5x/week. Control group trained 3x/week throughout.	Measured squat, countermovement jump, peak torque values for hamstrings and lean body mass changes.	Training in luteal phase had significant increases in all measured variables but not in group 2 (luteal phase training). No evident differences in the training effects between women with or without oral contraceptive.	Full text unavailable. Abstract does not contain numerical results.
	Bernardes 1998	7 healthy, eumenorrheic, nulliparous women aged 22-31 with an average age of 26yr whose only medications were for OC therapy.	Randomized 2x2 design of continuous and intermittent cycling protocols during OC use (days 7-11 of menstrual cycle) and non-use (days 3-5). Each trial was separated by at least 1 week and all trials were completed within 3 cycles. OC use included 21 days of ingestion and 7 days of non-use placebo ingestion.	Lactate, growth hormone, and estradiol/progesterone responses were analyzed and presented for women while taking and not taking OCPs.	Serum GH levels of OC users and nonusers were significantly elevated after 20 minutes of exercise and OC use (13ug/ml compared to 4ug/ml and the difference between groups measured P < 0.01).	A sample size of 7 makes it hard to generalize results to larger populations.
Body Composition:						

	Procter-Gray 2008	150 female competitive distance runners aged 18–26 y (mean age 22.1). Randomly assigned to OCP (n=69) vs non-OCP control group (n=81).	The goal was to examine the effect of oral contraceptives (OC) on bodyweight and body composition as a part of a study involving a 2-yr randomized trial of the effect of the OC Lo/Ovral (30Kg of ethinyl estradiol and 0.3 mg of norgestrel).	Investigating effects of OCPs on body composition (bodyweight, fat mass, percent body fat, and lean mass).	Women of the OC group gain slightly less weight (adjusted mean difference (AMD) = -0.54±0.31 kg/yr, P= 0.09) and less fat (AMD = -0.35±0.25 kg/yr, P= 0.16) than those of the control group (non-OC). OC users had significant gain in lean mass relative to controls among eumenorrheic women (those who had 10 or more menstrual cycles in the year before baseline; AMD = 0.77±0.17 kg/yr, P<0.0001) but not among women with fewer than 10 menstrual cycles in that year (AMD = 0.02±0.35 kg/yr, P= 0.96).	Main conclusion: supports research that says OC use does not cause weight or fat mass gain. OC may be associated with lean mass gain in eumenorrheic women. <i>Raises ethical concern about the use of a placebo for control compared to the contraceptive effects of OCPs.</i>
	Myllyaho 2018	18 healthy, physically active women (age 24–41) with 9 using OC for at least 1 year (avg. age 28.2±3.1) and 9 having never used OC (avg. age 31.3±5.4).	Observational study examining the effects of a 10-week program combining high intensity strength and endurance training.	Measures of performance (strength, endurance) were compared between OCP users and non-users.	Stress fractures reported in 22 athletes (34.4%). maximal bilateral isometric leg press (Isom), maximal bilateral dynamic leg press 1RM, countermovement jump (CMJ), 3k meter running test all with no significant differences between OC users and non-users.	Athlete's taking OC were not negatively impacted in any fashion in terms of their performance and response/adaptations to high intensity training. Same training protocols can be applied to both groups for equally as good results.
	Rechichi 2012	Six competitive swimmers and water polo players taking a monophasic OC (30mg EE, 150mg levonorgestrel).	Recorded split times, stroke rate, heart rate, blood lactate, glucose, pH measured after each performance test. Resting endogenous serum estradiol and progesterone concentrations were also assessed.	Investigating whether swimming performance was affected by acute hormonal fluctuation within a monophasic oral contraceptive (OC) cycle.	No significant differences were observed between phases for body composition, 200-m swim time, mean stroke rate, peak heart rate, or blood glucose (p>0.05).	Cycle phase does not appear to affect swimming performance
	Rickenlund 2004	Twenty-six endurance athletes (13 with oligo-/amenorrhea and 13 regularly menstruating athletes) and 12 sedentary controls before and after 10 months of treatment with a low dose, monophasic, combined OC.	Measured weight, total fat mass, total bone mineral density (BMD), total change in BMD	Goal was to investigate the effects of OC use on body composition and physical performance in female athletes.	There was an increase in weight and fat mass only in athletes with oligo-/amenorrhea (p<0.01). Little impact on physical performance was recorded. OC treatment also increased bone mineral density, with the largest increase in athletes with a low bone mineral density at baseline (p<0.05).	Changes in weight and fat mass did not appear to affect performance. OCPs may serve to increase BMD in those athletes that have chronic amenorrhea and corresponding estrogen deficiency.
Heat Ac-climation/ Perceived Exertion:						
	Armstrong 2005	36 inactive females with a mean age of 21 years. 15 were taking an oral estradiol-progestin contraceptive, 7 were on a contraceptive injection of depot medroxyprogesterone acetate, and 14 were not on contraceptives.	Participants underwent an 8-week HAPT program (heat acclimation and physical training). Indoor heat acclimation was 90 min/day, 3 days/wk. Outdoor physical training was 3 days/wk.	Standardized physical fitness and exercise heat tolerance tests administered before and after HAPT to assess for heat acclimation and training adaptations in OCP users vs non-users.	Post HAPT onset temperature of local sweating was significantly different between Oral (37.2±0.4°C) and injection (37.7±0.2°C) contraceptive users.	Results may not be applicable to athletes.

	Larsen 2018	18 recreationally active women (300-500 min/wk moderate intensity exercise). 9 were OC users for >12 months (aged 22±3 yrs) and 9 were eumenorrheic non-users for > 12 months (22±4 yrs).	3 exercise tests were completed: incremental cycling test to exhaustion, and two 3-stage cycling trials (one at 22°C and one at 35°C.) Blood and saliva samples were drawn at baseline, after 60min in environmental conditions, and then immediately post exercise. OC users were tested during days 2-21 of their cycles while non-users were tested during days 2-6 (i.e. follicular phase).	Statistical analyses were conducted to compare immune and stress responses of OC users vs non-users during exercises at different temperatures. (Immune and stress response measured through CRP, immune cell counts, serum cytokines (IL-1β, IL1RA, IL-6, IL-8, IL-10, and TNF-α) and salivary cortisol).	No differences (all P>0.05) in immune and stress responses between OC users and non-users regardless of temperature or exercise.	It is worth noting that there was a trend towards higher resting CRP in OC users than Non-users (1.102 ± 1.182 and 0.326 ± 0.228, respectively, p = 0.07). Small sample size.
	Minahan 2017	16 healthy, recreationally active women who exercised 300-500 min/week. 8 were eumenorrheic non-users (22±3) who had never taken oral contraceptives. The remaining 8 were OC users (aged 22±3 yrs) were taking low dose combined monophasic oral contraceptives for >12 months prior. Groups were matched based on age and BMI.	A three-stage cycling trial was performed at 90, 135, and 180% of the lactate threshold. Core body temperature and heart rate were measured continuously while blood pressure, perceived exertion, skin blood flow, and blood lactate were recorded every 7.5 minutes. Subjects performed these experiments during a 22°C trial (TEMP) and a 35°C trial (HEAT).	Results were analyzed to determine the effects of long-term contraceptive use on women exercising in heat.	Baseline core body temperatures are higher in OC users for 22.5 minutes of both TEMP (P=0.03) and HEAT (P=0.01) trials. Skin blood flow plateaued at 7.5 minutes in non-users and 15 min in OC users (P = 0.02). OC users had higher rates of perceived exertion than non-users in HEAT trial (P≤0.04).	The author notes that these results may have implications for exercise tolerance in hot conditions.
	Lei 2018	10 aerobically well-trained (VO2 max 57±7mL/min*kg) and competitive female cyclists or triathletes (age 25±5 yrs) taking monophasic OCs for >1yr, and 10 matched controls eumenorrheic controls (age 34±9).	During follicular (days 3-6 of cycle) and luteal (days 18-21) phases, participants underwent 4 trials of 12 min fixed intensity ergometer cycling followed by 30 min self-paced cycling. Tests were conducted in both dry and humid heat. Respiratory, cardiovascular and thermodynamic results were obtained.	Statistical analyses of results were conducted to determine the effects of OC use on these thermoregulatory responses.	No difference in performance between phases (268 ± 31 kJ, 263 ± 26 k, P = 0.31). Onset temperature of sweat rate not affected by OC use (P>0.30). Rectal temperatures 0.15°C higher on days 18-21 than 3-6 for OC users (P=0.05) regardless of environment (P=0.17).	Samples with such elite athletes generate concern for generalizability of results.
	Sunderland 2003	15 well-trained female athletes: Seven normally menstruating women (NM, mean age 20.3±0.3 yrs) and eight oral contraceptive users (OC, mean age 20.2±0.4 yrs).	Measurements collected during predicted midpoints of follicular and luteal phases of both groups. Loughborough Intermittent Shuttle Test (LIST) used as a running test which recorded total distance run during the trial.	Examined the impact of the menstrual cycle and oral contraceptive use on performance of high-intensity intermittent running in the heat.	The distance run during the LIST was not different between groups, all cycles considered (NM: 6059±89 m vs OC 6048±543 m). OC group ran further during days 15-28 compared to days 1-14 (1-14: 5481±612 m vs 15-28: 6615±893 m, p<0.05).	Those taking OC saw increased endurance performance during the luteal phase of their cycle.
Cognition:						
	Baskaran 2017	48 oligomenorrheic or amenorrheic females between 14-25 yr.	RCT without adequate blinding (those taking OC would notice their cycle differs). Three groups created: (i) 30 mg ethinyl estradiol and 0.15 mg desogestrel taken orally for 21 days and a placebo for 7 days with an n=16. (ii) transdermal estrogen patch (100mcg 17-beta-estradiol) applied twice weekly along with 200mg micronized progesterone taken orally for the first 12 days of every month where n = 13. (iii) no estrogen and n = 19. Cognitive assessments were taken at baseline and 6 months later.	Baseline and 6 months cognitive assessments utilized the California Verbal Learning Test II (CVLT-II) (for VM), and Delis-Kaplan Executive Function System Color-Word Interference Test (D-KEFS-CWIT) (executive control) to compare differences in cognitive function in athlete's on varying formulations of contraception.	Group (i) showed better immediate recall than (iii) over 6 months (P < 0.05) before controlling for baseline scores. D-KEFS-CWIT scores did not differ after 6 months between groups. Inhibition-switching (cognitive flexibility) of group (i) had greater improvements over 6 months than (iii) after controlling for baseline scores.	Difficult results to apply because female athletes have waxing and waning periods of oligo-amenorrhea. Adherence was a concern of theirs although they did have subjects keep a medication calendar and return empty pill packs/patches.

for athletes by regulating the menstrual cycle, giving the athlete the potential to plan training or competition around this if possible [18]. HC use may also affect fluctuations in knee flexion force and knee flexion-extension hysteresis along with ACL elasticity across the cycle, with one study reporting that HC use could diminish or eliminate these fluctuations altogether compared to non-HC users [21]. These findings in addition to other studies regarding HC effects on ligamentous laxity and subsequent degree of anterior tibial translation could support possible protective benefits of HC.

One would then question whether there would be a role of HC prophylaxis for ACL tear. One large case-control study reported that women aged 15-19 years old had the highest incidence of undergoing ACL reconstruction. This group was also less likely to be taking HC compared to the general population [25]. Additionally, when HC users were found to have significantly less anterior tibial translation compared to non-OC users, authors suggested this to be a protective effect justifying prophylactic HC use to mitigate this risk factor [15]. However, these studies suggested an association but was not confirmed. While some studies do support protective benefits of HC use, there is also evidence that shows no significant differences between users and non-users. Lefevre et al., and Ruedl et al., compared both those using and not using HC and found that there were no significant differences in their chances of suffering an ACL tear [22,23]. A recently published study of 165,748 female patients proposed that HC did have a protective effect against ACL tear, specifically in those 15-19 years old as they exhibited a 63% reduction in ACL tear incidence compared to those not using HC. These findings indicate that this younger group of athletes may be subject to different risks and benefits with HC use compared to older cohorts [26].

Overall, the field of research regarding HC and ACL injury in the female athlete is limited. HC may have a limited role in ACL prevention for 15-19 years olds. Additional high powered randomized-controlled studies of rigorous methodology will be required to allow providers to advise patients on these risks. The current body of evidence certainly does not suggest that these athletes are at any more risk of injury while taking HC.

Non-ACL MSK Injury

Although a significant amount of the current primary research into HC and injury risk/incidence in female athletes is focused on ACL injuries, some studies choose to focus on general MSK injuries. This includes traumatic injuries, back pain, ankle sprains, and concussions. In addition, the naturally fluctuating levels of estrogen could change mechanical properties of connective tissue and affect other factors related to injury risk, such as neuromuscular coordination and motor control. For example, one recent RCT by Maged et al. found that HC users had improved aspects of postural balance and stability compared to non-HC users. By stabilizing estrogen levels, it appeared that athletes had improved stability, something the authors suggested could lead to lower rates of injury [27].

Three additional studies by Konin et al., Lloyd et al., and Möller-Nielsen et al., measuring incidence of general MSK injury while taking into account HC status reported findings of lower

rates of injury in the HC group compared to the non-HC group [28-30]. While these studies did have statistically significant findings, it should be noted that they were of a small sample size. Opposing the findings of these studies were those conducted by Agel et al., and Thein-Nissenbaum et al., one regarding injury in general and one on non-contact ACL injury and ankle sprains, found that rates of injury occurrence were not significantly different depending on HC status [12,31].

Two studies from Bryhildsen et al. found that HC status was not associated with either increased prevalence of or severity of low back pain [32,33]. The authors noted a trend of providers recommending these athletes experiencing low back pain to avoid HC, as it was believed to potentially worsen symptoms. These studies did not support this belief.

Female athletes suffer from higher rates of concussions, have worse overall outcomes, and have increased levels of cognitive impairment [34]. Two separate studies by Gallagher et al. and Mihalik et al., though small in size with less than 50 subjects each, found that HC users reported less symptoms overall and had a lesser symptoms severity than their counterparts. It is crucial to note that neither study reported a statistically significant difference in time to return to competition. This could point to improved subjective outcomes and merit further study [35,36].

Chauhan et al., showed a possible increased risk of achilles injury with HC use. Athletes with active and symptomatic Achilles tendinopathy were found to have been more likely to have been using HC [37].

Performance

Previous studies have examined how hormonal fluctuations during the menstrual cycle affect athletic performance with mixed results. The mid-luteal phase of the menstrual cycle in particular seems to have the greatest impact on performance, when levels of progesterone and estrogen are increased and core temperature is elevated [44,45]. A total of 32 articles pertaining to HC impact on athletic performance were included in this review.

Aerobic capacity

Maximal oxygen uptake (VO_2max), is a widely reported measure of aerobic fitness. VO_2max is the point at which oxygen uptake does not increase (or increases only marginally), when work is increased [46]. Existing studies about HC effect on aerobic capacity have conflicting results, but the overall trend is that there is little to no decrease of VO_2max in women athletes taking HC. Several studies found no significant difference in VO_2max during exercise testing between women taking HC compared to those who were not taking HC [47-50]. Contrary to these findings, other studies demonstrated a decrease in VO_2max between 2-5.8% during exercise testing [51-53].

In the case that maximal oxygen uptake never occurs, VO_2 peak is used to predict VO_2max in submaximal exercise models [46]. Studies examining VO_2 peak found similar results as VO_2max studies in that there was little to no decrease in VO_2 peak between hormonal contraceptive users and nonusers. Of the studies that showed a decrease in VO_2 peak, the decrease was modest around 2% even with long term use (>12 months) of HC use [52,52]. Schaumberg et al., found that VO_2 peak increased

more in HC nonusers after sprint interval training, but HC users had longer sustained increases in $\dot{V}O_{2\text{peak}}$ at 4 weeks post-intervention [55]. It should be noted that different preparations of HC were used with different estrogen and progesterone concentrations in these studies. Furthermore, the sample sizes were small and methods of exercise testing varied widely making the generalization of these results difficult.

Anaerobic capacity

Anaerobic performance is seen in the first seconds to minutes of a high intensity activity [46]. Several studies have examined the effect of hormonal contraceptives on anaerobic capacity of women athletes. There appears to be no net effect on anaerobic capacity between HC users and nonusers at any point during the menstrual cycle [53,56, 57]. Redman et al. examined the effects of triphasic OCPs on anaerobic performance at different points of the menstrual cycle and saw an increased power output in OCP users vs nonusers during the first 10 seconds of rowing during low levels of estradiol and progesterone, which correlated to days 26-28 of the menstrual cycle [58]. There has been no consensus in the literature about hormonal fluctuations during the menstrual cycle for non HC users and the effect on anaerobic performance [58]. One study measured stiffness and foot center of pressure (COP) during hopping in HC users and non-users with the intent of elucidating exogenous estrogen's effect on the neuro-mechanics of hopping. Non-HC users saw a 30% higher COP path length at ovulation as well as a 25% increase in COP path velocity. These increases were not seen in HC users suggesting more stability and a correlation to the lower incidence of lower extremity MSK injury seen with HC use [59]. Small sample sizes as well as inconsistency in formulation of HC in that these studies used monophasic and triphasic OCPs. Measurements of anaerobic capacity varied as studies used force-velocity, squat jumps and rowing power to measure anaerobic capacity. Based on the current literature, the net effect of HC on anaerobic performance appears to be negligible.

Strength

The large majority of the literature suggests that hormonal contraceptives have no impact on strength [53, 60-66]. There is a wide array of how strength is measured in these studies including dynamometer measurements of hand grip, quadricep contraction, electromyography, mechanomyography and repetition maximums for different muscles groups. Experience ranged from recreational to elite level athletes taking a variety of formulations of HC. Several interesting findings should be noted from studies examining the effect of HC on strength. When caffeine is administered with OCPs, the half life of caffeine is extended, prolonging its effects on the body. Knee flexion power and strength increased during eccentric contractions when caffeine and monophasic oral contraceptives were combined, but had no effect on concentric knee flexion power or strength [67]. Gordon et al., found that, while there was no significant difference in strength, lower extremity torque was more consistent in HC users than non-users postulating that this may be injury protective [63]. In regards to strength, the question of the indirect effect of HC on potentially anabolic hormones has also been examined and largely not found to have a significant impact. High frequency lower extremity strength training program

showed no effect of hormonal contraceptives on growth hormone levels, cortisol levels and total body fat mass [68]. According to Bernardes et al., HC users had a small increase in GH release with intermittent exercise, but no effect on performance was seen. The authors postulated that the increase in GH was due to an increase in total estrogens (exogenous and endogenous) [69]. In contrast to these studies, when examining HC that have an anti-androgenic effect, such as formulations with added cyproterone acetate, were shown to minimize strength gains when compared to HC without an anti-androgenic component [48]. Based on the current literature, HC does not appear to have an effect on strength, unless there is an anti-androgenic component of the HC, but this is not a widely available formulation.

Body composition

A review of the literature on hormonal contraception's effect on body composition lead to conflicting results. A large scale study by Procter-Gray et al. examining 150 distance runners over a 24 month period demonstrated slightly less weight gain, less body fat gain and increase in lean mass in eumenorrheic runners taking HC when compared to those runners who were not taking HC [70]. In contrast to these findings, two smaller scale studies examining the effect of hormonal contraceptives on body composition found no difference between HC users and nonusers. Participants were subjected to strength training, plyometric exercises and high intensity interval training in the form of running and swimming [64,71]. Rickenlund et al., showed that weight gain and increase in fat mass occurred in oligomenorrheic and amenorrheic athletes taking HC, a finding that did not occur in those not taking HC [72]. More studies are needed in this area to elucidate the effect of HC on body composition, particularly the differences between eumenorrheic, oligomenorrheic or amenorrheic athletes as the current literature suggests this may have an impact on body composition.

Cognition

It is unclear if estradiol and progesterone fluctuations during the menstrual cycle has an impact on cognitive function based on the results of the current literature. Similarly, there is conflicting data about the effect of hormonal contraceptives on cognitive performance. Baskaran et al. demonstrated that verbal memory and executive function improved in oligo-amenorrheic women athletes who took oral contraceptives over a 6 month period. While this study highlights the effects hormonal contraceptives have on the hormonal state experienced during the female athlete triad, it does not account for eumenorrheic women athletes who are not estrogen deficient [73]. More research is needed in this area to further address the questions of the impact of HC on cognition.

Heat acclimatization

Hormonal fluctuations during the menstrual cycle are known to affect core body temperature, with the core temperature being 0.3-0.5 degrees Fahrenheit higher during the luteal phase compared to the late follicular phase [45]. Studies examining the effect of hormonal contraception on heat acclimation found no difference in between those using HC and those who did not in terms of physiological heat acclimatization [74-78]. Armstrong et al. did show that HC users (combined estrogen-progesterone

preparation) had a lower threshold for sweating than injectable contraceptive users and non-HC users, an occurrence that was not seen in elite level cyclists as reported by Lei et al. [75,78]. Another finding came from Minahan et al., that noted the resting core temperature was slightly higher in HC users compared to non-HC users, but that this discrepancy disappeared after 30 minutes of performing exercise in hot ambient temperatures. This study also found that women taking HC had a higher perceived exertion when compared to their non-HC using counterparts [77]. Study sizes ranged from 18 to 36. Different hormonal preparations included oral contraceptives, injectable contraceptives. Participants ranged from inactive to recreational athletes.

Risks

VTE: Increased coagulation is a well known risk associated with HC. This risk is often seen clinically in conjunction with smoking, long periods of immobility, or some other coexisting risk factors [38]. HC use was cited as the most common risk factor for development of VTE in one study, with another stating that these women taking HC were 3-11 times more likely to suffer from DVT compared to those not taking HC [39, 40].

Three of the case studies we reviewed involved athletes taking HC that were found to have inherited thrombophilia--namely, Factor V Leiden and one case of Factor II Prothrombin. This genetic risk factor was suspected to have been compounded by also taking estrogen-containing HC [39,41,42]. Two of these cases resulted in pulmonary embolism, a diagnosis that carries a significant risk of mortality and morbidity. These athletes not only missed significant time in their training and competition suffered from a life-threatening event that must always be considered in these athletes when presenting with vague respiratory symptoms or non-specific pain [40, 41]. We also found cases reporting on unique presentations of VTE, something that may be more common in this athletic population than the general population. Two cases reviewed reported spontaneous VTE of the subclavian and axillary veins, otherwise known as Paget-Schroetter syndrome. This effort thrombosis was the result of high volume repetitive activity in two different softball pitchers. Both were found to have either cervical rib or first rib obstruction, scalene hypertrophy from their significant training load, and HC use. One athlete also had Factor V Leiden mutation present as well [42, 43]. This combination of risk factors should be noted as something to remain aware of when counseling individual patients about possible risks and benefits of HC use. One final case resulted in the diagnosis of left common and external iliac vein compression with associated VTE, a condition known as May-Thurner syndrome, that presented as chronic left hip and groin pain [39]. These cases of venous thromboembolism are an important reminder of the risks of HC and should be considered when deciding whether prescription of HC is indicated.

DISCUSSION

One of the main goals of the systematic review was to provide the most up-to-date resource possible for providers to counsel their patients, specifically the female athlete population.

In regards to HC effects on injury, the current body of evidence does not support the prophylactic use of HC to reduce

risk of injury at this point. It is also important to note that there is not a trend of HC increasing risk of injury in this population, so clinicians should not discourage athletes from taking HC for fear of increasing their risk. While some studies do present evidence demonstrating protective effects of HC, many of these lack the statistical power and quality methodology to support their use in this capacity. Female athletes in the 15-19 year old age group may prove to be an exception for prophylactic protective use against ACL tear, especially if future prospective studies confirm the findings of recently published retrospective data. There does appear to be consensus that ligamentous laxity fluctuates throughout the menstrual cycle. Given the overall body of evidence, there appears to be potential for more research to further characterize this relationship between HC and injury incidence.

There does not appear to be a direct relationship, negatively or positively, with HC use an athletic performance in women athletes. Some literature exists demonstrating a modest decrease in aerobic capacity, but other studies demonstrate no difference between HC users and non users. Similarly, HC does not appear to have a significant impact on anaerobic performance, heat acclimatization or cognition. HC containing antiandrogenic components have been shown to decrease strength gains, but HC not containing antiandrogens do not appear to affect strength.

Overall, we found that there is a lack of well controlled, high powered studies in this field. By nature, studies pertaining to HC are difficult to design. The ability to conduct double-blinded RCT is difficult due the fact that many athletes are using HC primarily for its contraceptive purposes. It would present an ethical dilemma if potential subjects were receiving a placebo in place of HC. A large portion of these articles are retrospective and observational as well. This relies heavily on recall by subjects when it comes to questionnaires completed as a part of a study, introducing the potential for recall bias.

CONCLUSIONS

Regarding injury, HC does not appear to offer definitive protective benefit. Some evidence does exist to suggest a potential protective effect, but this must be considered in the context of several other studies finding no significant difference between HC users and non-users. Much of the current research is focused on ACL injuries, where there appears to be a clear connection between varying risk of injury depending on menstrual cycle phase. This peak risk tends to exist in the follicular and ovulatory phase, corresponding to the point of maximal estrogen levels. These levels are known to be stabilized by HC, and this supports the need for further exploration in this area to provide a robust amount of support if clinicians were to consider HC use for injury prevention. Being a higher risk population, 15-19 year olds may be considered for prophylactic protective use with careful assessment of their unique risk and expected benefit profile, but universal prophylactic use amongst all ages cannot be recommended at this time.

In terms of athletic performance, HC appears to have little to no effect on athletic performance in the areas of aerobic capacity, anaerobic capacity, strength, body composition, cognition and heat acclimatization. Some studies indicate a small decrease in VO2max and VO2peak. HC formulations that do not have an anti-

androgenic component do not appear to impact strength. For these reasons, it is our recommendation that clinicians should use this information to educate patients to make an informed decision about what is best for their unique situation and desire for contraception.

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REFERENCES

- Irick E. NCAA Sports Sponsorship and Participation Rates Report 1981-82 – 2017-18. Indianapolis, IN: National Collegiate Athletic Association. 2018.
- Daniels K, Abma JC. Current contraceptive status among women aged 15–49: United States, 2015–2017. NCHS Data Brief, no 327. Hyattsville, MD: National Center for Health Statistics. 2018.
- Martin D, Sale C, Cooper SB, Elliott-Sale KJ. Period Prevalence and Perceived Side Effects of Hormonal Contraceptive Use and the Menstrual Cycle in Elite Athletes. *Int J Sports Physiol Perform*. 2018; 13: 926-932.
- de Jonge J, Xanne AK. Effects of the menstrual cycle on exercise performance. *Sports medicine (Auckland)*. 2003; 33: 833-851.
- VanHeest JL. Female athletes: Factors impacting successful performance. *Current sports medicine reports*. 06/2007; 6: 190-194.
- Gwinn DE, Wilckens JH, McDevitt ER, Ross G, Kao TC. The relative incidence of anterior cruciate ligament injury in men and women at the United States Naval Academy. *Am J Sports Med*. 2000; 28: 98-102.
- Arendt EA, Agel J, Dick R. Anterior cruciate ligament injury patterns among collegiate men and women. *J Athl Train*. 1999; 34: 86-92.
- Nose-Ogura S. Oral contraceptive therapy reduces serum relaxin-2 in elite female athletes. *J Obstetrics Gynaecol Res*. 2017; 43: 530-535.
- Hansen M. Impact of oral contraceptive use and menstrual phases on patellar tendon morphology, biochemical composition, and biomechanical properties in female athletes. *J Applied Physiol*. 1985; 114: 998-1008.
- Pokorny MJ. Self-reported oral contraceptive use and peripheral joint laxity. *J Orthopaedic Sports Physical Therapy*. 2000; 30: 683-692.
- Herzog MM. Cost of outpatient arthroscopic anterior cruciate ligament reconstruction among commercially insured patients in the United States, 2005-2013. *Orthop J Sports Med*. 2017; 5: 2325967116684776.629-
- Hansen M. Sex hormones and tendon. *Metabolic Influences on Risk for Tendon Disorders*. 2016: 139-149.
- Agel J. Hormonal therapy: ACL and ankle injury. *Medicine and science in sports and exercise*. 2006; 38: 7-12.
- Liederbach M. Incidence of anterior cruciate ligament injuries among elite ballet and modern dancers: A 5-year prospective study. *Am J Sports Med*. 2008; 36: 1779-1788.
- Lee H. Do oral contraceptives alter knee ligament damage with heavy exercise? *Tohoku J Exp Med*. 2015; 237: 51-56.
- Martineau PA. Effect of the oral contraceptive pill on ligamentous laxity. *Clin J Sport Med*. 2004; 14: 281-286.
- Hicks-Little CA. Menstrual cycle stage and oral contraceptive effects on anterior tibial displacement in collegiate female athletes. *J Sports Med Physical fitness*. 2007; 47: 255-260.
- Trojan TH, Heiman D, Miller MG. The effects of OCP's on anterior cruciate ligament laxity. *Clin J Sport Med*. 2011; 21: 163.
- Arendt EA. Periodicity of noncontact anterior cruciate ligament injuries during the menstrual cycle. *The journal of gender-specific medicine: JGSM: the official journal of the Partnership for Women's Health at Columbia*. 2002; 5: 19-26.
- Herzberg SD. The effect of menstrual cycle and contraceptives on ACL injuries and laxity: A systematic review and meta-analysis. *Orthop J Sports Med*. 2017; 5: 23-25.
- Hewett TE. Effects of the menstrual cycle on anterior cruciate ligament injury risk: A systematic review. *Am J Sports Med*. 2007; 35: 659-668.
- Lee H. Differences in anterior cruciate ligament elasticity and force for knee flexion in women: Oral contraceptive users versus non-oral contraceptive users. *Eur J Applied Physiol*. 2014; 114: 285-294.
- Lefevre N. Anterior cruciate ligament tear during the menstrual cycle in female recreational skiers. *Orthop Traumatology, Surgery Res*. 2013; 99: 571-575.
- Ruedl G. Are oral contraceptive use and menstrual cycle phase related to anterior cruciate ligament injury risk in female recreational skiers? *Knee surgery, sports traumatology, arthroscopy: official journal of the ESSKA*. 2009; 17: 1065-1069.
- Wojtys EM. The effect of the menstrual cycle on anterior cruciate ligament injuries in women as determined by hormone levels. *Am J Sports Med*. 2002; 30: 182-188.
- Gray AM. Effects of oral contraceptive use on anterior cruciate ligament injury epidemiology. *Medicine and science in sports and exercise*. 2016; 48: 648-654.
- DeFroda SF, Bokshan SL, Worobey S, Ready L, Daniels AH, Owens BD. Oral contraceptives provide protection against anterior cruciate ligament tears: a national database study of 165,748 female patients. *Physician and Sports Med*. 2019; 47: 416-420.
- Maged AM. Effect of oral contraceptives on balance in women: A randomized controlled trial. *Taiwanese J Obstet Gynecol*. 2017; 56: 463-466.
- Konin J, McCoy M, Rosendale A. Effects of oral contraceptives and athletic injury. *British J Sports Med*. 2008; 42: 528-528.
- Lloyd T. Women athletes with menstrual irregularity have increased musculoskeletal injuries. *Med Sci Sports and exercise*. 1986; 18: 374-379.
- Möller-Nielsen J. Women's soccer injuries in relation to the menstrual cycle and oral contraceptive use. *Med Sci Sports Exerc*. 1989; 21: 126-129.
- Thein-Nissenbaum JM. Disordered eating, menstrual irregularity, and musculoskeletal injury in high school athletes: A comparison of oral contraceptive pill users and nonusers. *Sports health*. 2014; 6: 313-320.
- Brynhildsen JO. Does the menstrual cycle and use of oral contraceptives influence the risk of low back pain? A prospective study among female soccer players. *Scandinavian J Med Sci Sports*. 1997; 7: 348-353.
- Brynhildsen J. Oral contraceptive use among female elite athletes and age-matched controls and its relation to low back pain. *Acta obstetrica et gynecologica Scandinavica*. 1997; 76: 873-878.
- Dick RW. Is there a gender difference in concussion incidence and outcomes? *British J Sports Med*. 2009; 43: 46-50.

36. Gallagher V. The effects of sex differences and hormonal contraception on outcomes after collegiate sports-related concussion. *J Neurotrauma*. 2018; 35: 1242-1247.
37. Mihalik JP. The effects of menstrual cycle phase on clinical measures of concussion in healthy college-aged females. *J Sci Med Sport*. 2009; 12: 383-387.
38. Chauhan A. Risk factors associated with achilles tendinopathy: An observational study. *Clin J Sport Med*. 2014; 24: e29721
39. Cerquozzi S. Iliac vein compression syndrome in an active and healthy young female. *Case reports in medicine*. 2012; 2012: 1-5.
40. Crous-Bou M. Environmental and genetic risk factors associated with venous thromboembolism. *Seminars in thrombosis and hemostasis*. 2016; 42: 808-820.
41. Landesberg WH. Pulmonary embolism in a female collegiate cross-country runner presenting as nonspecific back pain. *J Chiropractic Med*. 2012; 11: 215-220.
42. Abbott K. Chest pain is bad for my hoops game-chest pain in a division I college basketball player. *Clin J Sport Med*. 2013; 23(2): e12-e13.
43. Dapul G. Atypical presentation of right arm swelling in a collegiate softball pitcher: a case report of paget-schroetter syndrome. *Am J Physical Med Rehabilitation*. 2014; 1 :a72-a72
44. Aquino BC. "Effort" thrombosis of the axillary and subclavian vein associated with cervical rib and oral contraceptives in a young woman athlete. *J Am Board of Family Practice*. 1989; 2: 208-211.
45. Notelovitz M. The effect of low-dose oral contraceptives on cardiorespiratory function, coagulation, and lipids in exercising young women: A preliminary report. *Am J Obstet Gynecol*. 1987; 156: 591-598.
46. Coyne MD. Circadian rhythm changes in core temperature over the menstrual cycle: Method for noninvasive monitoring. *Am J Physiol. Regulatory, integrative and comparative physiology*. 2000; 279: R1316-R1320.
47. McArdle WD, Katch FI, Katch VL. *Essentials of Exercise Physiology*. Philadelphia, PA: Lippincott Williams and Wilkins. 2006.
48. Bryner RW, Toffle RC, Ullrich IH, Yeater RA. Effect of low dose oral contraceptives on exercise performance. *Br J Sports Med*. 1996; 30: 36-40.
49. Ružić L. Antiandrogens in hormonal contraception limit muscle strength gain in strength training: Comparison study. *Croatian Med J*. 2003; 44: 65-68.
50. Vaiksaar S. No effect of menstrual cycle phase and oral contraceptive use on endurance performance in rowers. *J Strength Cond Res*. 2011; 25: 1571-1578.
51. Gordon D. The effects of menstrual cycle phase on the incidence of plateau at V'O₂max and associated cardiorespiratory dynamics. *Clin Physiol functional imaging*. 2018; 38: 689-698.
52. Giacomoni M. Decreased submaximal oxygen uptake during short duration oral contraceptive use: A randomized cross-over trial in premenopausal women. *Ergonomics*. 2000; 43: 1559-1570.
53. Casazza GA. Effects of oral contraceptives on peak exercise capacity. *J Appl Physiol*. 1985; 93: 1698-1702.
54. Lebrun CM, Petit MA, McKenzie DC, Taunton JE, Prior JC. Decreased maximal aerobic capacity with use of a triphasic oral contraceptive in highly active women: a randomised controlled trial. *Br J Sports Med*. 2003; 37: 315-320.
55. Joyce S. Effect of long-term oral contraceptive use on determinants of endurance performance. *J Strength Conditioning Res*. 2013; 27: 1891-1896.
56. Schaumberg MA. Oral contraceptive use dampens physiological adaptations to sprint interval training. *Med Sci Sports Exercise*. 2017; 49: 717-727.
57. Bushman B. Anaerobic power performance and the menstrual cycle: Eumenorrheic and oral contraceptive users. *J Sports Med Phys Fitness*. 2006; 46: 132-137.
58. Giacomoni M. Influence of the menstrual cycle phase and menstrual symptoms on maximal anaerobic performance. *Med Sci Sports Exercise*. 2000; 32: 486-492.
59. Redman LM. Measuring performance during the menstrual cycle: A model using oral contraceptives. *Medicine and science in sports and exercise*. 2004; 36: 130-136.
60. Bryant AL. Estrogen-induced effects on the neuro-mechanics of hopping in humans. *Eur J Applied Physiol*. 2011; 111: 245-252.
61. Drake SM. A pilot study on the effect of oral contraceptives on electromyography and mechanomyography during isometric muscle actions. *J Electromyography kinesiol*. 2003; 13: 297-301.
62. Ekenros L. Oral contraceptives do not affect muscle strength and hop performance in active women. *Clin J Sport Med*. 2013; 23: 202-207.
63. Elliott KJ. Does oral contraceptive use affect maximum force production in women? *Br J Sports Med*. 2005; 39: 15-19.
64. Gordon D, Hughes F, Young K, et al. The effects of menstrual cycle phase on the development of peak torque under isokinetic conditions. *Isokinetics and Exercise Science*. 2013; 21: 285-291.
65. Myllyaho MM. Hormonal contraceptive use does not affect strength, endurance, or body composition adaptations to combined strength and endurance training in women. *J Strength Cond Res*. 2018; 1.
66. Nichols AW. Effects of combination oral contraceptives on strength development in women athletes. *J Strength Condit Res*. 2008; 22: 1625-1632.
67. Peters C. Androgenicity of the progestin in oral contraceptives does not affect maximal leg strength. *Contraception (Stoneham)*. 2006; 74: 487-491.
68. Ali A. The influence of caffeine ingestion on strength and power performance in female team-sport players. *J International Society Sports Nutrit*. 2016; 13: 46.
69. Wikström-Frisén L. Increasing training load without risking the female athlete triad: Menstrual cycle based periodized training may be an answer? *J Sports Med Physical fitness*. 2017; 57: 1519-1525.
70. Bernardes RP. Growth hormone responses to continuous and intermittent exercise in females under oral contraceptive therapy. *Eur J Applied Physiol Occupational Physiol*. 1998; 79: 24-29.
71. Procter-Gray E. Effect of oral contraceptives on weight and body composition in young female runners. *Medicine and science in sports and exercise*. 2008; 40: 1205-1212.
72. Rechichi C. Oral contraceptive cycle phase does not affect 200-m swim time trial performance. *J Strength Condit Res*. 2012; 26: 961-967.
73. Rickenlund A. Effects of oral contraceptives on body composition and physical performance in female athletes. *J Clin Endocrinol Metabol*. 2004; 89: 4364-4370.
74. Baskaran C. Estrogen replacement improves verbal memory and executive control in Oligomenorrheic/Amenorrheic athletes in a randomized controlled trial. *J Clin Psychiatry*. 2017; 78: e490-e497.
75. Larsen B. Immune response in women during exercise in the heat: A spotlight on oral contraception. *J Sports Sci Med*. 2018; 17: 229-236.
76. Armstrong LE. Heat acclimation and physical training adaptations of

- young women using different contraceptive hormones. *Am J Physiol.* 2005; 288: E868-E875.
77. Sunderland C. Effect of the menstrual cycle on performance of intermittent, high-intensity shuttle running in a hot environment. *Eur J Applied Physiol.* 2003; 88: 345-352.
78. Minahan C. Response of women using oral contraception to exercise in the heat. *Eur J Applied Physiol.* 2017; 117: 1383-1391.
79. Lei T. On exercise thermoregulation in females: Interaction of endogenous and exogenous ovarian hormones. *J Physiol.* 2019; 597: 71-88.

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