A perspective on current research investigating the effects of hormonal contraceptives on determinants of female athlete performance

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Abstract

Hormonal contraceptives are used by approximately half of female athletes and may affect athletic performance as a result of their action on the endogenous hormonal milieu. In athletes, hormonal contraceptive use appears to have little effect on body composition, however further studies are needed assessing progestin-only contraceptives as they may have a negative effect in the general population. The type of progestin contained within the contraceptive may influence the anabolic response of muscle to loading although this relationship is complex as it may be due to either direct or indirect effects of exogenous hormones on protein synthesis and satellite cell proliferation. The altered hormonal milieu in hormonal contraceptive users has predominately been shown to have no effect on muscle strength and whilst maximal oxygen uptake is sometimes reduced, this does not translate into measures of performance. The majority of previous research has used cross-sectional designs and/or grouped together different types and brands of hormonal contraceptives and little research has been conducted on progestin-only contraceptives in athletes. Future research should use prospective, randomised-controlled designs to assess the effects of all types of hormonal contraceptives on athletic performance in females.

Key Words: Oestrogen; Progestin; Exercise; Body composition; Oral contraceptive.

Introduction

The possible interaction between exogenous reproductive hormones and athletic performance in females is an important issue that has been the topic of debate for at least four decades[1]. There are numerous review articles on the effect of oral contraceptives (OC) on athletic performance[2-6], however we feel that these reviews are insufficient as they do not include all categories of hormonal contraceptives. In addition to OCs, there are many other delivery systems for hormonal contraceptives including Intrauterine Devices (IUDs), injections, transdermal patches, implants and vaginal rings. TABLE 1 shows the characteristics of each type of hormonal contraceptive.

Most hormonal contraceptives contain the synthetic oestrogen Ethinyl Estradiol (EE), however there are four generations of progestins, each with varying androgenicity and potency; for a comprehensive review see Benagiano et al.[7]. Each type of hormonal contraceptive has multiple formulations and brands that supply oestrogens and/or progestins in various concentrations for different durations[8]. As such, the term "hormonal contraceptives" is an umbrella phrase that refers to any type of exogenous hormones that alters endogenous endocrine function and prevents pregnancy[8]. This is the first paper to consider the effects of a large variety of hormonal contraceptives on athletic performance, as opposed to focussing on OCs as previous reviews have.

Recent data suggest that ~22% of the general population uses OCs, with ~9% using other forms of hormonal contraceptives[9]. In athletes, the prevalence of OC use is estimated to be 40-50%[10-11], however the most recent large-scale data was published in 2005 and the use of other methods of hormonal contraceptives, beyond OCs, has not been reported.

Since this time, the use of long-acting contraceptive methods, such as the IUD and implant, has been increasing[12] and therefore we suggest that it is important to understand not only how OCs influence performance, but also how other methods of hormonal contraceptives may affect female athletes. This article will present a brief overview of the effects of different types of hormonal contraceptives on a number of factors that influence athletic performance.

TABLE 1 - Characteristics of different types of hormonal contraceptives.

Type	Delivery	Frequency	Example of brand
Contraceptive patch	Thin plastic patch that sticks to the skin & releases oestrogen & progestin through the skin into the bloodstream.	New patch once a week for 3 weeks, no patch on 4th week.	Evra®
Injectable birth control	Injection of a progestin.	Once every 3 months.	Depo-Provera® Noristera®
Implantable rods	Matchstick-sized, flexible, & plastic rod that is inserted under the skin and releases a progestin.	5 years.	Norplant® Implanon® Nexplanon®
Intrauterine devices	Small, T-shaped device, inserted into the vagina, that releases a progestin.	5 years.	Mirena® Skyla®
Oral contraceptives	Consumed in pill form.	Combined OCs are typically ingested for 21 days, followed by 7 non-pill taking days. Progestin-only pills are usually consumed every day.	Microgynon® Yasmin® Marvalon® Cilest® Cerazette®
Vaginal rings	Flexible plastic ring inserted into the vagina that releases oestrogen and progestin.	Worn for 21 days, removed for 7.	NuvaRing®

Do hormonal contraceptives affect body composition?

Body composition is an important determinant of athletic performance; excess fat mass can impair performance by negatively affecting the power-to-weight ratio[13], reducing speed and agility[14], limiting the availability of lean mass in weight category sports[13] and hindering aesthetic sports[15]. Hormonal contraceptives are widely purported to induce weight gain by athletes[16] and the general population[17] although systematic reviews of combined contraceptives[18] and progestin-only contraceptives[17] have reported inconsistent findings. In the general population, several studies have shown that the Depot Medroxyprogesterone Acetate (DMPA) injection increases fat mass when compared to combined OC use[19-20] and non-hormone controls[19, 21]. Levonorgestrel IUD use resulted in a 2.5% increase in fat mass after 12 months usage, compared to a non-hormonal copper based (TCu380A) IUD group who lost 1.3% fat mass[22] and Levonorgestrel implant (Norplant) use resulted in significant increases in body mass when compared to non-hormone groups after 6[23] and 12 months[24]. The use of an etonogestrel implant (Implanon) has also resulted in body mass increases of 3% over 2 years[25]. This evidence suggests that progestin-only contraceptives may result in greater increases in body mass than combined contraceptives in the general population, although these data may not be applicable to athletes as they exercise frequently and monitor their dietary energy intake closely[15].

In a prospective randomised-controlled study, Proctor-Gray et al.[16] demonstrated that athletes

who were given a combined OC (Norgestrel; n = 69) lost more body and fat mass and gained more lean mass than a control group (n = 81) not using hormonal contraception. Conversely, Rickenlund et al.[26] found that 10 months OC (Levonorgestrel) use increased body mass (4.3%) and fat mass (17.3%) in oligomenorrheic participants (n = 13) but did not significantly affect eumenorrheic participants body composition (n = 13), despite mean increases of 3.0% and 3.8% for body and fat mass. Rickenlund et al.[26] used a relatively small sample size and in the absence of a power calculation it may be that the sample size was not sufficient to detect significant changes in body composition. This highlights the need for further research before the relationship between hormonal contraceptive use and body composition is fully understood in athletes.

Although data are inconclusive for contraceptive use and weight-gain, mechanisms have been identified which support a role for both combined and progestin-only contraceptives increasing body mass. Synthetic progestins have been hypothesised to act in a glucocorticoid-like manner, which results in increased appetite and visceral fat deposition[27-30]. Androgenic contraceptives may also interfere with appetite regulation by suppressing the secretion of the satiating hormone cholecystokinin[25]. It is unclear whether the addition of oestrogens in combined contraceptives influences the effects of the progestins[26]. However, in both combined and progestin-only contraceptives there is a down-regulation of reproductive hormones which has been demonstrated to reduce basal metabolic rate[27-28], increase visceral fat deposition[29], increase concentrations of appetite-stimulating hormones[30] and reduce the concentrations of satiating hormones[30]. The combination of these factors suggests that contraceptive use may result in weight gain but this has not been demonstrated in athletes[16, 24].

Is there a relationship between hormonal contraceptives and muscle mass?

The ability to accrue muscle mass in response to training is beneficial as lean body mass is related to performance indices such as strength, speed and endurance[31-32]. The regulation of muscle anabolism and catabolism is affected by many factors and exogenous oestrogens and progestins may directly influence this process or indirectly influence hypertrophic adaptations by altering the concentrations of anabolic hormones[33]. In the general population, progestin only-contraceptives appear to have a negative effect on lean mass. Bonny et al.[20] reported that women who received the DMPA injection lost 3.6% lean mass over 2 years compared to a DMPA and oestradiol group (-1.2%), OC group (+0.6%) or control group with no hormones (+0.6%). Women using a Levonorgestrel IUD lost 1.4% of their lean mass after 1 year compared to a 1.0% increase in lean mass in women using a copper-based (Tcu380A) IUD[22] and combined OCs have also been observed to have a negative effect on lean mass compared to control populations[19].

In athletes, Proctor-Gray et al.[16] demonstrated that regularly menstruating runners assigned to a second generation OC (30 µg EE and 0.3 mg Norgestrel) for 2 years accrued a greater amount of lean mass (0.67 kg·year^{-1}) than a control group of runners given no hormones(-0.10 kg·year^{-1}). The mechanisms behind these changes were not reported and as no indices of performance were measured it is unclear whether these changes resulted in improved performance. To date, only two studies have examined how OC use influences the response to resistance training[34-35]. Nichols et al.[34] assessed the response of athletes using various preparations of OCs (n = 13) and athletes not using hormonal contraception (n = 18) to 12 weeks of resistance training. Strength was improved in both groups, with no apparent differences between groups, although this study did not control for menstrual cycle phase when measuring strength in the control group, which has been shown to affect force production[36]. In contrast, Lee et al.[35] found that non-OC users (n = 39) gained significantly more muscle mass (+3.5%) than OC users (n = 34; +2.1%) following a 10 week training programme. Further differences were observed within the OC group, with those taking low androgenicity OCs having a 2.5% increase compared to a 0.3% increase in high androgenicity OC users. It is likely that the differences in muscle mass shown by Lee et al.[35] of sufficient magnitude to effect overall athletic performance. The higher

androgenicity progestins may have a higher affinity to androgen receptors, which limits the binding of testosterone and thus supresses muscle strength gains[37]. These findings suggests that exogenous hormones may influence the anabolic response of muscle to resistance exercise.

The myofibrillar protein fractional synthetic rate (FSR) does not vary across the menstrual cycle[38], however Hansen et al.[39] demonstrated that females using a third generation OC (30 µg EE and 0.0075 g Gestogen) had a lower FSR than second generation users (35 µg EE and 0.25 mg Norgestimate) and no hormone controls. This suggests that the exogenous synthetic component of contraceptives can affect protein synthesis, unlike endogenous female reproductive hormones. Recent evidence suggests that oestrogen receptors (ERα and ERβ) within the muscle can stimulate the proliferation of satellite cells via the PI3K/Akt pathway for muscle growth and repair[33, 40]. EE increases the proliferation of satellite cells in rat muscle tissue[41], indicating that the synthetic component of hormonal contraceptives may have a direct anabolic effect on muscle, possibly due to a local activation of IGF-1 pathway through an autocrine or paracrine manner[42].

Hormonal contraceptives may indirectly influence muscle metabolism by altering the concentrations of anabolic hormones such as testosterone, Growth Hormone (GH) and insulin-like growth factor 1 (IGF-1)[43]. A recent meta-analysis showed that OC use reduced free testosterone by 61% compared to non-users[44], possibly due to an increase in sex hormone binding globulin concentration, which binds to testosterone rendering it inactive. OC use increases GH concentrations[45-46] with second (30 µg EE and 0.125 mg Levonorgestrel) and fourth generation (30 µg EE and 2 mg Dienogest) OCs reducing concentrations of IGF-1, but not affecting IGF binding protein-1 concentrations[45]. The generation of contraceptive influences the response of IGF-1; 30% reduction following fourth generation OC use compared to 12% reduction following second generation use[46], possibly as the androgenic Levonorgestrel opposes the effects of oestrogen on IGF-1 concentrations. In addition, twelve weeks use of a transdermal oestrogen patch (Estraderm) and oral oestrogen (Estrace) has also been shown to increase GH release[47]. It is currently unclear if these differences in anabolic hormone concentrations with different methods of contraception influence the response to strength training in female athletes.

How do hormonal contraceptives influence muscle strength?

A cross-sectional study found poorer handgrip force production and endurance in OC users (8 different types) than eumenorrheic controls[48]. However, studies comparing pill-taking days and non-pill taking days have generally found no difference in strength at these time points[49-52], although there is some limited evidence that strength is greater on non-pill taking days[53]. Lebrun[5], using a prospective research design, reported no difference in knee flexion and extension strength after 2 months of first generation OC use. To date, no research has been conducted assessing muscle strength in progestin-only OCs or other methods of hormonal contraception and few studies have been conducted in athletic populations[5, 53].

The reduction in free testosterone and oestrogen concentration with contraceptive use[18, 44] may affect muscle force production as both hormones have a non-genomic action on skeletal muscle, by increasing intracellular calcium concentrations and influencing the contractile properties of the muscle[54-55]. Despite this, few studies have shown an effect of down-regulated reproductive hormones on skeletal muscle force production[56]. Indeed, previous research from our group[57] demonstrated that supra-physiological concentrations of oestrogen and progesterone do not influence force production in non-trained women.

Is oxygen uptake affected by hormonal contraceptive use?

Many studies have shown that OC use results in a significant reduction in maximal oxygen uptake (VO_{2max}) in non-athletic women after 2-6 months use[53, 58-62] which is reversed when OC use is terminated[58, 60]. This may be due to a reduced activation of the sympathetic nervous system in ovarian suppressed women[63] or a reduction in mitochondrial citrate[58]. However, other more recent studies have found no effect of OC use on VO_{2max} in athletes[64-65], possibly due to the use of different formulations of OC or the training status of the participants.

What are the effects of hormonal contraceptives on performance tests?

Bryner et al.[60] detected a 7% reduction in VO_{2max} with OC use (35 µg EE, 1 mg Norethindrone), although this had no effect on performance in a treadmill running exercise capacity test. Similarly, Joyce et al.[62] observed a reduced VO_{2max} in OC users compared to eumenorrheic controls; however there was no difference in cycling capacity performance. In addition, no differences were observed in rowing exercise capacity[65] or 200 m swim performance[66] at different stages of the OC cycle in well-trained athletes. In a prospective study, Rickenlund et al.[26] measured endurance capacity, isometric quadriceps strength and handgrip strength in 26 female endurance athletes (13 eumenorrheic and 13 oligo-amenorrheic) before and after 10 months treatment with an OC (30 µg EE and 150 µg Levonorgestrel). There was no effect of OC consumption, except a small decrease in exercise capacity in the initially oligo-amenorrheic group, although this may have been due to the inferior response to training observed in ovarian/energy suppressed athletes[67]. Further studies using exercise performance tests are needed, as the majority of past research has examined exercise capacity tests, which are not as ecologically valid as performance tests.

Final considerations

As we have demonstrated in this paper, it is difficult to determine the role of hormonal contraceptives on performance as the majority of studies are cross-sectional and there is a paucity of prospective, randomised-controlled trials. This is especially true for studies using progestin-only contraceptives, which have barely been considered in the general population and have not been studied at all in an athletic population (TABLE 2). A large number of studies have compared pill-taking days to non-pill taking days, even though data from our laboratory has shown there is no significant difference in hormone profile between these conditions[68]. Moreover, different pill types and formulations are often grouped together making it difficult to discern possible effects, as the potency and androgenicity of the synthetic hormones may influence the response[7] and we have previously demonstrated that the hormonal profile is affected by the brand of hormonal contraceptive[68].

It appears that the effects of hormonal contraceptives observed in the general population are not apparent in athletes, however further research is required to assess this. In the case of body composition, it may be that athletes respond differently to hormonal contraceptives, as athletes exercise more frequently and monitor their dietary intake more carefully[15]. In terms of muscle mass, the increased habitual exercise level and loading in athletes may provide a greater stimulus for muscle anabolism, which may differentiate the two populations. There may be complex interactions between direct and indirect effects of hormonal contraceptive on the anabolic response of muscle to resistance exercise, however these effects are currently unclear. The acute effects of hormonal contraceptives are more apparent with the majority of studies observing no effect on muscle strength or performance, despite reductions in VO_{2max}. We believe that additional studies on the effects of progestin-only contraceptives on muscle strength and VO_{2max} are needed as this area has not been evaluated and newer formulations of OCs should be incorporated into research.

It is also useful to note that few studies address the issue of sample size and power, with only a small number of studies with athletic participants reporting priori power analysis[52, 62, 64]. This issue makes it difficult to conclude either the statistical or clinical significance of many of the studies included in this overview, however it is clear that further research on the effects of hormonal contraceptives is warranted and should not be confined to oral contraceptives only. In particular, we propose that the effects of long-acting, reversible, progestin-only contraceptives should be considered as their prevalence is increasing and these are likely to have different effects on performance than combined contraceptives.

This perspective also highlights the lack of information pertaining to the prevalence of hormonal contraceptive use in athletes. It would be beneficial to know the extent of hormonal contraceptive use in athletes so that future research can be directed appropriately. For example, in the general population the patch and ring are very rarely used: 0.1% use for patch and no recorded use of vaginal ring in 194,000 participants[9], therefore if athletes show a similar trend for usage, it may not be justified to recommend research into their effects in an athletic population. However, if athletes show an increased use of the patch or ring than the general population, then the composition of these contraceptives (exposure to ethinyl estradiol with the nuvaring is 3.4 times less than the contraceptive patch and 2.1 times less than OCs.[69] may indicate the need for more research. Therefore, we strongly recommend that research into the prevalence of hormonal contraceptive use in athletes should be conducted.

TABLE 2 - A summary of the effects of hormonal contraceptives on determinants of athletic performance.

Progestin-only contraceptives have been grouped together due to the paucity of research on these contraceptive delivery systems in athletes.

Determinants of athletic performance	**Combined oral contraceptives**	**Progestin-only contraceptives**
Body composition	Conflicting data showing combined oral contraceptive use both increased and reduced body mass and fat mass in athletes[16, 26].	Several reports of negatives effects in the general population although no studies have been conducted in athletes[19-25].
Muscle mass accretion	Combined oral contraceptive use may have a positive or negative effect on strength gains depending upon the progestin used[16, 19-20, 34-35].	Insufficient evidence, although the type of progestin-used may influence the anabolic response of muscle to resistance exercise[20, 22].
Muscle strength	The majority of studies have reported no acute effects of combined oral contraceptives on muscle strength[49-52].	Insufficient evidence to draw a conclusion.
Oxygen uptake	Combined oral contraceptive use may reduce VO_{2max} although this is less apparent in trained athletes[58-65].	Insufficient evidence to draw a conclusion.
Performance tests	Combined oral contraceptives do not appear to acutely effect exercise capacity or performance tests[26, 60, 62, 65-66].	Insufficient evidence to draw a conclusion.

Resumo

Uma perspectiva sobre a investigação dos efeitos dos contraceptivos hormonais sobre os fatores determinantes do desempenho de mulheres atletas

Os métodos contraceptivos hormonais são usados por aproximadamente metade das atletas do sexo feminino e podem afetar o desempenho atlético como resultado de sua ação hormonal sistêmica. Nas atletas, o uso de anticoncepcionais parece ter pouco efeito sobre a composição corporal, porém novos estudos são necessários para avaliar os efeitos dos contraceptivos derivados apenas de progestina, pois podem ter um efeito negativo na população em geral. O tipo de progestina contido dentro do contraceptivo pode influenciar a resposta anabólica do músculo, embora esta relação seja complexa em virtude dos efeitos diretos ou indiretos de hormônios exógenos na síntese da proteína e na proliferação das células satélites. A resposta sistêmica hormonal alterada em usuárias de contraceptivos parece não influenciar a força muscular e, embora o consumo máximo de oxigênio às vezes seja reduzida, isso não afeta as medidas de desempenho. A maioria das pesquisas utilizou desenhos transversais e/ou agrupou diferentes tipos e marcas de anticoncepcionais hormonais e poucos estudos têm sido realizada sobre anticoncepcionais com progestina em atletas. Futuros estudos devem usar desenhos experimentais prospectivos, randomizados e controlados para avaliar os efeitos de todos os tipos de contraceptivos hormonais no desempenho atlético em mulheres.

Palavras-chave: Estrogênio; Progestina; Exercício; Composição corporal; Contraceptivo oral.

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