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## „The effect of oral contraceptive pills on female athletes' endurance performance and physiology – a systematic review"


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## Abstract

**Background:** About 40% of exercising women believe that their menstrual cycle has a negative influence on their physical performance (Elliott-Sale et al., 2020) and nearly half are having irregularly menstrual cycles (Rosen et al., 2020). What if there was a possibility to know the exact day of onset of menses and even to skip menses if timing was bad? Intake of the oral contraceptive pill (OCP) has these desired advantages and latest research estimates that about a third of adolescents athletes are using OCPs (Rosen et al., 2020). But interventions on the complex hormonal cycle system might also have undesired impact on physiological processes. The aim of this research was to observe the influence of OCPs on the endurance performance of healthy, trained female athletes.

**Method:** This systematic review has been done using the criteria of the PRISMA statement. Inclusion criteria for the clinical trials was to observe cardiorespiratory parameter using spirometry at least at two different timepoints of the OCP cycle. Cross-sectional-studies as well as longitudinal studies have therefore been included and participants needed to be healthy and trained athletes. For the screening process the reference management program COVIDENCE has been used.

**Results:** After screening 185 abstracts inclusion criteria was met in 12 clinical trials. Significant differences in respiratory parameters have been found in four studies when comparing different timepoints in cycle of OCP users. Comparing non-OCP users with OCP users significant differences but somehow controversy effects in endurance parameters were found in five studies.

**Discussion:** Although most studies did not find significant influences of OCP use on endurance parameters, progesterone and estrogen are suggested to have several influences on the physiological processes of the female body. A shift in metabolism towards fat metabolism and increased ventilation during exercise is suggested in high progesterone levels. Estrogen might influence the stiffness on ligaments which effects biomechanics in running. In anthropometric parameters effects on bone mineral density and augmentation of body mass is suggested to appear in long-term use of OCPs but not to fluctuate through female cycles. To conclude, although there appeared several influences on female physiology, all in all most studies concluded that there is no effect on endurance performance.

## Zusammenfassung

**Hintergrund:** Etwa 40% der Athletinnen sind der Meinung, dass ihr Menstruationszyklus einen negativen Einfluss auf ihre körperliche Leistungsfähigkeit hat (Elliott-Sale et al., 2020) und fast die Hälfte der Athletinnen leidet unter einem unregelmäßige Menstruationszyklus. Wie wäre es, wenn man die Möglichkeit hätte, den genauen Tag des Beginns der Menstruation zu kennen und sie sogar überspringen könnte, wenn der Zeitpunkt gerade unpassend ist? Die Einnahme der Hormonpille (HP) bringt genau diese erwünschten Vorteile und eine aktuelle Studienergebnisse gehen davon aus, dass etwa ein Drittel der jugendlichen Athletinnen die HP verwenden (Rosen et al., 2020). Aber auch Eingriffe in das komplexe System des Hormonkreislaufs können unerwünschte Auswirkungen auf physiologische Prozesse haben. Ziel dieser Forschung ist es, den Einfluss der HP auf die Ausdauerleistungsfähigkeit gesunder, trainierter Athletinnen zu beobachten.

**Methode:** Dieser systematische Review wurde anhand der Kriterien des PRISMA-Statements durchgeführt. Einschlusskriterium für die klinischen Studien war die Erhebung kardiorespiratorischer Parameter mittels Spirometrie an mindestens zwei verschiedenen Zeitpunkten des HP-Zyklus. Daher wurden sowohl Querschnittsstudien als auch Längsschnittstudien eingeschlossen, und die Teilnehmerinnen mussten gesunde und trainierte Athletinnen sein. Für den Screening-Prozess wurde das Literaturverwaltungsprogramm COVIDENCE verwendet.

**Ergebnis:** Nach dem Screening von 185 Abstracts wurden die Einschlusskriterien in 12 Studien erfüllt. Beim Vergleich verschiedener Zeitpunkte im Zyklus von HP einnehmenden Athletinnen wurden in vier Studien signifikante Unterschiede bei den ventilatorischen Parametern festgestellt. Beim Vergleich von Nicht-HP-Einnehmerinnen mit HP-Einnehmerinnen wurden in fünf Studien signifikante, aber kontroverse Effekte bei Ausdauerparametern gefunden.

**Diskussion:** Obwohl die meisten Studien keinen signifikanten Einfluss der HP auf Ausdauerparameter fanden, wird angenommen, dass Progesteron und Östrogen verschiedenste Einflüsse auf die physiologischen Prozesse des weiblichen Körpers haben. Bei hohem Progesteronspiegel wird eine Verschiebung des Stoffwechsels und eine erhöhte Atmungsfrequenz vermutet. Östrogen kann die Flexibilität des Bandapparats beeinflussen, was sich auf die Biomechanik beim Laufen auswirkt. In Bezug auf anthropometrische Parameter wird vermutet, dass eine Auswirkung auf die Knochenmineraldichte und die Zunahme der Körpermasse bei langfristiger Anwendung der HP auftreten, aber nicht innerhalb des Zyklus schwanken. Es lässt sich zusammenfassen, dass, obwohl mehrere Einflüsse auf die weibliche Physiologie bestehen, kamen die meisten Studien zu dem Schluss, dass die Ausdauerleistungsfähigkeit nicht beeinflusst wird.

# Table of content

# 1 Introduction

About 40% of exercising women believe that their menstrual cycle has a negative influence on their physical performance. It is therefore a desire of many women and particularly in competitive athletes to have the opportunity to influence timing of menstruation (Elliott-Sale et al., 2020). A recent survey demonstrated that about the half of eumenorrheic adolescent athletes have irregular menstrual cycles (Rosen et al., 2020). A typical menstrual cycle lasts 28-32 days (Sims & Heather, 2018). In some women the expected day of onset of menstruation is more reliable than in others were length of menstrual cycle can vary within a view days. Menstrual cycle includes a lot of hormonal ups and downs through these 28-32 days (especially estrogen and progesterone). It is somehow not surprising, that these hormonal fluctuations have influences on physiological and mental effects which might somehow influence sports performance. Some women want to use these physiological actions of the female body to optimize their training strategies around their menstrual cycle. Others desire to turn down the hormonal influences and train with a low and stable hormone balance by using the oral contraceptive pill (OCP). Another advantage of the OCP use is to know the exact day of onset of menstruation (withdrawal of OCP intake) or even the possibility to skip menstruation (skipping withdrawal) if it does not fit the schedule of competition and training. These advantages lead to a rising number of OCP intake not only in general population but also in female athletes.

OCP use is the most frequent form of birth control in the general population and particularly the use of low dose hormone pills has been rising in the past years. Number of OCP users worldwide is not clear but scientific research estimates that the distribution of OCP use in athletic women matches the prevalence of OCP use in the general population (Burrows & Peters, 2007). According to earlier research it might be even higher in athletes than in non-athletes (Emslander et al., 1998). Latest research estimates that about a third of adolescents athletes is using OCP (Rosen et al., 2020). According to a recent survey 70% of female elite athletes have already used hormonal contraceptives and even 50% are using it currently (Martin et al., 2018). Although, the intake of OCPs in athletes is widespread, still the result of previous research on the influence of OPCs on performance output is controversy. Even if hormonal fluctuation is suppressed due to the hormonal pill, it is still of great interest to find out, if there are differences in performance output through the oral contraceptive cycle. While in strength performance no differences have been found when comparing performances of different cycle phases through oral contraceptive cycle (Reif et al., 2021), in endurance actual study results are less clear. While some studies have not found any differences through OCP cycle (Barba-Moreno et al., 2019; Bryner et al., 1996; Rechichi et al., 2008), others suggest that the estrogen levels plays an important role in oxygen ($O_2$) consumption (Gordon et al., 2018) and endurance performance therefore differs through oral contraceptive cycle (Casazza et al., 2002). Especially in endurance sports but also in other weight sensitive sports like aesthetic sports or sports with weight categories the body composition is of great interest. Therefore, potential influences

through menstrual cycle and also by OCP intake on several anthropometric parameter are of interest. Again, research is not in accordance when it comes to the effects of OCP. While an increase of body fat after four months of OCP intake has been found (Casazza et al., 2002) in another study results are not in accordance (Nakamura & Nose-Ogura, 2021). Small changes in body weight can be of high importance in high performance athletes and therefore results in anthropometric measurements are additionally addressed in the following systematic review. Controversial findings might be explained by different training status of the sample and several types of study design. This systematic review is therefore designed to focus on a uniform sample of trained women and additionally anthropometric data and blood samples are compared. To compare performance output through the oral contraceptive cycle selected studies must have collected data at least two different timepoints of oral contraceptive cycle. Further, if the trial had control groups of females which were not using OCPs, these results were analysed as well. It is therefore the aim of this master thesis to evaluate the influence of the oral contraceptive cycle on female athletes' physiology and especially on their endurance performance.

## *1.1 Research gap*

Recent research reported that a general lack in women in sport science exists, not only in position of researchers but also in female participants of studies (Mujika & Taipale, 2019). A reason that we do not fully understand the influence of menstrual cycle and hormonal contraceptives on the exercising female body might not only be a lack of data. Additionally, a lack of detailed data analyses might be a reason as results of male and female participants are often not reported separately. It would enable discussions of possible influence of sex and reproductive hormones on the outcome measures (Mujika & Taipale, 2019). Studies explicitly done on female participants are often investigated on physical inactive or active women but not on competitive athletes. Transferring these data on competitive athletes brings up several difficulties in physiological parameter (Meignié et al., 2021). For example, in immunological reactions (which are of great importance in sports athletes of all sexes) studies monitoring influences of sex and hormonal influences due to menstrual cycle are rare. Anyway, differences in immunological response between OCP users and non-users are suggested with pro inflammatory reactions in luteal phase of non-users (Northoff et al., 2008). Further studies found positive effects of OCP intake on inflammation markers and endothelial function (Rickenlund et al., 2005).

Of course, monitoring and reporting menstrual cycle phases takes some extra time and costs. To avoid this extra work, test-timing in female athletes is often in low hormone phases (when hormone profile is most comparable to males – often FP) or women are even excluded from research (Mujika & Taipale, 2019). From an ethnical point of view, it is doubtful if this is a future-oriented and correct research. Therefore, Mujika and Taipale (2019) requested in their work more research on the effects

of different cycle phases on training response, adaptations, and performances. Further, it is criticized that sometimes menstrual bleed is confounded with ovulation. Consequently, research which is distinguishing between cycles with and without ovulation as their hormonal cycle is not the same. For example, separate groups for females with and without intake of oral contraceptives might be necessary depending on the observed parameters.

Actual research papers criticize that case reports, clinical series and cross-sectional studies have been done on these topics but often lack of control groups. They often do not bring much helpful information as a generalization for a larger population is often not possible. Further, case-control studies are often prone to subjective research, one reason is that questionnaires have been used frequently (Constantini et al., 2005; Meignié et al., 2021). Only high qualitative studies like randomized clinical trials would provide useful information. Reports of cycle phase definition and verification, timing of hormone measurement, as well as injury documentation and associations are therefore needed (Constantini et al., 2005). Another difficulty is that the available studies are conducted in laboratory settings and lack in transferability to real life sports-settings (Meignié et al., 2021).

Closing this research gap is of high interest due to many reasons, for example: (1) Female athletes suffer from the (side) effects of menstrual cycles in training and performance instead of benefiting from using potential advantages. (2) Evidence-based recommendations on training individualization could not only push performance but also prevent from injury risks.

## *1.2 State of research*

The use of OCP is wide spread in athletes and has increased through the past years. It influences hormonal profile of women, particularly the endogenous hormone levels are affected as they are downregulated due to the exogenous estrogen and progesterone (Elliott et al., 2005). It is common knowledge, that there are several advantages but also disadvantages by OCP intake, which need to be considered before the intake of this medication. Anyway, many athletes use it due to the possibility to control their menstrual cycle timing but several other influences on the female body are known or even discussed. A recent review showed that the current state of research is not in agreement about the effects of OCP intake on various physiological factors related to performance. These complications are somewhat due to the formulations of OCP pills containing different types and doses of hormones (Burrows & Peters, 2007).

Previous research agrees that the influence of the menstrual cycle phases on the performance of female elite athletes is not yet fully understood (Constantini et al., 2005; Meignié et al., 2021; Mujika & Taipale, 2019). Anyway, a recent review of McNulty et al. (2020) concludes that physical training of female athletes benefits from being adjusted to menstrual cycle. It is seen critically whether there is one optimal phase of menstrual cycle for physical performance. Endurance performance might

improve during luteal phase (LP), impulsivity is suggested to benefit during ovulation. For sprinting and lower limb power no preferred menstrual cycle phases have been found (Meignié et al., 2021). Somehow results are suggested to be influenced by the ratio of estrogen and progesterone, which lead to a better performance in LP when ratio between estrogen and progesterone is high (Oosthuyse & Bosch, 2010).

Besides performance, physiological parameters are suggested to be influenced. A negative correlation between estradiol and anterior cruciante ligament (ACL) stiffness has been found (Romani et al., 2003). Knee stiffness was reduced during ovulation for approximately 17% (Park et al., 2009) which might indicate a phase of less injury risk. Somehow, ligament stiffness is not only a parameter for interpretation in injury risk but also in performance. It is therefore hypothysized that premenstrual symptoms have an effect on performance due to an influence on the stretch shortening cycle of ligaments and tendons (Giacomoni et al., 2000). The premenstrual symptoms are diverse such as fluid retention, mood changes, dysmenorrhea and weight gain which obviously might not only effect anthropometric parameters but also physical performance output (Foster et al., 2019). In studies with untrained women anaerobic power has been measured using a force-velocity cycling test and several jump tests. No differences have been found in maximal power and jump heights between menstrual cycle phases (Giacomoni et al., 2000). To conclude, findings are inconsistent concerning the effects of menstrual cycle on exercise performance.

In anaerobic capacity it is suggested that performance would be influenced in cycling patterns throughout OCP cycle. Best performances were found when exogenous hormones were lowest. In monophasic OCP use no differences were found for performance time of 20 m sprints or blood lactate parameters (Lynch et al., 2001). Monophasic pills seem to provide a stable level to not influence anaerobic capacity, while in triphasic OCP use controversial results have been found. These hormone levels lead to a physiological setting where buffering capacity might be lowest and carbohydrate metabolism might be facilitated (Akin, 2002). In a four months intervention of triphasic OCPs, Casazza et al. (2002) found significant decreases in peak power output and peak exercise capacity. Interestingly, in Suh et al. (2003) the same pill formulation had been used but no significant effects in blood lactate had been found. Effect of OCPs on anaerobic capacity is obviously complex and not fully understood.

When it comes to effects on muscle strength it is suggested that androgenic components of the OCP have positive effects on the development of strength. But the majority of studies are assessing estrogen and not progesterone because of postmenopausal samples with hormone replacement therapy. Anyway, it seems like there is less effect in strength than in anaerobic and aerobic capacity. For example, Wirth and Lohman (1982) found lower values in isometric handgrip strength of OCP users than in the control group. Contrary, a more recent study of Petrofsky et al. (2007) found no difference in static muscle strength of forearm but the study design is somewhat limited to a small sample size of only seven women. When comparing the exercise performance of OCP users through

OCP phases (OCP intake vs. withdrawal), no differences have been found in strength performance of lower extremities for maximal voluntary isokinetic and isometric strength (Reif et al., 2021). When it comes to muscle damage, OCP users had less soreness after cessation of exercises than control groups which indicates a higher pain tolerance due to exogenous hormones. Consequently, this might advert also a higher pain tolerance when it comes to maximal force tests (Thompson et al., 1997). It is somehow hypothesized that the progestogen in the OCP might determine the positive effect on strength development of estrogen. Anyway, more long-term controlled trials are needed to draw firm conclusions on the effects of progesterone and estrogen on muscle strength development and output (Burrows & Peters, 2007).

According to cardio vascular responses, Walters and Lim (1969) found out that systolic blood pressure and cardiac output were increased when inactive women took OCPs for 2-3 months. Interestingly, heart rate has not been affected. It is suggested that the higher cardiac output might lead to increased $O_2$ delivery and as a secondary effect, it could enhance vascular volume (Walters & Lim, 1969). However, some studies did not find significant alterations in cardio vascular responses (Littler et al., 1974; Willekes et al., 1999).

In aerobic capacity a decrease in peak $O_2$ uptake had been suggested when using monophasic OCPs. Notelovitz et al.(1987) found a 7-8% decrease of $VO_{2peak}$ in active monophasic OCP users while in the mean time in the control group an increase of $VO_{2peak}$ has been found. On the other hand Giacomoni and Falgairette (2000) stated that although lower $VO_{2peak}$ might appear in OCP use, the running economy during pill intake in active women is enhanced. Another study reporting $VO_{2peak}$ and aerobic performance through initiation of monophasic OCP use found no effects of OCP intake on the mentioned parameters (Lynch & Nimmo, 1998). Different results might be explained by different ingredients and doses in OCPs. It is suggested that the effects of monophasic OCP formulations on the aerobic capacity are less intense than in triphasic OCP formulations. Anyway, a combination of endogenous and exogenous hormones might be responsible by the total effect on the aerobic system. And although the hormonal contraceptive pill suppresses the endogenous hormone levels still it is the combination of ex- and endogenous hormones which can hardly be measured exactly but still might influence physical performance. It is therefore suggested to interpret results with caution (Burrows & Peters, 2007).

Effects of hormonal fluctuations have also been observed on body composition in menstrual cycle and also in OCP-controlled cycle. In natural menstrual cycle, during luteal phase high levels of progesterone lead to loss of water and electrolytes which further stimulates the body to a concurrent increased concentration of aldosterone. The rapid drop off of the progesterone level when cycle changes from luteal to follicular phase results in premenstrual water and electrolyte storage in the female body (Gaebelein & Senay, 1982). Also, in OCP user's fluid retention and the feeling of being bloated are quite common side effects when using monophasic OCPs. The endogenous progestogen concentrations are suggested to be responsible for this effect (Rosenberg et al., 1999). In a study with

active women, body mass increased by two kilograms after six months of monophasic OCP intake. When the sample stopped the intake of OCPs it returned to baseline weight after one month (Notelovitz et al., 1987). A large effect on performance is suggested by two additional kilograms of body weight particularly in sports with weight-classifications, aesthetic sports with focus on body shape or sports were own bodyweight has to be supported for a specific distance (Burrows & Peters, 2007). In a placebo-controlled trial a non-significant trend of one kilogram increase was found after 6 months of OCP use in physically active females (Coney et al., 2001). In another study of Tantbirojn and Taneepanichskul (2002) inactive women were observed for six months of OCP intake and no significant changes in body mass had been found. Interestingly, there was even a trend of weight loss for both of the two different tested monophasic pill formulations. All in all, it is somehow suggested, that the activity of the sample combined with the formulation of OCP may explain the controversial findings (Burrows & Peters, 2007). (2002)In active women using triphasic OCPs a significant increase of body mass and fat mass increased has been found after four months, while after two cycles this effect has not been found. The endogenous hormones might need some time to produce a certain effect on body composition (Casazza et al., 2002). On the other hand, already after two cycles significant increases in body mass and percentage of body fat have been found in a randomised controlled trial with trained women (Lebrun et al., 2003). Again, this controversy leads to the suggestion that the different formulations of triphasic OCPs might have influenced the result. Formulations with high progestational and androgenic activities may lead to a faster onset of the effect on body composition. Further, a study of Suh et al. (2003) supports the hypothesis of influence on body composition due to OCP intake. After the use of triphasic OCPs over 4 months significant increase in body mass and percentage of body fat were observed. Consequently, the change in body composition might also influence performance (Burrows & Peters, 2007). Anyway, as findings are controversial the topic of body composition might need some more attention in the research field.

**Influence of exercise on menstrual cycle and vice-versa?**

The interaction between menstrual cycle and exercise is of great interest for many research fields. For example when comparing the results of studies observing heart rate and metabolism through menstrual cycle some results complete each other, while others are inconsistent. In Solomon et al. (1982) the resting metabolic heart rate has been observed through the menstrual cycle. A distinct pattern of change has been found, with a steadily decrease of resting heart rate in in follicular phase and again a decrease through luteal phase. Lowest point of resting heartrate was found directly before ovulation (Solomon et al., 1982). When comparing single measurements of follicular and luteal phase, an elevated fasting metabolic rate was found in luteal phase (Matsuo et al., 1999; Melanson et al., 1996). Further, the effect on exercise related metabolism was of interest and earlier research showed greater oxidation of carbohydrates in follicular phase (Zderic et al., 2001). But subsequent research is in contrast as no differences in substrate use had been found between menstrual cycle

phases in prolonged endurance exercise (Horton et al., 2002; Suh et al., 2002). Anyway, it seems there is little influence on recovery energy expenditure through menstrual cycle. When eumenorrheic women were cycling for one hour, no differences between pre and post post exercise $O_2$ uptake was found in follicular phase but in luteal phase directly after cycling there was a greater reliance on fat as fuel source (Matsuo et al., 1999). On the other hand in the research of Fukuba et al. (2000) these effects were not found. Consequently, it remains questionable whether and when these effects on accessing fuel sources occur.

On the other hand, reverse effects, namely influences of exercise metabolism on menstrual cycle, are evident and consistent. The reproductive system of women including the menstrual cycle is sensitive on various stressors. Sports and exercise are one of these physiological stressors which can impact the onset of menstruation. Excessive exercise in combination with inadequate diet or even weight loss can lead to abnormalities in menstrual cycle like amenorrhea. First onset of menses starts in 95% of women at the age of about 15 years (Chumlea et al., 2003). Genetic, hormonal or physical factors might lead to primary amenorrhea which means that onset of first menses is delayed. In case that onset of menses was regularly but stopped after at least three regular and consecutive cycles, this abnormality is called secondary amenorrhea. Majority of these cases is due to hypothalamic irregularities and combined with low body mass or excessive weight loss. Characteristics of secondary amenorrhea are hormonal imbalances including low level of LH, FSH and estrogen and high levels of cortisol. A common disease pattern is the combination of menstrual disfunction, low energy availability and low bone mineral density. Combination of these three characteristics is called female athlete triad (Thompson, 2019). Up to 80% of women which are exercising regularly are concerned by abnormalities in menstruation (Warren & Perlroth, 2001). A previous study on 289 Swedish adolescent athletes showed that nearly half of the athletes not using OCP had menstrual irregularities. This group had significantly lower BMI and consisted of a higher proportion of endurance athletes compared to other sports. This shows that in endurance sports menstrual irregularities are quite widly spread (Rosen et al., 2020). Amenorrhea has the most serious long-term effects for bone and cardiovascular health. When it comes to bone mineralization, a promoting and protective effect is expected by estrogen meaning that healthy hormone levels correlating with regular menstrual cycles are of importance for bone mineral density (Thompson, 2019). A study on female cross-country runners supports that menstrual irregularities go along with higher risk factor for stress fracture. Further a higher age of menarche was associated with higher risk for stress fracture. When taking into account that a stress fracture might lead to a very long time off training and maybe missing important competitions, it is of high importance to know about risk factors which could be avoided. The importance of further research in this area is therefore obvious (Kelsey et al., 2007). Research has found higher bone mineral density in athletes using OCP (Emslander et al., 1998) a supporting effect by the exogenous estrogen can therefore be suggested. On the other hand,

a study of Hartard et al. (2004) found out that low bone mineral density goes along with OCP intake and especially when OCP intake started in early age of endurance athlete.

## *1.3 Definitions and theoretical explanation of the research field*

### *1.3.1 Menstrual Cycle*

The menstrual cycle is a female reproductive life cycle which effects various biological systems in women's body. It is an interplay of hypothalamic, hypophyseal, and ovarian hormones and influences not only local organs of the reproductive tract, but many more. Hormone levels of female athletes are constantly shifting through different stages of life like prepuberty, to menarche, conception, pregnancy, menopause etc. estrogen and progesterone are the most important hormones when it comes to the female menstrual cycle, but anyway many more hormones such as testosterone, leptin etc. have recently been explored to affect the body system in the female cycle. These endogenous hormones are produced by the body itself to regulate physiological systems. They need to be distinguished by the so-called exogenous hormones which are supplied from the outside, for example through the OCP (Constantini et al., 2005).

The menstrual cycle can be divided into two phases – *follicular phase (FP) and luteal phase (LP)*, into three phases – *FP, ovulation phase, and LP (Constantini et al., 2005), or into five phases* – early *FP, late FP, ovulation phase, early LP and late LP (Draper et al., 2018).* First phase is the follicular phase, also called proliferative phase (Reed & Carr, 2000). Follicles grow and develop due to the release of follicle-stimulating hormone (FSH), which is a hypophyseal hormone. This phase starts with the first day of menses and lasts an average of nine days. The cells surrounding the follicle secret the endogenous hormone estrogen (Draper et al., 2018). Consequently, also the secretion of the hypophyseal luteinizing hormone (LH) increases which further leads to ovulation which happens about one day after the increase of LH. This is when ovulation phase starts and lasts about five days. Endometrial thickness increases to prepare for a potential embryo and a few days after the follicle has released the ovum, a progesterone-secretion happens from corpus luteum and the ovulation phase ends (Constantini et al., 2005). Subsequently, the luteal phase (also called secretory phase) starts and lasts for 14 days. Progesterone secretion rises due to stimulation of granulosa cells (Reed & Carr, 2000) and supports the endometrium. When the embryo can create a placenta, placenta takes over this function of progesterone. At the end of the LP secretion of progesterone from *corpus luteum* stops. Endometrium is therefore no longer supported and consequently leaves the body as menstrual bleeding. Also, estrogen levels decrease in these days which leads to FSH secretion and the cycle starts from the beginning with menses (Constantini et al., 2005). Typical volume of blood loss in menses is about 30 mL of blood, and it is considered as abnormal when blood lose in menstruation rises above 80 mL (Reed & Carr, 2000). Definition of the two, three or five cycle phases can therefore be drawn by the ratios of estrogen and progesterone: In the first phase (FP) both hormone levels are

low, in the second phase (ovulation phase) the estrogen level is high but the progesterone level is slow, and in the third phase (FP) both hormone levels are high (Constantini et al., 2005). Duration of the menstrual cycle is in average about 28 days, whereat most women`s cycle lengths last between 25 and 30 days. Intervals lasting more than 35 days (oligomenorrheic) and less than 21 days (polymenorrheic) are considered as abnormal. Duration of LP of 14 days is relatively constant. If lengths are varying it is usually due to variation of lengths in FP in a range of approximately 10 to 16 days (Reed & Carr, 2000). To define a cycle of five phases, LP and FP are divided in the middle as illustrated and therefore can be seen more clearly in the following figure 1.

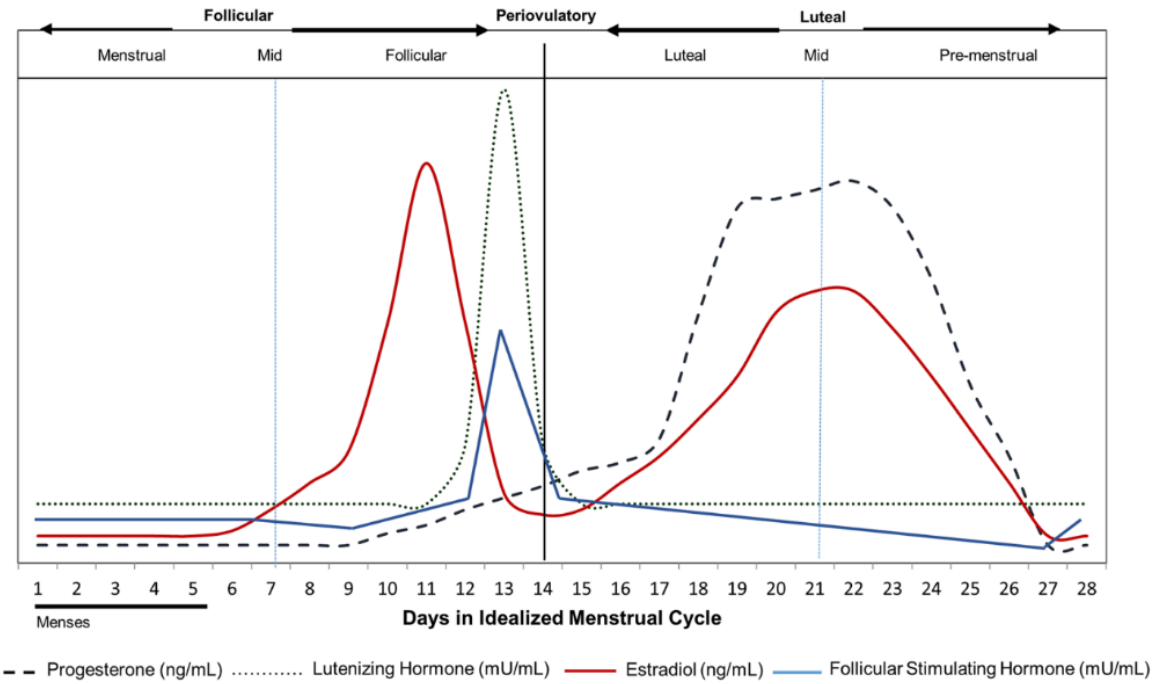


*Figure 1: Menstrual cycle and endogenous hormone levels (Draper et al., 2018)*

Figure 1 shows that FP starts with menses andall hormone levels are low and in late FP all hormone levels (except progesterone) increase for a short time. In average in the middle of the cycle ovulation happens and all hormone levels drop off steeply. At the transition from early to late LP progesterone rises to its peak and also estradiol increases, but at the end both drop. LSH and FSH stay low in the LP.

### *1.3.2 Endogenous hormones of the menstrual cycle*

The most common endogenous hormones of the menstrual cycle are estrogens (17-beta estradiol and estrone) and progesterone (Sims & Heather, 2018). Estrogens are the most important sex hormones in females and are also called follicular hormones. There are three types of estrogen: estradiol, estrone, estrone sulfate and estriol. These types differ in the structures of molecules depending on which hydroxy group it belongs to. This influences the intensity of the estrogenic effect which is ten

times higher in estradiol than in the other types (Bachl et al., 2017). Estrone has weaker estrogenic effects and can be converted into estradiol (Sims & Heather, 2018). Estradiol is an important hormone for the development of primary and secondary sexual organs in females (Chan et al., 2001). Estrogen is produced in the granulosa cells of ovaries, follicles, corpus luteum and in small parts also in adrenal glands. Production of estrogen is influenced by the menstrual cycle of women. It is significantly less in menopause and then production is mainly in adrenal glands (Bachl et al., 2017). Estrogen has various influences on body composition, for example, increasing fat mass (Ziomkiewicz et al., 2008) and supporting retention of water (Stachenfeld et al., 2001). Further, estrogen extends the capacity of muscle glycogen storage and the availability of free fatty acids. Also, the use of fatty acids as a fuel source is increased due to changes in oxidative pathways (Hackney, 1990). Consequently, use of carbohydrates is decreased and glycogen is maintained. The influence on oxidative pathways leads to an increase of oxidative capacity which further leads to less dependency on anaerobic pathways for ATP production. It can be concluded that decreased blood lactate levels and less time-to-exhaustion goes along with high estrogen levels (Oosthuyse & Bosch, 2010). Another process which goes along with high estrogen levels is extended gluconeogenesis. This is a metabolism process which transfers non-carbohydrates into glucose and enables a constant blood-glucose-levels. Further, estrogen augments the uptake of glucose in type I muscles (Campbell & Febbraio, 2002). The effects of estrogen on an athlete's metabolism and body composition are manifold and still not fully understood.

Progesterone belongs to the sex hormone group of gestagens which a steroid is, just like estrogens are. Its main task is the preparation of the implantation of the fertilized egg, which explains why it is mostly released during the second half of menstrual cycle and stimulates also release of LH. Progesterone is an intermediate product of the synthesis of estrogen. Progesterone is released and generated in *corpus luteum* and granulosa cells and in smaller amounts also in other tissues. Beside its ability to partly regulate menstrual cycle, progesterone further influences mammary gland and supports retention of fluids in body. It is therefore also responsible for an increase in body mass and shift in body composition before the onset of menstrual bleeding. If pregnancy does not occur, the level of progesterone and estrogen decreases at the end of menstrual cycle and bleeding of the endometrium beginns (Bachl et al., 2017).

Physiological parameters which are influenced by progesterone are for example resting heartrate (Sedlak et al., 2012) and basal body temperature (Charkoudian et al., 1999). While the raise of estrogen level decreases body temperature, distribution of progesterone increases body temperature (Charkoudian & Johnson, 2000). This might be the reason for alterations in body temperature through menstrual cycle. Higher values in luteal phase are suggested because progesterone level rises at the late menstrual cycle in luteal phase. For athletes this means, that the high body temperature leads to a subjective feeling of greater exertion. This appears especially in humid and hot areas (Sims & Heather, 2018). Progesterone has also an effect on ventilation (Charkoudian et al., 1999).

Progesterone augments frequency of ventilation and it is suggested that this leads to a beneficial effect on maximal exercise capacity at elevated environments. Further, it is of importance that progesterone and estrogen work in antagonistic directions. For example, estrogen promotes, and progesterone inhibits carbohydrate metabolism (D'Eon et al., 2002). In contrary, progesterone promotes and estrogen inhibits protein catabolism and consequently muscle protein syntheses (Lamont et al., 1987). The balance between progesterone and estradiol is of importance. If the ratio gets unbalanced this can lead to various symptoms during the menstrual cycle like pain, fatigue, problems with sleeping routine, disordered mood and transient weight gain due to water retention or increased hunger (Chan et al., 2001).

An interesting parameter for physical performance and training adaption is testosterone which is highest in preovulation. Also, in estrogen highest values are suggested in preovulation, while in progesterone the peak is found in the middle of LP (Reed & Carr, 2000). Values and variation through menstrual cycle phases are presented in table 1.

*Table 1: Production rate of sex steroids through menstrual cycle (modified after Reed & Carr, 2000)*

| | Daily production rate | | |
|---|---|---|---|
| **Sexsteroids (mg or µg per 24h)** | **Early Follicular Phase** | **Preovulatory** | **Middle of Luteal Phase** |
| Testosterone (µg) | 144 | 171 | 126 |
| Estradiol (µg) | 36 | 380 | 250 |
| Progesterone (mg) | 1 | 4 | 25 |

### *1.3.3 Methods for detection of menstrual cycle*

To make hypotheses concerning effects in different menstrual cycle phases, it is of vital importance to verify on which day of cycle the timing of data collection is set. Detection of menstrual cycle can be done by different methods which require different amount of time and budget. Most methods of cycle verification investigate the ovulation to enable a division into FP and LP (Janse de Jonge, 2003).

(1) Counting days from the onset of menses is an often-used method. Participants were required to have a regular ovulatory menstrual cycle and it is suggested that this goes along with “normal” dynamic in hormone levels. Time amount required is less than for other methods but if participants have to do exact protocols over more cycles, obviously the required time amount rises. A problem with this method is that FP is more effected in duration variations than LP which is often not taken into account in elderly studies. Often timing of ovulation is set in the middle of the cycle without further detection. Another problem is that it can not be suggested that all women with regular menses have regular ovulations which consequently influences hormone levels. Counting days for menstrual cycle detection can give an orientation on the menstrual cycle but can also give misleading

information of exact phases. Therefore some additional detection methods are suggested (Janse de Jonge, 2003).

(2) Another method for menstrual cycle detection is charting basal body temperature. Usually, body temperature increases after ovulation for approximately 0.3°C. This method can therefore help to detect if ovulation has happened at all and draw conclusion on timing of LP and FP. On the other hand information on hormone levels is missing and reliability has to be treated with caution (Janse de Jonge, 2003).

(3) Using urine stripes to detect LH in urine can be useful to detect menstrual cycle phase. On the stripes are colorimetric enzyme immunoassays and if LH is detected a coloured sign appears. It has been detected that it lasts about two hours from peak LH concentration in blood serum to peak LH in urine, which can be interpreted as quite quickly and accurate. This detection method has a confidence level of 95% due to the accuracy that if LH surge has been shown.

(4) Last and most reliable practice for menstrual cycle detection is the determination of estrogen and progesterone level. It can be detected by collection of urine, saliva or blood serum. Estimation by urine is quite difficult as one urine sample might lead to errors in detection and therefore 24-h urine collections are needed. This sample collection is rather time expensive and uncomfortable for participants compared to alternative methods. Detection of hormones by samples of saliva has the advantage of being less time consuming and non-invasive. On the other hand, steroid concentrations in saliva are much lower than in blood serum and detection methods in laboratories need greater sensitivity to enable precise measurement. Consequently, samples are more erroneous. A well-established and invasive method is the measurement of hormones in blood samples which is used in most recent studies. This cycle phase verification observes level of progesterone to distinguish FP from LP. If the level has increased, it is concluded that ovulation has happened. Anyway, exact detection of ovulation day is not so precise as progesterone level needs some time to increase and does not rise right after ovulation (Janse de Jonge, 2003). For research purposes usually the detection limit of 16 nmol/L is set to verify that ovulation has happened (Landgren et al., 1980). Further, the detection of estrogen identifies the late-follicular phase, as the estrogen level rises in the middle of FP. Timing of taking blood samples is suggested to be at rest, because it is known that exercise increases progesterone and estrogen levels (Frankovich & Lebrun, 2000). Consequently, blood serum is the only way to distinguish not only FP and LP but also early and late stages of those phases (Janse de Jonge, 2003).

### *1.3.4 Different types of oral contraceptive pills*

In general, the use of OCPs significantly reduces the release of endogenous cycle hormones. Concentrations of endogenous estradiol and progesterone are lower during OCP cycle due to the intake of synthetic-exogenous estradiol and progesterone (Elliott-Sale et al., 2020).

There are three main types of OCPs, mono-, bi- and triphasic hormone pills. This is the description of the number of variations of the hormonal formulations in OCPs. While in monophasic pills the same formulation continues through the whole cycle (meaning that each hormone pill is equal through the cycle), in biphasic hormonal doses change once and in triphasic there are three different formulations of OCP. Mono and triphasic oral contraceptives are the mainly prescribed OCP types. The use of biphasic OCPs is less and still decreasing (Burrows & Peters, 2007).

Monophasic OCPs contain low to standard doses of ethinyl estradiol and some kind of synthetic progesterone. All pills contain the same doses of the hormones. The fixed number of hormones is delivered by taking one pill each day for 21 days and is followed by a withdrawal of 7 days free of pills. Some producers do offer placebo pills for this periode (Elliott et al., 2005). Due to the continuous intake of exogenous hormones (despite one week of withdrawal), the endogenous progesterone is supressed and continually low. Also, endogenous estrogen level is on a stable and low level but rises through withdrawal (see also figure 2 – daily hormonal levels of monophasic OCP). In the triphasic OCPs the formulation aims to simulate a natural hormone cycle (Rechichi et al., 2009). As seen in figure 1, in the natural cycle level of progesterone rises in luteal phase, due to that in the triphasic OCP formulation progestogen is highest shortly before withdrawal. In the natural cycle on about day 7 the level of estrogen augments for the first time. Formulation of triphasic pill imitates this effect and as is illustrated in figure 3 progesterone level gets higher step by step. All in all, when comparing the hormone levels of mono- and triphasic pill formulations it can be observed that exogenous hormone levels of triphasic OCPs appear to be more similar to natural cycle. In endogenous levels it seems that reaction on OCP use is similar in both formulations. These stay low and stable, except during withdrawal, where these rise.

a.

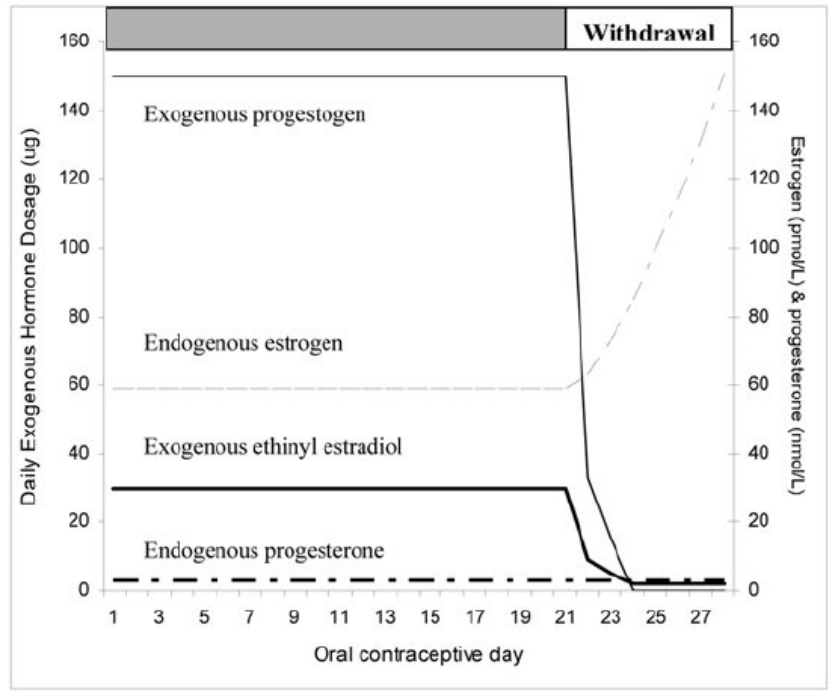


*Figure 2: Hormone levels of monophasic oral contraceptive pill (Rechichi et al., 2009)*

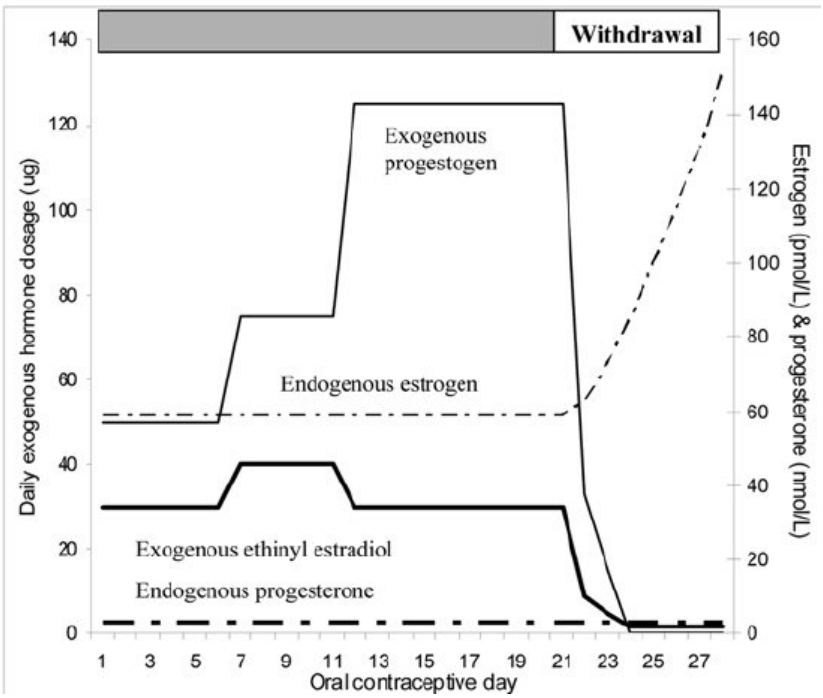


*Figure 3: Hormone levels of triphasic oral contraceptive pill (Rechichi et al., 2009)*

### *1.3.5 Exogenous hormones*

Still, it is questionable if different OCP formulations might lead to a variation in the results of research trials concerning sports performance. Previous research suggests that this is an often missed-out bias. Not only between mono-, bi- and triphasic OCPs variations on research results are suggested, but also between different manufacturers. But how come, that two monophasic OCPs might influence female physiology differently? It is due to the ingredients used in different recipes of producers. Having a closer look on the OCP recipes it is perceptible, that the exogenous hormone for estrogen is always ethinylestradiol, while for progesterone various different exogenic hormone ingredients are used as progestogens. According to Burrows (2007) there are six mainly used ingredients: desogestrel, levonorgestrel, norethindrone, norethisterone acetate, and two of the family of norgestimate (norgestrel and etynodiol). What is important to consider at this point, is that some impacts of ethinylestradiol and progestogen oppose each other. Ethinylestradiol causes the uncomfortable side effects of the medication such as nausea and tender feeling in breasts (Rosenberg et al., 1999). On the other hand, it leads to less intermenstrual bleeding due to the beneficial effect on the endometrium (Rosenberg et al., 1999). In various effects progestogen acts opposed to estrogen. Intensity of opposite effect depends on the kind of progestogen because they differ in *potency* and *androgenocity* (Phillips et al., 1990). The *potency* is the intensity of the effect of progestogen. *High potency* leads to high progestational activity (Greer et al., 2005). The term *androgenocity* means the ability of progesterone to produce masculine abilities (Greer et al., 2005). Depending on the *potency* the amount of progesterone is measured. This means if an OCP has a higher dose of progesterone this does not always mean that it has a higher progestational effect. It depends of the type of progestogen and the *potency* (Burrows & Peters, 2007). As already mentioned progestogen and estrogen have somehow opposed effects. OCPs with high androgenocity have more negative adverse effects because they counteract to a high extend with the positive effects of estrogen potency (Burrows & Peters, 2007). This leads to the conclusion that research results of athletes using OCPs can not always be compared to other athletes using OCPs of another manufacturer, but ingredients and especially *potency* of the progestogen must be considered when comparing results of research trials (Burrows & Peters, 2007). OCPs with high androgenocity are suggested to have larger impact on physical performance because they have higher opposed effect on estrogens than OCPs with low androgenicity (Scharnagl et al., 2004). Table 2 from Burrows and Peters (2007) gives an overview on commonly used OCP products and their ingredients and doses. It can be seen, that *potency* and androgenicity varies through products. Table 2 further shows how many different types of progestogen are used and that dose and *potency* varies, while in estradiol only dose varies between 0.02 and 0.05 mg and the type does not differ between the different brands.

*Table 2: Overview on OCP products and their doses of steroid hormonal ingredients (Burrows & Peters, 2007, p. 559)*

| Trade name | Ehinylestradiol dose (mg) | Progestogen type | dose (mg) | potency[a] | androgenicity[a] |
|---|---|---|---|---|---|
| Alesse® 21 or 28 | 0.020 | Levonorgestrel | 0.10 | 0.53 | 0.83 |
| Brevinor®-1 | 0.035 | Norethindrone | 1.0 | 1.0 | 1.0[b] |
| Cilest® | 0.035 | Norgestimate | 0.25 | 0.33 | 0.48 |
| Demulen® 1/35–28 | 0.035 | Etynodiol | 1.0 | 1.4 | 1.6[b] |
| Demulen® 1/50 | 0.050 | Etynodiol | 1.0 | 1.0 | 1.0[b] |
| Diane® 35 (Dianette®[c]) | 0.035 | Cyproterone | 0.20 | NA[d] | NA[d] |
| Femodene® | 0.030 | Levonorgestrel | 0.15 | 0.8 | 1.25[b] |
| Femodette® | 0.020 | Gestodene | 0.075 | 0.68 | 0.26 |
| Loestrin® 1/20 | 0.020 | Norethindrone | 1.0–1.5 | 1.0 | 1.0[b] |
| Loestrin® 1.5/30 | 0.030 | Norethindrone | 1.5 | 1.5 | 1.5[b] |
| Marvelon® | 0.030 | Desogestrel | 0.15 | 1.35 | 0.51 |
| Mercilon® | 0.020 | Levonorgestrel | 0.15 | 0.80 | 1.25[b] |
| Microdiol® | 0.030 | Desogestrel | 0.15 | 1.35 | 0.51 |
| Microgynon® 30 | 0.030 | Levonorgestrel | 0.15 | 0.8 | 1.25[b] |
| Minovral® | 0.030 | Levonorgestrel | 0.15 | 0.8 | 1.25[b] |
| Minulet® | 0.030 | Gestodene | 0.075 | 0.68 | 0.26 |
| NeoGentrol® 30/150 | 0.030 | Levonorgestrel | 0.15 | 0.8 | 1.25[b] |
| Norimin-1® | 0.035 | Norethindrone | 0.50 | 0.5 | 0.5 |
| Norinyl-1® | 0.050 | Norethindrone | 1.0 | 1.0 | 0.34 |
| Norlestrin® 21 | 0.050 | Norethindrone | 1.0 | 1.0 | 1.0[b] |
| Ortho-Novum® | 0.050 | Norethindrone | 1.0 | 1.0 | 1.0[b] |
| Ortho-Novum® 1/35 | 0.035 | Norethindrone | 1.0 | 1.0 | 1.0[b] |
| Ortho-Novum® 1/50 | 0.050 | Norethindrone | 1.0 | 1.0 | 1.0[b] |
| Ovcon 35® | 0.035 | Norethindrone | 0.40 | 0.4 | 0.4 |
| Ovral® | 0.030 | Norgestrel | 0.30 | 0.78 | 1.26[b] |
| Ovran® 50 | 0.050 | Levonorgestrel | 0.25 | 1.33 | 2.1[b] |
| Ovranette® | 0.030 | Levonorgestrel | 0.15 | 0.8 | 1.25[b] |
| Sterdiril-m® | 0.030 | Levonorgestrel | 0.15 | 0.8 | 1.25[b] |

a Progestogen potency and androgenicity values are calculated using the method of Greer et al.[12] The OCP progestogen dose is multiplied by its progestational activity (for potency) or by its androgenic activity (for androgenicity). Progestational and androgenic activity are calculated relative to a 1mg dose of norethindrone.

b OCPs that may have the potential to alter performance, based on androgenicity cut-off value of ≥1.0 (Greer et al.[12]).

c Alternative name for OCP.

d Antiandrogen so no potency or androgenicity values.

## *1.4 Rationale of this study*

As explained above, the endocrine process has an influence on physical systems and in particular on metabolism which might influence endurance performance and also body composition. The consumption of estrogen and progesterone might have an effect on the endogenous hormone balance and therefore on physical performance (Barba-Moreno et al., 2019) and anthropometric body composition (Casazza et al., 2002).

The effects of OCP intake and its effects on the female body are gaining interest in the past years. Intake of OCP is common in female athletes in several types of sports and various countries. Therefore, this systematic review aims to elaborate the consequences of the hormonal pill on endurance performance and metabolism during endurance exercise. The aim is to systematically collect information of clinical trials in healthy female athletes. If body composition or other anthropometric parameters are measured as well, then these results will also be interpreted.

## *1.5 Research question*

The research questions were created according to PICO (population, intervention, comparator, and outcome): “What are the effects of OCP intake on endurance performance in healthy trained females?” Further, a second research question has been made “What are the effects of OCP intake on anthropometric parameter concerning OCP use and endurance performance in healthy trained females?”. As such, this systematic review aims to identify whether the use of OCP provides any benefits or disadvantages on the physiological of endurance exercise or anthropometric data of healthy female athletes and if so, which physiological processes are responsible for this.

# 2 Methods

The reporting has been done in accordance with the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) statement (Page et al., 2021). In- and exclusion criteria as well as the selection process are described to enable a transparent and comprehensibly research process.

## *2.1 Eligibility criteria*

To describe the eligibility criteria systematically and enable a transparent research process, the PICO (Patients, Intervention, Control, Outcome) for the following review were determined as follows:

- *Patients*: healthy and regularly active female individuals
- *Intervention*: intake of any type of OCP
- *Control*: comparison to another phase within the contraceptive cycle of the same individuals and if applicable a control group (male or female) without OCP-intake
- *Outcome*: effects on endurance performance and if applicable anthropometric measurements

All studies were selected for eligibility if they met the following criteria:

- clinical trials
- studies in humans without any diseases or orthopaedic symptoms
- studies including endurance/cardiorespiratory physical activity or exercise intervention
- studies which analysed cardiorespiratory parameters using spirometry
- measurement of at least two different timepoints in OCP cycle
- cross-sectional studies and longitudinal studies
- studies in English, German or Spanish

The exclusion criteria were defined as the following:

- reviews, meta-analysis and other study designs except clinical trials
- animal studies
- studies in humans with any disease
- studies without intake of oral contraceptive pill
- studies measuring endurance performance without using spirometry
- longitudinal-studies with exercise intervention
- measurement of only a single phase in OCP cycle
- studies in other language than German, Spanish or English

As the intervention of OCP has been approved and revealed in 1960 (Christin-Maitre, 2013), publications before this date are not available and consequently not been included to this systematic research.

## *2.2 Sources and search strategy*

The scientific databases PubMed and Web of Science were used to search for studies which fit to the selection process. The database PubMed is known for its research on life sciences and biomedical topics, while the database Web of Science addresses studies from several different disciplines including life sciences. Two databases were used to have a wider range of research articles and to avoid that one database might exclude relevant literature. This procedure helps to set the quality of this research process as high as possible. Research process was finished in September 2021. No filter or limitations were set in the search process. Reference lists and suggested articles of the database were screened as well, but no further articles were found by hand search. The keywords can be seen in the original search string, which was for both databases the following: (endurance OR cardiorespirator* OR fitness OR stamina OR aerob*) AND (oral contraceptive pill)

## *2.3 Selection and data collection process*

The screening process was performed by the reference management webpage "Covidence" (https://www.covidence.org/) which is a web-based program for systematical research organisation. Files with lists of the references which appeared by the search string were exported from Pubmed and Web of science and imported into Covidence. Most of the duplicates were automatically removed by Covidence. Inclusion and exclusion criteria were applied in the program and afterwards literature was screened by title and abstract to assess eligibility. The remaining articles were chosen for the full-text analysis, read in detail to assess if it really meets in- and exclusion criteria. This process and the number of articles for each step can be seen in the PRISMA flow chart. Following informations were extracted of the finally included research articles:

*General characteristics:*

- Authors
- Year
- Country
- Study design
- Study setting (OCP only or including no pill use)
- Number of participants enrolled and completed

*Study characteristics:*

- Type of exercise
- Intensity of exercise protocol
- Measured parameters
- Type of OCP
- Duration of OCP intake before the study
- Control group

*Sample characteristics:*

- Sample number
- Sex
- Age
- Fitness level
- Baseline subject characteristics of endurance performance
- Baseline subject characteristics of anthropometric data

*Outcome:*

- Cardiorespiratory parameter
- Performance output
- Body composition and anthropometric parameter

If standard deviation (SD) or standard error of the mean (SEM) in the articles were not presented clearly it was declared as not reported. If not described otherwise mean ± SD are reported.

## *2.4 Risk of bias assessment*

To make the quality of research article and research methods of the selected studies comparable, a risk of bias assessment has been done. Therefore, the PEDro scale assessment tool has been applied. The included studies were scattered by points and ranked. The tool consists of eleven items (random allocation, concealed allocation, similarity at baseline, subject blinding, therapist blinding, assessor blinding, more than 85% follow up for at least one key outcome, intention-to-treat analysis, between-group statistical comparison for at least one key outcome, and point and variability measures for at least one key outcome (De Morton, 2009) and the score ranges from zero to ten points. Consequently, studies can be assigned to the following three clusters: low methodological quality (<4 points), moderate quality (4-6 points) and high methodological quality (>6 points) (De Morton, 2009).

# 3 Results

The following section includes two parts to present the results to answer the research question. At first the results of the selection process are presented. Following, the results of the studies are reported to answer the research questions according the influences of the menstrual cycle and the oral contraceptive use. To make the results section more readable, citations in the following section is done by parantheses and numbers. The numbers assigned for the studies are written in the tables below.

## *3.1 Results of study selection process*

The process of the study selection revealed 185 article which were screened by their abstracts, after duplicates were removed. After inadequate records were excluded 18 records remained and read in full text. Not all of them revealed data to compare different menstrual cycle phases but collected data only at one timepoint in menstrual cycle. Therefore, criteria were confirmed in 12 research article and therefore included in the following systematic review. Selection process is presented in figure 4.

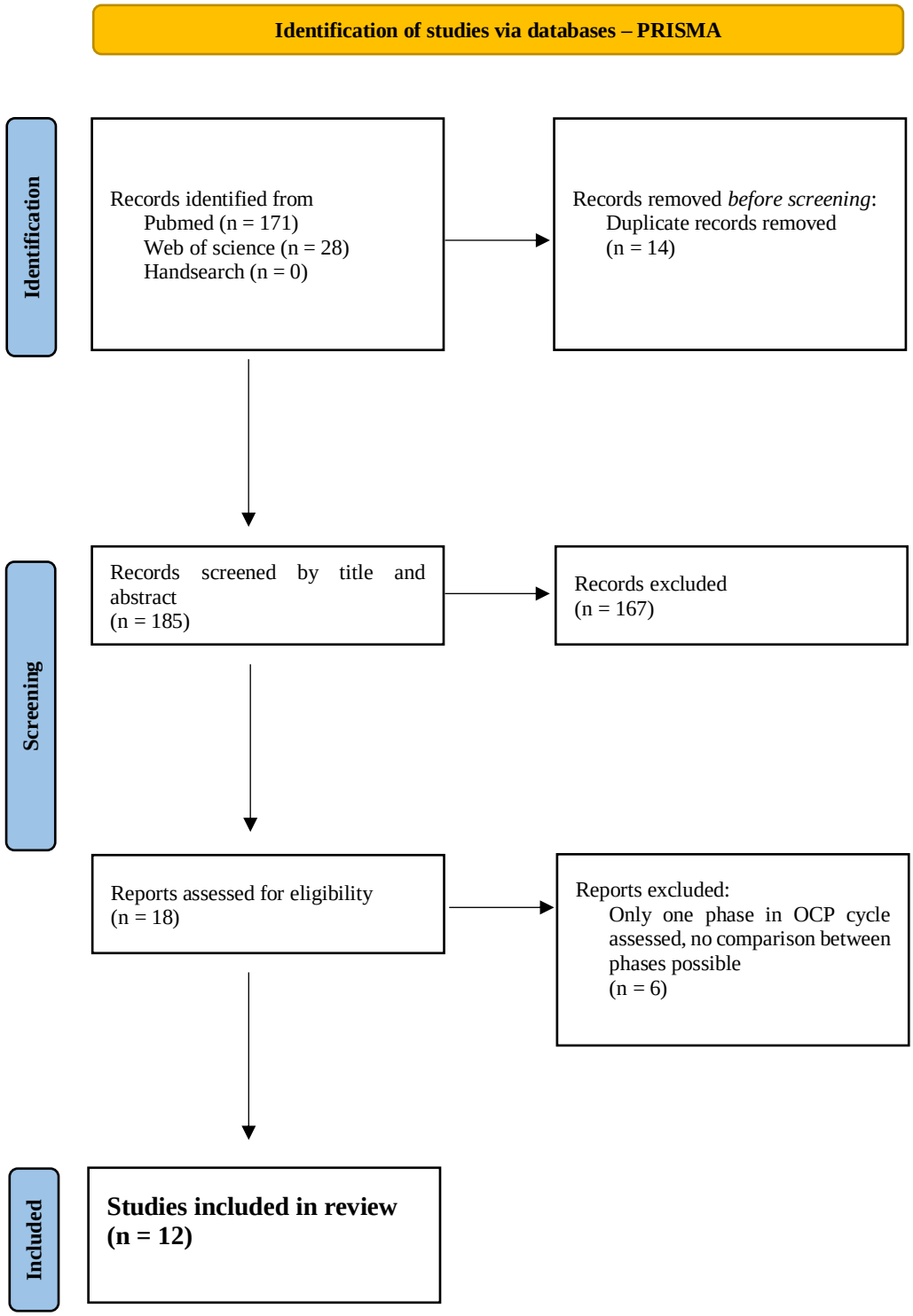


*Figure 4: PRISMA flow chart (Page et al., 2021)*

## *3.2 Study characteristics*

In the following section a comparison of the characteristics, general information and methodologies of the selected studies is presented. The selected research articles have been published in different genres of scientific journals. Therefore, journals with medical point of views and especially endocrinological, clinical physiology as well as gynaecological research are included. But, also articles published in journals with sport scientific content (specified for example in strength and conditioning, applied physiology and motor skills) have been included. Publication years of the included articles show a range of 27 years with the oldest publication from 1993 and the newest from 2020. The majority (n = 9) of the study designs are cross-sectional research methods. Six of these had a control group which were non-OCP users while three studies were without control groups. Another three article were intervention studies. These longitudinal studies investigated a sample of non-OCP users which started using OCPs as an intervention. Therefore, the studies calculated a pre-post comparison and one study additionally had two control groups, women with placebo pills and men. See further information on this context in table 3.

*Table 3: General characteristics of the studies*

| Code | Author | Year | Titel | Journal | Study design | Control group |
|---|---|---|---|---|---|---|
| **1** | Barba-Moreno et al. | 2019 | Cardiorespiratory Responses to Endurance Exercise Over the Menstrual Cycle and With Oral Contraceptive Use | Journal of Strength and Conditioning Research | randomized-controlled cross-sectional study | non-OCP users |
| **2** | Bryner et al. | 1996 | Effect of low dose oral contraceptives on exercise performance | Sports Medicine | Intervention-Study (double blind, randomized, controlled, longitudinal-duration unclear) | pre and post OCP-Intervention - control group: men and placebo group |
| **3** | Casazza et al. | 2002 | Effects of oral contraceptives on peak exercise capacity | Journal of Applied Physiologie | Intervention-Study (longitudinal - duration of intervention periode 4 months of cycle) | pre and post OCP-Intervention - no control group |
| **4** | Giacomoni et al. | 2000 | Decreased submaximal $O_2$ uptake during short duration oral contraceptive use: a randomized cross-over trial in premenopausal women | Ergonomics | cross-sectional study | no control group |
| **5** | Gordon et al. | 2017 | The effects of menstrual cycle phase on the incidence of plateau at $VO_{2max}$ and associated cardiorespiratory dynamics | Clinical Physiology and Nuclear Medicine | controlled cross-sectional study | non-OCP users |
| **6** | Grucza et al. | 1993 | Influence of the menstrual cycle and oral contraceptives on thermoregulatory responses to exercise in young women | European Journal of Applied Physiology | controlled cross-sectional study | non-OCP users |
| **7** | Joyce et al. | 2013 | Effect of long-term oral contraceptive use on determinants of endurance performance | Journal of Strength and Conditioning Research | controlled cross-sectional study | non-OCP users |
| **8** | Jürimäe et al. | 2010 | Adiponectin and bone metabolism markers in female rowers: Eumenorrheic and oral contraceptive users | Journal of Endocrinological Investigation | controlled cross-sectional study | non-OCP users |
| **9** | Nakamura et al. | 2020 | Effect of administration of monophasic oral contraceptive on the body composition and aerobic and anaerobic capacities of female athletes | Journal of Obstetrics and Gynaecological Research | Intervention-Study (double blind, randomized, controlled longitudinal-duration of intervention periode 3 months) | pre and post OCP-Intervention - no control group |
| **10** | Rechichi et al. | 2008 | Oral Contraceptive Phase Has no Effect on Endurance Test | International Journal of Sports Medicine | cross-sectional study | no control group |
| **11** | Vaiksaar et al. | 2011a | No effect of menstrual cycle phase and oral contraceptive use on endurance performance in rowers | Journal of Strength and Conditioning Research | controlled cross-sectional study | non-OCP users |
| **12** | Vaiksaar et al. | 2011b | Phase of oral contraceptive cycle and endurance capacity of rowers | Perceptual and Motor Skills | cross-sectional study | no control group |

OCP oral contraceptive pill, non-OCP no intake of oral contraceptive pill

Having a closer look on the publishing year, it is obvious that more than half of the articles are published after 2010. The timeline in table 4 it illustrates that research on this topic was conducted more often in recent years than in years far back. The names of the authors and codes given in this paper are put on the timeline to give a better overview.

*Table 4: Timeline - Overview of years of publications*

| **Year** | **1993** | **1994** | **1995** | **1996** | **1997** | **1998** | **1999** |
|---|---|---|---|---|---|---|---|
| **Code** | **6** | → | → | **2** | → | → | → |
| **Author** | Grucza et al. | | | Bryner et al. | | | |

| **Year** | **2000** | **2001** | **2002** | **2003** | **2004** | **2005** | **2006** |
|---|---|---|---|---|---|---|---|
| **Code** | **4** | → | **3** | → | → | → | → |
| **Author** | Giacomoni et al. | | Casazza et al. | | | | |

| **Year** | **2007** | **2008** | **2009** | **2010** | **2011** | **2012** | **2013** |
|---|---|---|---|---|---|---|---|
| **Code** | → | **10** | → | **8** | **11, 12** | → | **7** |
| **Author** | | Rechichi et al. | | Jürimäe et al. | beide Vaiksaar et al. | | Joyce et al. |

| **Year** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019** | **2020** |
|---|---|---|---|---|---|---|---|
| **Code** | → | → | → | **5** | → | **1** | **9** |
| **Author** | | | | Gordon et al. | | Barba-Moreno et al. | Nakamura et al. |

Concerning the quality of the study design results of PEDro scale analyses are presented in the following table 5. High methodological quality has been analysed in one study [2]. For most studies, seven, moderate quality [1, 5, 6, 7, 8, 10, 11] and for another four research trials low quality [3, 4, 9, 12] has been determined.

*Table 5: Analysis of research methods of selected studies by pedro scale*

| **Authors** | **Barba-Moreno et al.** | **Bryner et al.** | **Casazza et al.** | **Giacomoni et al.** | **Gordon et al.** | **Grucza et al.** | **Joyce et al.** | **Jürimäe et al.** | **Nakamura et al.** | **Rechichi et al.** | **Vaiksaar et al.** | **Vaiksaar et al.** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Code** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
| **random allocation** | 0 | 1 | 0 | 0** | 0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **concealed allocation** | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **similarity at baseline** | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **subject blinding** | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **therapist blinding** | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **assessor blinding** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **85% follow up*** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **intention to treat analysis** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **between-group statistical comparison*** | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 |
| **point measures*** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **variability measures*** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **total points** | **5** | **8** | **3** | **3** | **4** | **4** | **4** | **4** | **3** | **4** | **4** | **3** |

*for at least one key outcome
**testing time was randomized but not allocation to group

The samples of the studies are compared in the following table 6. Number of participants ranged from minimum 8 to maximum 24 participants. The mean number of participants is 15 persons with a standard deviation of 6. In some studies age of each participant is reported but some papers presented only the mean and standard deviation. All studies had to have a group of OCP users and the n of these groups ranged from 6-13 participants. The mean was 9 participants with a standard deviation of 2. Of the 12 research article 5 had no group of non-OCP users and another three article were longitudinal studies were the group started using OCPs, therefore the same persons were in the non-OCP/pre-intervention and OCP using/post-intervention group. Another five papers had separated non-OCP using groups which´s number of participants ranged from 3 to 15 persons (figure 5). The mean was 10 and the standard deviation was 4 participants. All in all, a range of 18 to 40-year-old study sample can be concluded. Only in the research of Rechichi et al. (2008) and of Barba-Moreno (2019) also participants older than 30 years were included. Therefore, the majority of the participants was younger than 30 years. Inclusion criteria selected papers with participants which were healthy and regularly active female individuals, but some papers reported it more detailed than others. Anyway, training status of the participants differed and also discipline of sports. In one paper the quantity of physical activity was reported in times per week and additionally minutes of practice (Joyce et al., 2013). Further, it was described that they were generally physical active, including the information that they were students of a sports university. On the other hand, exact sport types, like rowing, triathlon etc. were reported, which can be seen more clearly in table 6.

*Table 6: Sample comparison*

| Code | Author | Year | Age | N total | n in group of non-OCP Users | n in group of OCP Users | Trainingsstatus of participants |
|---|---|---|---|---|---|---|---|
| **1** | Barab-Moreno et al. | 2019 | 35.6 ± 4.2 years; range: 28-40 years | 23 | 15 | 8 | endurance trained |
| **2** | Bryner et al. | 1996 | 18-30 years | 10 | 3 | 7* | young women |
| **3** | Casazza et al. | 2002 | 25.5 ± 1.5 years | 8 | | 8* | moderately active women |
| **4** | Giacomoni et al. | 2000 | 23 ± 3 years | 10 | | 10 | physical education students |
| **5** | Gordon et al. | 2017 | NOCP: 20.6 ± 1.6 years; OCP: 21.7 ± 2.16 | 16 | 10 | 6 | physically active |
| **6** | Grucza et al. | 1993 | OCP: 21.3 ± 0.6 years; NOCP: 22.0 ± 1.7 years | 20 | 10 | 10 | young healthy women |
| **7** | Joyce et al. | 2013 | NOCP: 22 ± 3 years; OCP: 20 ± 2 years | 16 | 8 | 8 | recreationally active individuals (exercised >3 days per week for 30 minutes per session) who currently participated in formally scheduled team sports |
| **8** | Jürimäe et al. | 2010 | NOCP: 18.3 ± 1.6; OCP: 21.0 ± 2.6 | 24 | 15 | 9 | female rowers |
| **9** | Nakamura et al. | 2020 | 23.0 ± 4.1 years | 10 | | 10* | various sports groups (two to middle distance running groups; two to archery groups; and one each to soccer, ski-alpine, kayaking, bobsledding, short track and fencing groups). |
| **10** | Rechichi et al. | 2007 | 34 ± 7 years | 13 | | 13 | female cyclists or triathletes |
| **11** | Vaiksaar et al. | 2011a | Non-OCP competitive athletes : 18.8 ± 2.1 years; Non-OCP recreationally athletes: 18.0 ± 0.9 years, OCP recreationally athletes: 21.0 ± 2.6 years | 24 | 15 | 9 | female rowers divided into competitive cyclic athletes (n = 8), recreationally trained cyclic athletes (n = 7), and recreationally trained athletes |
| **12** | Vaiksaar et al. | 2011b | 21.0 ± 2.6 years | 8 | | 8 | recreationally trained female rowers |

* OCP users did not intake OCPs at the beginning of the study but started as an intervention
OCP oral contraceptive pill, non-OCP no intake of oral contraceptive pill

Two groups, the group of OCP users as well as the group of non-OCP users, need to be focused on in this systematic review to answer the research questions. Also, the ratio between the groups is of interest. In two studies the sample is half of both groups, in four studies the group of non-OCP users is bigger and in one study the group of OCP users is bigger. The illustration shows the ratio and the sample sizes in a diagram (figure 5).

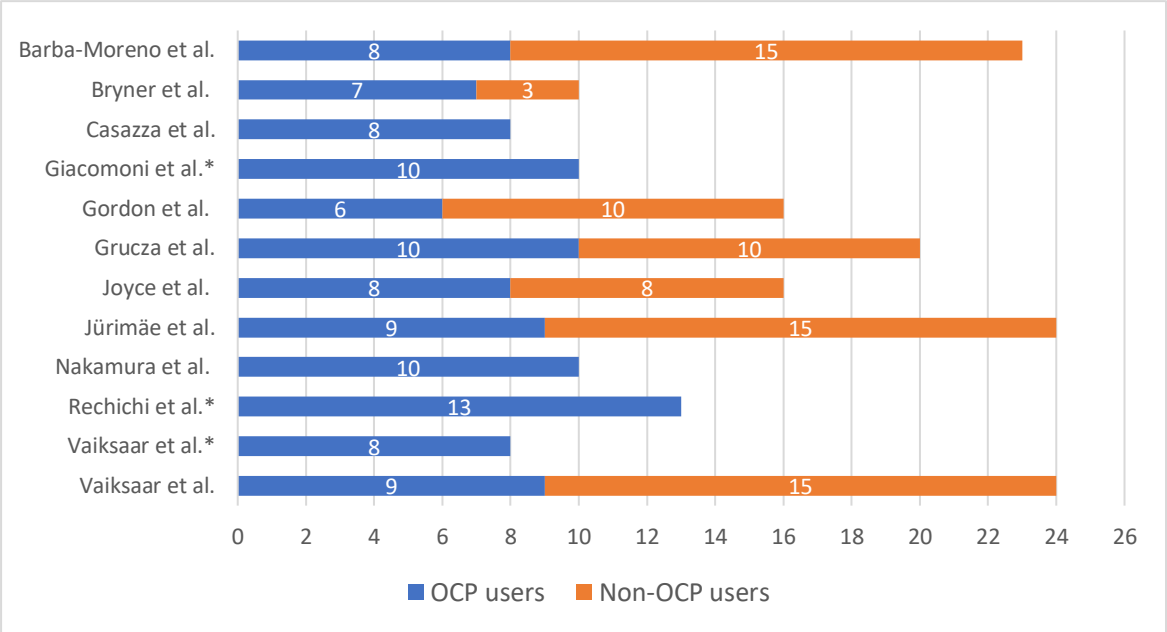


*Figure 5: Number of participants and ratio between OCP users and Non-OCP users (*longitudinal-interventional study, groups are pre-post intervention)*

**Exercise protocols**

According the performance tests, different test protocols have been used. The exercise modes were running on treadmills and cycling or rowing on ergometers and the protocols included submaximal and also incremental protocols. In three submaximal tests the intensity was calculated as a ratio of $\dot{V}O_{2max}$: 50% of $VO_{2max}$ for 45 min [6], 70% of $VO_{2max}$ for 1 h [12], and three different stages at 50%, 60% and 65% of $VO_{2max}$ each for 4 min [4]. In another study the intensity of the submaximal test was calculated by maximal aerobic speed and participants had to run at 75% for 40 min [1]. The intensity of another submaximal test protocol had been chosen at 40% and 80% of the power output achieved at the aerobic threshold, which had to be cycled for 6 min. Additionally, another 6 min had to be cycled at 50% of the delta of the power output at aerobic treshold and peak power output [7]. Another endurance test was set for 1 h at greatest average power output [10].

For the incremental tests two protocols were not until volitional exhaustion: One study on the cycling ergometer was until 4 mmol/L blood lactate concentration starting at 60 W and an increment of 30 W every 3 minutes [9] and another one with participants running on the treadmill until 80% of maximum heart rate [1]. All the other incremental tests were until volitional exhaustion: Two studies with incremental tests on rowing ergometer started with 40 W and increased by 15 W every minute. Using cycling ergometers, start was set either at 30 W with increment of 20 W every minute [7], or starting at 50 W with an increment of 25 W/min [5], or start at 75 W with increment of 25 W every 3 minutes [3].

**Timing of menstrual cycle phases**

Data collection of the studies was chosen to compare phases or hormone statuses during the menstrual cycle. The timing differed between the studies and therefore phases of menstrual cycle or even more detailed, days of the menstrual cycle, were reported. In OCP users most studies tested on two timepoints. In days 2-5 (withdrawal) and days 17-18 (OCP intake) [12], in days 3-7 (withdrawal) and days 14-18 (OCP intake) [1]; or in day 2 and day 5 (both in withdrawal) [7], or between day 8 ± 3 (withdrawal) and day 20 ± 2 (OCP intake) [8, 11], days 2-5 (withdrawal) and days 10-22 (OCP intake) [9], in days 5-8 (withdrawal) and 18-24 (OCP intake) [6]. In one study only, phases but not exact days were reported, and it was described that FP and LP have been compared [2]. In another three studies three or four timepoints in menstrual cycle have been tested and compared, in days 2-4 (withdrawal), days 7-9, and days 19-21 (both OCP intake) [4]; in days 2-3, days 6-7 (both in withdrawal) and days 13-17 (OCP intake) [10]; or in days 1-3 (withdrawal), days 9-11, days 19-20, and 27-28 (all OCP intake) [5].

In non-OCP users most studies tested two times during the cycle. Timing of tests was on day 7 ± 1 (FP) and 21 ± 1 (LP) [3]; days 5-8 (FP) and days 18-24 (LP); day 2 (FP) and day 5 (FP) [7]; day 8 ± 3 (FP) and day 20 ± 2 (LP) [8]; days 4-8 (FP), days 19-29 (LP) [9]; day 8 ± 3 (FP) and day 20 ± 2 (LP) [11]. In one paper the days were not reported but luteal phase has been compared to follicular phase [2]. In one study three timepoints were compared, days 2-4 (FP), days 7-9 (FP), and days 19-23 (LP) [1]. One study tested four timepoints, days 1-3 (FP), days 9–11 (FP), days 19-20 (LP) and days 27-28 (LP) [5].

*Table 7: Test protocols*

| Code | Author | Year | Exercise | Type of test and device | Test protocol | Timing of data collection in menstrual cycle |
|---|---|---|---|---|---|---|
| **1** | Barba-Moreno et al. | 2019 | running | submaximal test on treadmill | 40 minutes of continuous running at 75% of max. aerobic speed | 2x in OCP: OCP use (day 14-18) and WITH (day 3-7) and 3x in Non-OCP: early FP (day 2-4), mid of FP (day 7-9) and LP (days 19-23) |
| **2** | Bryner et al. | 1996 | running | incremental test on treadmill | start at 6.4 km/h for women (and 8.1 km/h for men for 3 minutes), then + 0.8 km/h every 5 minutes at elevation 5% until subject reached 80% of maximum heart rate | 2x in OCP: LP and FP (day n.a.) 2x bei Non-OCP: LP and FP (day n.a.) (expected to be one cycle inbetween testing time points) |
| **3** | Casazza et al. | 2002 | cycling | incremental test on cycling ergometer | start at 75 W, + 25 W every 3 minutes until volitional exhaustion | 2x Non-OCP in FP (day 7 ± 0.7) and LP (21 ± 1.1) /same participants after 4 months OCP use 2x: during OCP intake (day 26 ± 0.39) and in WITH (day 6 ± 2.0) |
| **4** | Giacomoni et al. | 2000 | running | submaximal test on treadmill | 3x 4 minutes of continuous running at 50%, 60% and 65% of $VO_{2max}$ | 3x in OCP users: WITH (days 2-4), early OCP (days 7-9) and late OCP (days 19-21) |
| **5** | Gordon et al. | 2017 | cycling | incremental test on cycling ergometer | start at 50 W for 1 minute, then + 0.42 W/s[1] (= about 25W/min) until volitional exhaustion | 4x in OCP and 4x in Non-OCP: both at (Menstruation/WITH (day 1-3), mid of FP (days 9–11), mid of LP (day 19-20) and pre-menstruation/pre WITH (day 27-28) |
| **6** | Grucza et al. | 1993 | cycling | submaximal test on cycling ergometer | 45 minutes of continuous cycling at 50% of $VO_{2max}$ | 2x in OCP and 2x in Non-OCP: both at FP (days 5-8) and LP (days 18-24) |
| **7** | Joyce et al. | 2013 | cycling | Incremental and submaximal test on cycling ergometer | • Start at 30 W for 3 minutes, then + 20 W every minute until exhaustion<br>• 3 constant-load work stages:<br>first work stage: 6 minutes at 40% of power output achieved at the aerobic threshold<br>second work stage: 6 minutes 80% of power output achieved at the aerobic threshold<br>third work stage: till exhaustion; 50% of the difference between power output achieved at aerobic threshold and peak power output | 2x in OCP: WITH 1 (day 2) and WITH 2: (day 5) and 2x in Non-OCP Users: FP 1 (day 2) and FP 2 (day 5) |
| **8** | Jürimäe et al. | 2010 | rowing | incremental test on rowing ergometer | start at 40 W, + 15 W every minute until volitional exhaustion | 2x in OCP and 2x in Non-OCP: both at FP (day 8 ± 3) and LP (day 20 ± 2) |
| **9** | Nakamura et al. | 2020 | cycling | incremental test and wingate on cycling-ergometer | start at 60 W, + 30 W every 3 minutes until 4 mmol blood lactate and 30 s wingate anaerobic test | before intervention of 3 months OCP 2x Non-OCP: early FP (days 4-8), mid of LP 19-29; 2x in OCP: WITH (days 2–5) and OCP (10–20 days of OC use) |
| **10** | Rechichi et al. | 2007 | cycling | time-trial on cycling ergometer | 1 h cycling test at highest average power output | 3x OCP: WITH 1 (day 2-3), WITH 2 (day 6-7) and OCP use (day 13-17) |
| **11** | Vaiksaar et al. | 2011a | rowing | incremental test on rowing ergometer | Start at 40 W; + 15 W every minute until voluntary exhaustion | 2x in OCP and 2x Non-OCP: both at FP (day 8 ± 3) and LP (day 20 ± 2) |
| **12** | Vaiksaar et al. | 2011b | rowing | submaximal test on rowing ergometer | 1 h continuous rowing at 70% of $VO_{2max}$ | 2x in OCP users: during WITH (day 2 to 5), OCP intake (day 14-18), |

$VO_{2max}$ maximum oxygen consumption, W Watt, h hour, OCP oral contraceptive pill, non-OCP no intake of oral contraceptive pill, FP follicular phase; LP lputeal phase; WITH OCP Withdrawal, counted and reported in a different way in the paper starting to count the days at another timepoint of the cycle

The selected research papers used combined OCPs with a combination of synthetic estrogen and synthetic progesterone. In all pills ethinyl estradiol was used as the synthetic estrogen (range of 20-40 µg). In progesterone the type of hormone varied between levonorgestrel, dienogest, drosperenone, gestodene, norethindrone, norgestimate, desogestrel, cyproterone and norethisterone (range of 75-3000 µg). Two of the twelve papers used triphasic pills, with different dose of synthetic hormones each week. One triphasic OCP had a stable dose of estrogen but increased synthetic progesterone each week [3]. In the second type of triphasic pills the estrogen dose was increased in the second week, while the dose of progesterone was a bit higher each of the three weeks [6]. The other ten papers used combined monophasic pills which means that dose of hormones does not vary throughout the circle (Table 7).

Further, the methodology of the papers varied in terms of controlling the menstrual cycle to have the right timing of the testing days. Most methodologies used menses protocols and were counting the days [1-5,9]. Ovulation was often expected to be at half of the cycle duration. To verify the menstrual phase detection many studies took additionally blood samples to measure the hormone status at testing days [1,3,4,7-12]. Which blood parameter had been analysed can be seen in the table below of the measured parameter (table 8). Additionally, one study confirmed ovulation by ultrasound diagnostic [2] or by estimation of basal body temperature [6].

*Table 8: Oral contraceptive pills*

| Code | Author | Type of OCP | Type of synthetic estrogen | Type of synthetic progesteron | Measurement of timing of menstrual cycle |
|---|---|---|---|---|---|
| **1** | Barab-Moreno et al. | monophasic pill | 20-30 µg ethinyl estradiol | 100 µg levonorgestrel, 2000 µg dienogest, 3000 µg drosperenone, 75 µg gestodene | protocol of previous 4 cycles standardised number of days from first day of menses predicted ovulation; blood samples in each menstrual phase |
| **2** | Bryner et al. | monophasic pill | 35 µg ethinyl estradiol | 1000 µg norethindrone | after review of menstrual history, estimated expected day of ovulation by average cycle length divided by two; serial transobdimal ultrasound to confirm ovulation |
| **3** | Casazza et al. | triphasic pill | 35 µg ethinyl estradiol at all days | day 1-7: 180 µg norgestimate, day 8-14: 215 µg norgestimate, day 15-21: 250 µg norgestimate | counting days after menses and ovulation, which was confirmed by blood samples |
| **4** | Giacomoni et al. | monophasic pill | 20-30 µg ethinyl estradiol | 150 µg desogestrel or 75 µg gestodene | counting days of OCP use |
| **5** | Gordon et al. | monophasic pill | 30 µg ethinyl estradiol | 150 µg levonorgestrel | OCP: diary of two consecutive menstrual cycles, non-OCP: blood samples |
| **6** | Grucza et al. | triphasic pill | day 1-6: 30 µg ethinyl estradiol, day 7-11: 40 µg ethinyl estradiol, day 11-21: 30 µg ethinyl estradiol | day 1-6: 50 µg levonorgestrel, day 7-11: 75 µg levonorgestrel, day 11-21: 125 µg levonorgestrel | measurement of basal body temperature (oral/ rectal) early in the morning during at least one menstrual cycle before; temperature charts used for estimating LP and FP (a priori) |
| **7** | Joyce et al. | monophasic pill | 30-35 µg ethinyl estradiol | 200 µg cyproterone or 150 µg levonorgestrel | Resting venous blood samples |
| **8** | Jürimäe et al. | monophasic pill | 20 µg ethinyl estradiol | 75 µg gestodene | menstrual cycle phases confirmed by blood samples (in LH prog level has to be higher than 16 nmol/l) |
| **9** | Nakamura et al. | monophasic pill | 20 µg ethinyl estradiol | 1000 µg norethisterone | counting days of OCP and blood samples |
| **10** | Rechichi et al. | monophasic pill | 20-35 µg ethinyl estradiol | 100-150 µg levonorgestrel, 2000 µg cyproterone acetate, 1000-500 µg norethisterone, 150 µg desogestrel, 3000 µg drospirenone | blood samples were taken |
| **11** | Vaiksaar et al. | monophasic pill | 20 µg ethinyl estradiol | 75 µg gestodene | blood samples were taken |
| **12** | Vaiksaar et al. | monophasic pill | 20 µg ethinyl estradiol | 75 µg gestodene | blood samples were taken |

LP luteal phase, FP follicular phase, OCP oral contraceptive pill, non-OCP no intake of oral contraceptive pill

The collected exercise parameters were mainly obtained through respiratory gas analysation. Various parameters concerning $O_2$ uptake, carbon dioxide production, breathing frequency but also heart rate and power output have been measured. Exact parameters are listed in table 9. Concerning the anthropometric parameter in almost all studies (except [2]) body mass and body statue has been measured. Additionally, parameter to assess body composition, bone mineral density and gynaecological information such as age of menarche have been collected. In one study [2] no such parameters were assessed. The blood parameter which were measured most often were estradiol and progesterone, two studies measured additionally LH and FSH [1, 9], and adiponectin, osteocalcin, a bone turnover marker called collagen type I carboxy terminal telopeptide (ICTP), insulin, glucose and homa have been collected in one study [8]. Three studies [2,4,6] did not measure any blood parameters at all.

*Table 9: Measured parameter of exercise, anthropometry and blood samples*

| Code | Author | Exercise parameter | Anthropometric parameter | Blood parameter |
|---|---|---|---|---|
| **1** | Barab-Moreno et al. | $VO_2$, $VO_{2peak}$, $VCO_2$, HF, VE, VT, BF, EO, $EqO_2$, $EqCO_2$, BF, tidal volume | body composition, height, body mass, body fat mass, total body fat mass, free fat mass (using DEXA) | estradiol, progesterone, FSH, LH |
| **2** | Bryner et al. | $VO_2$, $VCO_2$, BF, VE | n/a | n/a |
| **3** | Casazza et al. | PO, time, HR, VE, $VO_{2peak}$, $VO_{2peak}$/body mass, $VO_{2peak}$/lean body mass, $VCO_{2peak}$/body mass, RER | body statue, body mass, body fat, lean body mass, fat mass | estradiol, progesterone |
| **4** | Giacomoni et al. | HF, VE, $VO_2$, $VO_2$/body mass, $VCO_2$, RER, $VE/VO_2$, $VE/VCO_2$, | body statue, body mass, sum of skinfolds | n/a |
| **5** | Gordon et al. | $VO_{2max}$, $VO_{2max}$/body mass, $VCO_{2max}$/body mass, VEmax, HFmax, RERmax, GET, GET/$VO_{2max}$%, exercise time, PO | body statue, body mass, | estradiol, progesterone |
| **6** | Grucza et al. | $VO_{2max}$/body mass, 50% of $VO_{2max}$, delta in HR | body statue, body mass, body surface area | n/a |
| **7** | Joyce et al. | $VO_{2peak}$, RER, VE, HR, PO, $VO_2$AT, AT | age of menarche, body statue, body mass, BMI | estradiol, progesterone |
| **8** | Jürimäe et al. | $VO_{2max}$, $VO_{2max}$/body mass, energy intake, | age of menarche, body statue, body mass, BMI, body fat, fat mass, fat free mass | estradiol, progesterone, adiponectin, osteocalcin, ICTP, insulin, glucose, homa |
| **9** | Nakamura et al. | Lactate, $VO_{2max}$, $VO_2$/body mass, VEmax, HRmax, peak lactate, exercise time | body statue, body mass, body fat, circumferences of upper and forearm, thigh, calf, waist and hip | estradiol, progesterone, FSH, LH |
| **10** | Rechichi et al. | Lactate, PO, HR, %peak heart rate, RPE, VE, $VO_2$, %$VO_{2peak}$, blood glucose, RER | body mass, sum of skinfolds | estradiol, progesterone |
| **11** | Vaiksaar et al. | POmax, $VO_{2max}$, $VO_{2max}$/body mass, VE, $VO_2$, $VCO_2$, RER, HRmax, Peak lactate, delta of lactate | age of menarche, gynaecological age, height, body mass, BMI, body fat, fat mass, fat-free mass, bone mineral content, bone mineral density (using DEXA), | estradiol, progesterone |
| **12** | Vaiksaar et al. | PO, VE, $VO_2$, $VO_{2max}$, $VO_{2max}$/body mass, $VO_2$AT, % of $VO_{2max}$, HR, La, RER, carbohydrate energy expenditure, lipid energy expenditure, total energy expenditure | body mass, body fat, fat mass, fat free mass, bone mineral density, bone mineral content (using DEXA) | estradiol, progesterone |

BMI body mass index, AT aerobic threshold, PO power output, HR heart rate, $VO_2$ oxygen uptake, $VO_{2max}$ maximum oxygen uptake, $VO_{2peak}$ peak oxygen uptake, $VCO_2$ carbon dioxide production, BF breathing frequency, VT ventilatory treshold, VE ventilatory equivalent for oxygen, RPE rating of perceived exertion, RE running economy, RER Peak respiratory exchange ratio, VE peak minute expired ventilation, ICTP a bone resorption marker, OCP oral contraceptive pill, non-OCP no intake of oral contraceptive pill

## *3.3 Results of the selected studies*

The following section describes the results of the selected studies. Body statue of the participants ranged between 163.9 and 174.0 m and body mass were between 56.6 and 69.6 kg. $VO_{2max}$ or $VO_{2peak}$ at the baseline or at the first testing timepoint gives an overview on the training status and the endurance capabilities of the samples. It has been reported relative and absolute values and was between 39.4-53.0 ml/min/kg (or 2.13 l/min were $O_2$ uptake per kilogram body mass has not been estimated). Exact data on these parameters can be seen in table 10.

*Table 10: Data on body statue, body mass and $O_2$ uptake at baseline or first data collection time point*

| Code | Author | body statue | body mass | $VO_{2max}$ at baseline or first measurement timepoint |
|---|---|---|---|---|
| **1** | Barba-Moreno et al. | OCP: 1.64 ± 0.09 m; Non-OCP: 1.63 ± 0.06 m; | OCP: 59.3 ± 6 kg; non-OCP: body mass 58.1 ± 5.2 kg | OCP: 51.7 ± 3.9 ml/min/kg; non-OCP: 50.3 ± 3.6 ml/min/kg * |
| **2** | Bryner et al. | n/a | n/a | 40.2 ml/min/kg |
| **3** | Casazza et al. | 1.64 ± 0.02 m | 59.4 ± 2.3 kg | 42.3 ± 3.3 ml/min/kg |
| **4** | Giacomoni et al. | 1.67 ± 0.05 m | 56.6 ± 6.8 kg | n/a |
| **5** | Gordon et al. | non-OCP: 1.70 ± 0.06 m; OCP: 1.68 ± 0.07 m | non-OCP: 68.7 ± 7.9 kg; OCP: 61.6 ± 6.8 kg | 44.9 ± 5.0 ml/kg/min |
| **6** | Grucza et al. | OCP: 1.68 ± 0.09 m; non-OCP: 1.67 ± 0.02 m | OCP: 62.3 ± 0.6 kg; non-OCP: 62.3 ± 2.1 kg | OCP: 39.4 ± 1.2 ml/kg/min, non-OCP: 40.2 ± 1,7 ml/kg/min |
| **7** | Joyce et al. | non-OCP: 1.68 ± 0.05 m; OCP: 1.65 ± 0.05 m | non-OCP: 63.0 ± 7.9 kg; OCP: 60.1 ± 5.7 kg | 2.13 ± 0.20 l/min |
| **8** | Jürimäe et al. | non-OCP: 1.72 ± 0.05 m; OCP: 1.73 ± 0.04 m | non-OCP: 67.5 ± 8.8 kg; OCP: 69.6 ± 12.7 kg | OCP: 45.2 ± 5.7 ml/kg/min, non-OCP: 47.2 ± 7.9 ml/kg/min |
| **9** | Nakamura et al. | 1.60 ± 0.06 m | 57.7 ± 10.1 kg | 41.8 ± 6.1 ml/kg/min |
| **10** | Rechichi et al. | n/a | 61.6 ± 15.3 kg | 53.0 ± 5.6 ml/kg/min |
| **11** | Vaiksaar et al. | non-OCP competitive athletes: 1.74 ± 0.04 m; non-OCP recreationally athletes: 1.70 ± 0.05 m; OCP recreationally athletes: 1.73 ± 0.04 m | non-OCP competitive athletes: 69.0 ± 10.7 kg; non-OCP recreationally athletes: 65.7 ± 6.5 kg; OCP recreationally athletes: 69.6 ± 12.7 kg | 45.2 ± 5.7 ml/kg/min |
| **12** | Vaiksaar et al. | 1.73 ± 0.04 m | 69.6 ± 2.3 kg | 44.3 ± 5.5 ml/kg/min |

***** $VO_{2peak}$
$VO_{2max}$ maximum oxygen uptake, OCP oral contraceptive pill, non-OCP no intake of oral contraceptive pill

Concerning the differences between OCP users and non-OCP users, significant differences have been found in four studies [3, 7, 9, 11] and another four studies did not measure these group differences [1, 4, 10, 12]. An intervention study found significant differences after four months of OCP use. Time to peak and $PO_{peak}$ were decreased significantly after the intervention [3]. On the other hand, for spirometry parameters differences have been found. It has been noticed that in each participant $VO_{2peak}$ and $VCO_{2peak}$ decreased (but interference statistic showed no significant results) [3]. Further, $VO_2$peak and $VO_2$ at AT were higher in the non-OCP group than in the OC group [7]. Relative $VO_{2max}$ mass was significantly lower in LP of OCP users than in non-OCP [11]. RER at AT was significantly higher in LP in OCP users than in non-OCP group [11]. Relative $VO_{2max}$ mass was significantly higher in mid FP than in non-OCP. Difference of $VO_2$ was significantly higher in WITH of OCP users than in menstruation phase of non-OCP users at all eight stages [5]. In some studies, no significant effects in maximal $O_2$ uptake have been found [2, 3, 6, 9]. HR was significantly lower

in LP of OCP users than in non-OCP [11]. In the competitive non-OCP users $PO_{max}$ values were significantly higher than in OCP users [11]. The peak blood lactate (LA) was higher during the OCP cycle than during the menstrual cycle [9].

Exercise performance parameters have been estimated and compared between cycle phases of OCP users. No significant differences between cycle phases of OCP users have been found in several studies [2,3,6,7,8,9,12]. Significantly higher values for VE have been found in OCP intake than in WITH [1, 11], $VE/O_2$ [1, 4, 11], breathing frequency (BF), $VE/CO_2$ [1], RER [4], mean LA and RPE [10]. Also, significantly higher values in WITH than in OCP intake have been found for $VO_2$, running economy (RE) and energy expenditure irrespective of exercise intensity [4]. In a study which did not compare OCP intake with WITH but compared LP and FP following result has been found: $VE/VCO_2$ were significantly higher in LP than in FP of OCP users [11].

When studies summed up their findings on the influence of OCP phases on physical performance, most concluded that there is no need to consider cycling phases in competition [1,2,7,8,9,10,11,12]. Anyway, there were some differences which need to be considered and had been mentioned in the conclusions. For example, in one study it was mentioned that low dose-triphasic OCPs appeared to decrease peak exercise performance [3] and that $O_2$ uptake was decreased during the period of OCP intake [4]. Further, the interaction between estrogen and $O_2$ extraction [5] was mentioned and that OCP enables a more uniform exercise due to less variations in sweating and body temperature [6] (see table 11).

*Table 11: Results of the influence of oral contraceptive pill on exercise performance*

| Code | Author | Differences between OCP and non-OCP | Differences between OCP Phases | Conclusion |
|---|---|---|---|---|
| **1** | Barba-Moreno et al. | n/a | **VE, BF, $VE/O_2$, and $VE/CO_2$ were significantly higher in OCP intake than in WITH.** | Use of OCP did not influence maximum or endurance test performance. No need to avoid OCP use in athletes. OCP use has many other benefits on athletes. |
| **2** | Bryner et al. | No significant differences have been found. | No significant differences have been found. | Low does OCP does not affect the performance in maximal treadmill tests. |
| **3** | Casazza et al. | **After 4 months of OCP use, time to peak power output and $PO_{peak}$ decreased significantly.** In all participants $VO_{2peak}$ decreased (in L/min and in mL/kg/min) and in $CO_{2peak}$ production but not significantly. | No significant differences have been found. | Endogenous hormones have little effect on endurance exercise performance and low dose-triphasic OCPs appear to decrease peak exercise performance. |
| **4** | Giacomoni et al. | n/a | **$VO_2$, RE and energy expenditure were significantly higher in WITH than in both OCP phases irrespective of exercise intensity. RER and $VE/VO_2$ were significantly higher in both OCP phases than in WITH.** | O2 uptake was decreased during the period of OCP intake. Better running economy during OCP usage possibly due to biomechanical factors. |
| **5** | Gordon et al. | **$VO_{2max}$/body mass was significantly higher in mid FP than in non-OCP. Diff. of $VO_2$ was significant higher in WITH of OCP users than in menstruation phase of non-OCP at all stages (30%, 40%, 50%, 60%, 70%, 80%, 90% and $VO_{2max}$).** | No significant differences have been found. | Although there was no change in $VO_{2max}$, the $VO_2$ plateau was affected and almost non-existent. The findings support the hypothesis for interaction between estrogen and O2 extraction at the muscle. |
| **6** | Grucza et al. | No significant difference has been found. | No significant differences have been found. | In non-OCP users performing moderate exercise a greater threshold and larger gains for sweating appeared in LP than in FP. These effects were reduced in OCP users which responses in more uniform exercise. |
| **7** | Joyce et al. | **$VO_{2peak}$ and $VO_2$ at AT were higher in the non-OCP group than in the OC group.** When AT was expressed as a percentage of $VO_{2peak}$, there were no differences between groups. RER, VE, peak HR, and peak PO were not different between OCP and non-OCP. There were no differences in HR, VE, [LA], RPE (at any stage), cycling economy or time-to-exhaustion. | No significant differences have been found. | Despite a reduction in $VO_{2peak}$ and $VO_2$ at AT long-term OCP use does not influence endurance exercise. |
| **8** | Jürimäe et al. | No significant differences have been found. | No significant differences have been found. | Results showed no significant effect on aerobic capacity. |
| **9** | Nakamura et al. | **Peak LA was higher during the OCP cycle than during the menstrual cycle**. There were no significant differences in PO and HR at a blood lactate concentration of 2 and 4 mmol/L between the menstrual and OCP cycle phases. There were no significant differences in $VO_{2max}$, $VO_{2max}$/body mass, $VE_{max}$, $HR_{max}$, peak LA concentration and time-to-exhaustion between non-OCPs and OCP cycle phases. | No significant differences have been found. | Intake of monophasic OCPs did not alter aerobic parameters. Peak blood lactate after wingate test was significantly higher when OCP has been consumed. |
| **10** | Rechichi et al. | n/a | **VE and $VE/VO_2$ were significantly higher during OCP intake compared to both WITH. Mean LA and RPE were higher in OCP intake than in WITH.** | Female athletes taking a monophasic OCP do not need to be concerned about the timing of their cycle to optimised endurance performance and competition. |

| | | | | |
|---|---|---|---|---|
| **11** | Vaiksaar et al. | **$PO_{max}$ in the competitive non-OCP users were significantly higher than in both phases of OCP users. HR and $VO_{2max}$/body mass were significantly lower in LP of OCP users than in non-OCP. RER at AT was significantly higher in LP in OCP users than in non-OCP.** No significant differences were found in $VO_{2max}$, VE, $VE/O_2$, $HR_{max}$, peak La, and ΔLa values. | **$VE/VCO_2$ were significantly lower in FP than in LP in OCP users.** | No influence of OCP intake on maximum load or aerobic performance neither between phases nor between users and non-users. Some influences on ventilatory response values should be considered in results of OCP but there is no need to consider cycling phases in competition. |
| **12** | Vaiksaar et al. | n/a | No significant differences have been found. | No significant effect on substrate oxidation and blood lactate concentration have been observed in OCP phases when exercising slightly over 70% $VO_{2max}$. |

Significant effects are in fat letters

Blood hormones were compared between OCP users and non-OCP users. Estrogen levels have been significantly lower during OCP intake than during withdrawal [1,10]. Estradiol was significantly lower in early withdrawal than in late withdrawal [10]. But, also no significant differences between cycle phases have been found [8,11,12]. Further, blood hormones were compared between phases of OCP users. Estradiol and progesterone were significantly higher in non-OCP users than in OCP users [3,7,8, 11]. Also, in progesterone differences have been found, in LP and estrogen was higher in non-OCP than in OCP [8]. But, also no significant differences have been found [9].

In most studies no significant differences have been found in anthropometric parameters concerning OCP intake and OCP phases [1,4,7,10,11,12]. Anyway, the intervention of OCP intake for four months led to a significant increase in body mass and fat mass [3]. Further, waist circumference was significantly lower in OCP use than in non-OCP use [9]. For bone markers significant differences were found in blood samples. ICTP and osteocalcin were lower in OCP than in non-OCP users [8] (see table 12).

*Table 8: Results of blood hormones and anthropometric parameter*

| Code | Author | Results in blood hormones | Results in anthropometric parameter |
|---|---|---|---|
| **1** | Barba-Moreno et al. | **Significant higher estrogen level in WITH than during OCP intake.** | No significant differences |
| **2** | Bryner et al. | n/a | n/a |
| **3** | Casazza et al. | **Significantly higher estradiol and progesterone levels have been found in LP of non-OCP than in OCP intake.** | **After 4 months of OCP use significant increase of body mass and fat mass.** |
| **4** | Giacomoni et al. | n/a | No significant differences |
| **5** | Gordon et al. | n/a | n/a |
| **6** | Grucza et al. | n/a | n/a |
| **7** | Joyce et al. | **Estradiol was significantly higher in non-OCP than in OCP.** There was no difference in progesterone between groups. | No significant differences |
| **8** | Jürimäe et al. | **Progesterone in LP and estrogen was higher in non-OCP than in OCP.** It was not different between OCP Phases. Progesterone was similar in both groups in FP. | **In osteocalcin and in ICTP were lower in OCP than in non-OCP.** |
| **9** | Nakamura et al. | Estradiol, progesterone, FSH and LH levels were lower in the OC cycle compared to non-OCP. No significant differences have been found. | **Waist circumference was significantly lower in OCP cycle phase than during non-OCP cycle.** The other circumferences did not differ. |
| **10** | Rechichi et al. | **Estradiol was significantly higher in late WITH than in early WITH and OCP intake.** | No significant differences |
| **11** | Vaiksaar et al. | **Estradiol concentrations were higher in non-OCP than in OCP. Progesterone in LP was significantly higher in non-OCP than in OCP users.** Estradiol did not differ between phases of OCP Users. | No significant differences |
| **12** | Vaiksaar et al. | In estradiol and progesterone no significant differences have been found between OCP phases. | No significant differences |

Significant effects are in fat letters, X has not been assessed, FP follicular phase, LP lutea phase, OCP oral contraceptive pill, non-OCP no intake of OCP

# 4 Discussion

The results of this systematic research aimed to analyse the influence of OCPs on endurance performance of healthy, trained female athletes. The analysis showed that 12 clinical trials met the inclusion criteria and analysed the influence of OCP use on aerobic capacity comparing at least two phases of oral contraceptive cycle. Three of the trials observed the initiation of OCP intake by methodology of a long-term research. The major finding of this systematic research was that most studies suggest that endurance performance is not affected by the use of OCPs. Anyway, some significances in physiological parameters have been found. Lower $O_2$ uptake and better running economy has been detected in phase of OCP intake (Giacomoni & Falgairette, 2000) while $VO_2$ plateau was affected (Gordon et al., 2018). Even in studies with significant differences between oral contraceptive phases it is suggested that timing of oral contraceptive cycle needs to be considered to optimise endurance performance and competition (Rechichi et al., 2008; Vaiksaar et al., 2011a). Further, it is suggested that starting the intake of OCPs might lead to decrease in performance (Casazza et al., 2002) and higher peak blood lactate (Nakamura & Nose-Ogura, 2021). Type of OCPs and ingredients might influence the different results in various trials. When it comes to anthropometric measurements, these were only found in few studies between OCP users and non-OCP users (Casazza et al., 2002; Jurimae et al., 2011; Nakamura & Nose-Ogura, 2021).

## *4.1 Comparison of OCP phases*

The majority of studies concluded, that the intake of OCPs did not influence endurance performance in female athletes through cycle phases (Barba-Moreno et al., 2019; Bryner et al., 1996; Casazza et al., 2002; Grucza et al., 1993; Joyce et al., 2013; Jurimae et al., 2011; Nakamura & Nose-Ogura, 2021; Vaiksaar et al., 2011b). For example, in an one-hour submaximal test no significant variations were suggested to be influenced by sex hormones (Vaiksaar et al., 2011b). Anyway, in some studies, significant differences between OCP phases have been found. These parameters and the possible explanations for these differences are discussed in the following paragraphs. At this point it should be mentioned that an interaction of these suggestions might be possible as well.

*Increased ventilation frequency by progesterone*

Significant differences between oral contraceptive phases were found in monophasic OCP use. VE, BF, $VE/O_2$, and $VE/CO_2$ were significantly higher in the phase of OCP intake than in withdrawal (Barba-Moreno et al., 2019). These results go along with those of Rechichi et al. (2008) which found significant difference in VE and $VE/O_2$, and they further agree that endogenous progesterone levels were low.

Consequently, exogenous progesterone is suggested to play a role in physiological performance. An impaired aerobic capacity and a lower ventilatory efficiency is suggested in OCP delivery phases (Barba-Moreno et al., 2019). But in both studies $VO_2$ and % of $VO_{2peak}$ did not differ significantly between OCP phases. A decrease in $O_2$ uptake has been found in OCP intake phases. $VO_2$, RER and energy expenditure were significantly higher in withdrawal than in both OCP intake phases irrespective of exercise intensity. RER and $VE/VO_2$ were significantly higher in both OCP phases than in withdrawal. The authors explained this phenomenon by a reduced $O_2$ uptake for a given value of VE. In earlier studies endogenous progesterone and also some exogenous ones, were suggested to evaluate suggested that the used third-generation OCP containing gestodene and desogestrel as progesterone might not have the same effect on ventilation, because VE did not vary between OCP phases (Giacomoni & Falgairette, 2000). The supplementation of progesterone might stimulate ventilation in patients with pulmonary disease but is not suggested to influence respiration in a form that effects athletic performance (Bryner et al., 1996).

Beside progesterone, also estrogen is suggested to have cardiorespiratoric effects. But it is suggested that exogenous and endogenous estrogen has different effects on the female body and therefore these effects are not suggested in exogenous estrogen (Barba-Moreno et al., 2019). This goes along with the results on HR which has not been significantly affected in the selected studies. This is in accordance with research in monophasic OCPs (Giacomoni & Falgairette, 2000) and in triphasic OCPs (Lebrun et al., 2003).

*Shift in substrate use from carbohydrate to fat use*

Giacomini et al. (2000) explained the higher $VO_2$ and RER by a change in substrate use. An increase in carbohydrate metabolism as an energy source has been suggested when participants were using OCPs or on the other hand, a shift from carbohydrate metabolism to lipids when in withdrawal. Somehow this explanation of Giacomoni et al. (2000) is in contrary to Gordon et al. (2018) which suggested a shift to a higher use of fatty acids as an energy source when OCP were used. Vaiksaar et al. (2011b) and Rechichi et al. (2008) supported the hypothesis of a shift in substrate metabolism to increased fat oxidation and decreased carbohydrate oxidation in active pill phase of OCP users. While in the results of Vaiksaar et al. (2011b) only a tendency but no significant evidence has been found, Rechichi et al. (2008) even hypothesized optimal endurance performance during OCP intake phase. Glycogen metabolism is reduced, and blood lactate is accumulated. A suppression of fatigue might enable to sustain a higher power output. Specific parameter ($VO_2$/VE, VE and blood lactate) might be influenced (increased in luteal phase of non-OCP users and pill consumption phase of OCP users) due to the variation of endogenous progesterone/exogenous progestogen and might therefore be carefully interpreted in performance tests. But it is of importance to mention that even Rechichi et al. (2008) concluded no change in performance. There might be shifts in substrate use but as the output for

performance is not impinged, they recommend athletes that there is no need to be concerned about the timing of their cycling concerning competition.

When it comes to blood lactate, a significant higher mean blood lactate was found in OCP consumption phase compared to withdrawal, but the authors reported that the difference of only 1 mmol/L between a status of 5 and 6 mmol/L might not be physiologically relevant. It might even have been an error in measurement. The authors did not further explain a physiological explanation for this change (Rechichi et al., 2008).

*Biomechanical influences on stiffness by estrogen*

Another explanation for the results of Giacomini et al. (2000) might be a biomechanical one. Tendons and ligaments have collagen structural proteins and their amount of stiffness influences elastic energy which is stored. Consequently, the stretch-shortening cycle activation is of great importance for the mechanical energy and also for running economy. It has been observed that local estrogen concentrations induce a greater stiffness in ligaments (Liu et al., 1997). A similar effect is suggested on the tendon collagen proteins by ethinylestradiol. That would mean that during OCP intake tendon stiffness and consequently also amount of the stored energy during stretching phase of running is increased. This theory is further supported by the argument that an earlier literature (Walden et al., 1986) found that low-dose OCPs were associated with an increase in tyroid (which is estrogen mediated) hormone concentration which is known to effect the reflex of tendon (Giacomoni & Falgairette, 2000). As the results for the metabolic explanation are controversy for the results of Giacomoni et al. (2000) the biomechanical explanation seems to be more comprehensible.

## *4.2 Comparison of OCP and non-OCP users*

Controversial results have been found in studies with group comparisons between OCP users and non-OCP users. In some studies no changes in endurance parameters were detected (Bryner et al., 1996; Grucza et al., 1993) while in following studies significant differences have been found: A notably reduced plateau in $VO_2$ has been found in all phases when monophasic OCPs have been used. An impact of the OCP on either muscle glycogen or the utilization of muscle glycogen or even both is therefore suggested and explained by Gordon (2018) as following: An increased reliance on fatty acids is associated with OCP use. This is explained by higher lipid synthesis and lipolysis which if further due to activation of lipoprotein lipase. Substrate use is affected and glycolysis is downregulated and further anaerobic capacity is more inefficient in OCP use. This can also be seen in the $VO_2$ response which demonstrates a diminished or nearly not existing plateau. $VO_{2max}$ was not affected significantly in most studies and Gordon (2018) explains this by a delay of onset of volitional exhaustion. This is a consequence of the spare of carbohydrates and higher amount of use of fatty acids while the body tries to supply energy. Coupled with the non-detected changes in HR, and $VO_{2max}$, it is suggested that the

limiting effect of $O_2$ uptake can be explained rather due to a change in substrate use and less by a change in $O_2$ delivery. To sum up, an interaction between monophasic OCP use and anaerobic energy is seen in a diminished plateau response of $VO_2$ due to a change in substrate use and sparing of carbohydrate use (Gordon et al., 2018). Differences in peak blood lactate concentration after an anaerobic test were found with higher values in OCP use than in non-OCP users. Again, a shift in metabolism is suggested to be the explanation. Progesterone might decrease carbohydrate metabolism with increased fat oxidation. Although estradiol is supposed to have an antagonistic mechanism in this shift in metabolism (Nakamura & Nose-Ogura, 2021). This is another hint that the exogenous progesterone has a higher input on the physiology than the exogenous estrogen. Anyway, the authors suggested that the effect on peak lactate concentration remains unclear.

In some studies, an effect on $\dot{V}O_{2peak}$ has been found. For example in Joyce (2013) in a group of females with long-term use of OCPs (>12 months) a 22% lower $VO_{2peak}$ than a control group of naturally menstruating females was found. In Casazza (2002) athletes started to intake OCPs and used it for four months. The use of low-dose triphasic OCPs resulted in significant decrease of $VO_{2peak}$ of about 11%. As this effect did not appear between the OCP phases it is suggested that the effect of persistent synthetic ovarian hormones is not sensible on short deviations but rather consistently stable. Further a certain time to enrol the hormonal effect is needed as another study with 1-3 weeks of OCP use found no significant effects on $VO_{2peak}$ (Bryner et al., 1996). The effect of the $VO_{2peak}$ decrease in triphasic OCPs has been 7% greater than in previous research on monophasic OCPs (Notelovitz et al., 1987). Again, this supports the suggestion that comparison between different OCP types must be interpreted with caution. And although the sample was not that large (N = 8) a decrease of $VO_{2peak}$ has been found in each of the participants. Casazza et al. (2002) excluded changes in stroke volume, haemoglobin levels and muscle blood flow to be the reason. It is suggested that sympathetic nervous system activity (SNA) and plasma catecholamine concentrations explain the study results. Estrogen and progesterone levels which are lower for a consistent time period are not only seen in OCP use but also in pregnancy. This is due to a protective mechanism which remains that blood can flow to the uterus to avoid contraction in uterus and maternal hypoglycaemia (McMurray et al., 1992 in Casazza et al., 2002). In strenuous exercise catecholamines are directly involved in the glycogen mobilisation. As the foetus relies nearly exclusively on maternal glucose for its development it could be a preventive mechanism of the maternal body to spare glycogen. Exogenous estradiol has been shown to decrease SNA at rest, catecholamine levels and glucose level and it is suggested to be a maternal prevention effect induced by pregnancy and also in OCP users (Casazza et al., 2002).

## *4.3 Detection of blood parameters*

For the interpretation of results of non-OCP users the exact detection of menstrual cycle phase is of fundamental importance and blood sample analysis is the method which is used most often. The

previously set minimum for serum progesterone levels to detect luteal phase must therefore be discussed. Two progesterone levels are therefore analysed in Barba-Moreno et al. (2019). To detect the luteal phase in a regular natural menstrual cycle 6.0 ng/mL has been supposed in a more recent study (Schaumberg, 2017) and in contrary 3.0 ng/mL has been set as a limit in earlier research (Israel et al., 1972). Results of the study do not clearly prefer one or the other theory and therefore additionally urinary ovulation prediction tests are suggested for exact evidence (Barba-Moreno et al., 2019). The detection of exogenous hormones might be a difficulty in determining timing of cycle phases even in OCP usage. Rechichi (2008) tested two times during withdrawal, and for the first data-collection timepoint estrogen and progesterone remained suppressed. But for the second data-collection timepoint, which was 3-5 days later, they found out that exogenous estrogen (ethinylestradiol) was not detectable while exogenous progesterone was (Rechichi et al., 2008). Whilst exogenous estrogens are detectable up to two days after interruption of OCP consumption, some exogenous progestins remain detectable for up to five days (Fortherby et al., 1996 in Rechichi et al., 2008). Rechichi (2008) discusses the individuality of hormone levels by the argument of a very high standard deviation. In the two different measurement timepoints within the withdrawal of OCP use standard deviation was quite high (first withdrawal measurement 87.3 ± 73.6 pmol/L and second withdrawal measurement 178.6 ± 189.9 pmol/L) (Rechichi et al., 2008).In conclusion, the detection of exogenous hormones has notably individual-differences and is not easy to detect. The results must therefore be interpreted with caution.

## *4.4 Anthropometric measurement and body temperature*

In most studies no significant changes in anthropometric parameters like in body mass or body composition were found between OCP phases (Barba-Moreno et al., 2019; Casazza et al., 2002; Giacomoni & Falgairette, 2000; Joyce et al., 2013; Rechichi et al., 2008; Vaiksaar et al., 2011a, 2011b). Significantly lower waist circumferences have been found in OCP intake phase compared to non-consumption phase (Jurimae et al., 2011). All the other circumferences did not differ, which makes it hard to find a clear explanation for this phenomenon and the authors of the trial did not offer one (Jurimae et al., 2011). Interestingly, in Casazza (2002) significant increase in body mass and fat mass have been found after four months of low-dose triphasic OCP use. The authors did not offer an explain for this augmentation. Retention of liquids in the body might be an explanation. In Nakamura (2021) percentage of body fat and body mass did not differ before and after three months of OCP use. The authors suggested that maybe in athletes in weight-restricting sports changes in body mass might appear but did not add a further argument for this suggestion.

Also, body temperature fluctuations are suggested through the female cycle. Progesterone might have an impact to increase body temperature in luteal phase of naturally menstruating women and consequently also the threshold of sweat. Anyway, this effect has not been found in OCP users (Grucza

et al., 1993). It can therefore be proposed that exogenous progesterone consumed by the OCP does not lead to the same effect on body temperature.

In females were amenorrhea and hypo-estrogenic states might be an issue, a known consequence is a decrease in bone mineral density. This often leads to a higher rate of injuries with long drop outs from training or even long-term adverse effects for their health. To prevent from further loss of bone density or even partially restore of density, supplementation of estrogen is a common medical recommendation (Bryner et al., 1996). In contrast, the bone metabolism marker (osteocalcin) was found to be significantly lower in OCP users than in non-OCP users. But osteocalcin did not fluctuate through natural menstruation cycle or OCP users' cycle. The authors concluded that adipose and bone tissue markers are not affected by a change in sex hormones at different cycle phases. The effect of the OCP on bone mineral density needs further research especially multiple blood samples during the female cycle are needed to achieve more detailed information (Jurimae et al., 2011).

## *4.5 Limitations and outlook*

The comparison of studies about the influence of OCP use are limited by problems in definitions and wordings considering timing of menstrual phases. It is often not clear if the counting of days through cycles includes menses at the very beginning or at the end of the 28 days of cycle. Further, the abbreviation of CONS has been used for pill intake (consumption) but also for non-OCP users (conservative method). This leads to misunderstandings in comparison of research results. Another problem in interpretation is that results of studies mix-up the use of monophasic, two-phasic or triphasic pills. Especially in earlier studies significantly higher steroid doses (progesterone) are biasing the results and lead to a non-comparable study design (Barba-Moreno et al., 2019). These studies need to be analysed and interpreted separately as they might influence female body differently concerning their potency and androgenicity. Further type and dosage of estrogen and progestogen might differ between the OCP products and should be explained clearly in methods sections for more transparency in research. One study chose a group of men as control group. In earlier literature this was justified due to the stable hormone levels of men, but it is nowadays seen as a limitation as it is simply not that easy to compare. Comparison is drawn between men and women's first week of cycle because hormone levels are lowest in this phase. Anyway, there are a lot more differences in male and female body which might bias this comparison. Wider and lower pelvis, lower position of the centre of gravity, valgus position of leg axis, difference in leverage ratio of extremities are only some anatomical differences beside much more physiological ones between male and female bodies. Further, female bodies have less body mass and also body composition differs. Female athletes with higher percentage of body fat, about 25% while in men 15% are normal in skinny and athletic men. In female athletes lean body mass is about 30-35% and in male athletes it contains about 40%. Consequently, muscular strength is 20-35% lower in female at

the same body mass. Further the ability of $O_2$ transport in female is lower due to smaller lungs and cardiac muscle mass (Bachl et al., 2017). Therefore, it is not justified to only pay attention on hormonal levels as there are much more physiological and anatomical biases which might affect the results.

Less menstrual pain and more independency on timing of menstrual side effects is also a reason to use pills. Therefore, rate of perceived exertion is an important parameter to detect in OCP studies. Following studies should observe this parameter to find out if it has negative effects on data which was collected during menses.

As an outlook, more studies on immunological parameters should be done. They are of great importance on performance output as well. Somehow, research is missing in this field although it is suggested to have a big influence on (Northoff et al., 2008; Rickenlund et al., 2005). This topic leads to another approach: Interdisciplinarity is of importance in a lot of sport scientific contexts but especially in female research. The connection between endocrinology, nutrition, substrate use, science of training, body temperature and body composition considering influences due to gynecological influences is often not considered in studies. Inclusion of explanations with context to gynecological research is desired to be more often implemented. Often reasons and explanation might be found in other scientifical disciplines. Therefore, female physiological extraordinariness should include gynecological research. Including female participants is necessary to avoid bias in procedure of sampling. Excluding females from research is clearly not following the criteria of science of transferable results on whole population and sustainable scientific research.

# 5 Conclusion and practical application

The majority of studies did not find significant differences in measured parameters concerning endurance performance between OCP phases (Barba-Moreno et al., 2019; Bryner et al., 1996; Casazza et al., 2002; Grucza et al., 1993; Joyce et al., 2013; Jurimae et al., 2011; Nakamura & Nose-Ogura, 2021; Vaiksaar et al., 2011b). Anyway, some physiological influences have been found. When it comes to continuous use of OCP for example over four months a decrease in $VO_{2peak}$ is suggested to appear which might negatively influence training induced adaptations in female athletes. As a practical application, it is recommended to interpret $VO_2$ plateau in OCP users with caution as it might be influenced or even non-existent. It must therefore be considered especially when the plateau is used for a primary indicator in comparison between athletes. Further substrate use might be shifted to a higher metabolism of fat, which might affect female athletes in long-distance disciplines. But all in all, state of research is that modern OCPs with low hormonal levels do not affect female athlete's endurance performance.

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# List of figures

# List of tables

# Abbreviations

| | |
|---|---|
| ACL | anterior cruciante ligament |
| AT | aerobic threshold |
| BF | breathing frequency |
| BMI | body mass index |
| HR | heart rate |
| non-OCP | no intake of oral contraceptive pill |
| OCP | oral contraceptive pill |
| PO | power output |
| RPE | rating of perceived exertion |
| RE | running economy |
| RER | Peak respiratory exchange ratio |
| SNA | sympathetic nervous system activity |
| $VCO_2$ | carbon dioxide production |
| $VO_2$ | oxygen uptake |
| $VO_{2max}$ | maximum oxygen uptake |
| $VO_{2peak}$ | peak oxygen uptake |
| VT | ventilatory treshold |
| VE | ventilatory equivalent for oxygen |
| VE | peak minute expired ventilation |

# Statutory declaration

*"I declare that I have authored this thesis independently, that I have not used other than the declared sources / resources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources."*

Vienna, April 2022 Mag. Dr. Astrid Reif Bakk.