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REVIEW ARTICLE

Resistance Training and Skeletal Muscle Protein Metabolism in Eumenorrheic Females: Implications for Researchers and Practitioners

Olivia E. Knowles[1] · Brad Aisbett[1] · Luana C. Main[1] · Eric J. Drinkwater[2] · Liliana Orellana[3] · Séverine Lamon[1]

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Abstract
Resistance training is essential for health and performance and confers many benefits such as increasing skeletal muscle mass, increasing strength and power output, and improving metabolic health. Resistance training is a major component of the physical activity guidelines, yet research in female populations is limited. Recent increases in the promotion of, and the participation by, females in sport and exercise, highlight the need for an increase in understanding of evidence-based best practice exercise prescription for females. The aim of this review is to provide an overview of the current research regarding resistance training performance and skeletal muscle adaptation in females, with a focus on the hormonal variables that may influence resistance training outcomes. Findings suggest that the menstrual cycle phase may impact strength, but not skeletal muscle protein metabolism. In comparison, oral contraception use in females may reduce skeletal muscle protein synthesis, but not strength outcomes, when compared to non-users. Future research should investigate the role of resistance training in the maintenance of skeletal muscle protein metabolism during pregnancy, menopause and in athletes experiencing relative energy deficiency in sport. The review concludes with recommendations for researchers to assist them in the inclusion of female participants in resistance training research specifically, with commentary on the most appropriate methods of controlling for, or understanding the implications of, hormonal fluctuations. For practitioners, the current evidence suggests possible resistance training practices that could optimise performance outcomes in females, although further research is warranted.

1 Introduction

The increasing development of and investment in women's professional sporting leagues represents an important platform for promoting physical activity and exercise in the female population [1, 2]. However, research that informs practitioners of best-practice methods for maximising exercise performance and training adaptation in females is limited. In the top-ranked 'sport science' category journals, 39% of study participants are female, but only 4–13% of participant groups in original research are made up of

Key Points

Females performing resistance training achieve similar relative strength and hypertrophy gains compared to males and may be able to optimise performance or muscle adaptation by emphasising training frequency during the follicular phase of the menstrual cycle, or with combined strength/power training throughout the cycle.

The oral contraceptive pill, but not the menstrual cycle, may negatively influence skeletal muscle protein turnover in response to resistance training. Further evidence is needed to determine the influence of endogenous and exogenous estrogen, and other key hormones, on resistance training outcomes in young females.

Researchers are encouraged to include female cohorts in resistance training research, and a number of strategies could be employed to ensure they investigate a homogenous cohort or control for potentially confounding variables.

✉ Séverine Lamon
severine.lamon@deakin.edu.au

[1] Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, 221 Burwood Highway, Geelong, Burwood, VIC 3125, Australia

[2] Centre for Sport Research, School of Exercise and Nutrition Sciences, Deakin University, Geelong, VIC, Australia

[3] Biostatistics Unit, Faculty of Health, Deakin University, Geelong, VIC, Australia

females only [3]. This suggests that a large proportion of the exercise prescription information for females is based on research conducted in males. Hence, there is a need to better understand the exercise and training outcomes for physically active females and female athlete populations [3, 4]. Understanding the outcomes of exercise for females is critical for exercise professionals and coaches to appropriately prescribe training. The ability to implement exercise training interventions that are specifically designed to optimise females' performance and health will transform the sport and health sector with an evidence-based approach for females aspiring to reach fitness and health goals.

Resistance training is a critical component of an athlete's training programme to improve skeletal muscle strength and power, reduce the likelihood of injury and rehabilitate any injuries [5]. Further, the idea that 'resistance training is medicine' is now well established [6], with recent high-impact reviews highlighting the benefits of resistance training for increasing skeletal muscle mass [7] and reversing skeletal muscle loss [8], reducing body fat [9], improving cardiovascular [10], metabolic [11] and mental [12] health, and promoting physical function and strength [13]. The maintenance of skeletal muscle mass preserves or improves the health and functional capacity of skeletal muscle. Skeletal muscle cells are made up of ~ 80% proteins [14, 15] and skeletal muscle mass is regulated by the balance between the rate of protein synthesis and the rate of protein degradation in the muscle [15]. Resistance exercise stimulates contraction- and hormone-induced signalling pathways that upregulate skeletal muscle protein synthesis in the cell [7]. Acute increases in muscle protein synthesis after resistance exercise translate to the adaptive hypertrophic response to long-term resistance training [16]. Therefore, skeletal muscle protein metabolism underpins the benefits of resistance training in improving short- and long-term health and performance.

The relationship between resistance training and skeletal muscle adaptation has received substantially less attention in females than in males. This relative lack of research in females is mostly owing to researchers' reluctance to account for the additional variability in dependent variables that is created by factors that are unique to females, such as the menstrual cycle, pregnancy, breastfeeding, hormonal contraceptives, or menopause [4]. However, it is the complexity of the female biological and physiological systems that makes research in this population so important. Researchers need to understand the interplay between these systems and decide how best to account for their interaction in their study designs so they can accurately forecast training implications for the wider female exercise community [4]. Therefore, the aim of this review is to outline key considerations for resistance training research conducted with females. The review first presents a brief overview of the performance outcomes and skeletal muscle adaptations that result from resistance training in females. Thereafter, the unique variables that may influence resistance training outcomes in females are discussed. Finally, a summary of the practical implications for researchers conducting resistance training studies with female cohorts, and for practitioners training female clients or athletes, is presented.

2 Sex Differences in Resistance Training Performance and Skeletal Muscle Adaptation

As in many aspects of sport performance, sex differences exist in muscle strength and adaptation to resistance training. Males demonstrate up to 157% greater relative upper and 60% greater relative lower body strength, respectively, than females in resistance exercise tests such as one repetition maximum (1 RM) testing [17]. Females also demonstrate 73% greater relative lower body strength compared to their upper body strength, yet this difference in relative muscle group strength is not observed in males [17]. In contrast, females demonstrate approximately twofold lower muscle fatigability [18]. Studies that have tested relative strength at 20–70% of maximum voluntary contraction report 46–87% greater fatigue resistance in females in comparison to males [19]. However, the advantage females hold over males in fatigability may dissipate at intensities beyond 80% 1 RM [19]. Additionally, females training at the same relative workload (i.e. an equal volume at a given percent of 1 RM) as males need less recovery time for force return both immediately post-exercise and over 24 h [18, 20, 21]. These differences may be explained by sex-specific lean body mass distribution, or by the greater proportion of type I muscle fibres in females that are more resistant to fatigue than type IIa and IIx muscle fibres [22].

While various sex differences exist in skeletal muscle strength and structure, several established resistance training methods for increasing muscle strength and hypertrophy are equally valid for both males and females. In trained males and females, multiple-set training is superior to single-set training [23, 24] and exercise sequence dictates the volume load output for each exercise performed in a training session [25, 26]. It follows that the relative performance adaptation (e.g. relative increased maximal strength output) to long-term resistance training is similar between males and females performing the same resistance training protocols. With up to 20 weeks of the same resistance training protocol, relative percentage strength increases from baseline are similar in males and females [27–29], and sometimes up to 10% greater in females [30, 31]. Nevertheless, while males

and females may respond similarly to resistance training protocols for developing strength, albeit females at a lower absolute load, there may be optimal training approaches to maximise performance adaptations in females [32, 33].

Understanding how females can most effectively make improvements in strength is not only relevant to health and performance, but also to certain occupational circumstances whereby a minimum standard must be met, e.g. strength requirements for military personnel. Females performing combined strength and power training may make greater relative improvements compared with their male counterparts as judged in multi-joint exercises such as the 1-RM squat, 1-RM bench press, and 1-RM high pull, when compared with six months of combined strength and hypertrophy training [32]. Low-volume high-intensity training, typical of strength or power but not hypertrophy training, may therefore be most suitable for strength adaptations in female participants [32]. Certainly, there may be an upper threshold for the volume of resistance training (i.e. sets per muscle group) performed by trained females to achieve optimal muscle hypertrophy and strength gains [33]. Some authors have proposed that females may have a greater capacity for neural adaptations over hypertrophic adaptations [34–36], which could explain these findings. While neural adaptations are beyond the scope of this review, it is important to consider that strength develops through a combination of neural, structural and hypertrophic adaptations [36].

Muscle protein synthesis is a primary component of the skeletal muscle anabolic response following resistance exercise [16]. Muscle protein synthesis increases similarly in females and males in the immediate 1- to 5-h post-resistance training and remains elevated, compared with resting levels, up to 26 h post-training with feeding [37]. In their study, West et al. [37] disregarded the female menstrual cycle in their protocol because of previous findings that skeletal muscle protein metabolism is not influenced by the menstrual cycle phase (discussed in Sect. 3.1) [38]. Their findings are perhaps unsurprising, given that males and females express similar basal protein synthesis and protein degradation rates in skeletal muscle, when normalised to lean mass [39]. This lack of difference in skeletal muscle protein synthesis rates [37] is in line with the frequent observation that relative increases in muscle cross-sectional area with long-term resistance training are similar in males and females [31, 40]. This suggests that sex differences in lean muscle mass and absolute strength and hypertrophy across the lifespan [28, 41, 42] may be driven by other mechanisms, including mechanical (e.g. sarcomerogenesis) or metabolic stress (e.g. elevated hormone release) [43]. Based on the known sex differences in circulating hormone levels, the following section examines the role that anabolic and catabolic hormones may play in females' responses to resistance training.

3 Hormonal Factors Influencing the Resistance Training Response and Adaptation in Females

The hormonal environment, both basal and exercise induced, is one of several key mechanisms for resistance training adaptation. A bout of resistance exercise triggers the secretion of specific hormones, which engage with their receptors on or within the target cell [44]. These ligand-receptor interactions initiate a cascade of events, leading to specific physiological outcomes such as an increase in muscle protein synthesis [44]. The following sections discuss how hormones, both endogenous and exogenous (e.g. hormonal contraceptives), may affect skeletal muscle protein metabolism and adaptation to training.

3.1 Endogenous Sex Hormones and the Menstrual Cycle in Young Females

Estrogens and androgens are groups of endogenous sex hormones that are produced by both males and females [44]. Testosterone is the most abundant androgen hormone [45]. By binding the androgen receptor at the surface of the muscle fibre, testosterone increases intracellular calcium release and activates the pathways that promote muscle protein synthesis [46] while inhibiting the pathways that promote muscle protein degradation [47]. Testosterone also stimulates growth hormone (GH) secretion [45]. The level of testosterone found in females is about 10% of that in males [45, 48]. In males, resistance exercise triggers the release of testosterone [45, 49]. The resulting elevated anabolic environment may promote skeletal muscle hypertrophy [50], potentially by enhancing androgen receptor content [51], a key factor driving relative increases in skeletal muscle hypertrophy in males [52]. In females, the exercise-induced testosterone response is limited, with most studies finding no testosterone response post-resistance exercise [49, 53–55]. Androgen receptor protein content in females is however upregulated at a faster rate than in males following an acute bout of resistance exercise [48]. This upregulation is not sufficient to counteract females' low baseline level of testosterone, nor does testosterone fluctuate across the menstrual cycle [56]. Consequently, females have little opportunity to capitalise on the anabolic effects of testosterone and, in addition to the intrinsic (e.g mechanical loading) and extrinsic (e.g. protein ingestion) factors, must rely on other sex and non-sex hormones to increase skeletal muscle protein synthesis.

Estrogen and progesterone are two primary sex hormones that fluctuate with, and regulate, the menstrual cycle. Approximately 50% of both active and elite female athletes perceive that their menstrual cycle affects their exercise training and performance [57]. The menstrual cycle is part

of the human reproductive process and is made up of two phases: the follicular phase, which is characterised by the onset of menses, and the luteal phase, which is characterised by the onset of ovulation (Fig. 1) [58]. From the early- to mid-follicular phase, estrogen and progesterone levels are low, with a spike in estrogen occurring during the late-follicular phase, meaning that the ratio of estrogen to progesterone is at its largest [58, 59]. Following ovulation, both progesterone and estrogen levels are high before decreasing again prior to menses (Fig. 1) [58, 59].

The possible implications of the surge in estrogen during the late-follicular phase on resistance training performance are evident from findings that maximal force is increased from the follicular phase to ovulation and declines in the early to mid-luteal phase [60–62]. The area under the curve of estradiol (the most abundant estrogen) increases for 65–95 min following an acute bout of resistance exercise, but substantially more so in the luteal phase compared with the follicular phase [63, 64]. Estradiol then remains up to 21% higher than resting levels at 24 h post-resistance exercise [65]. Long-term resistance training studies support a possible causal relationship between the heightened estrogen-progesterone ratio and performance, with greater muscle diameters and strength observed with up to 4 months of resistance training performed frequently in the follicular phase (e.g. five times per week in the follicular phase and two times per week in the luteal phase) compared with training performed frequently in the luteal phase or consistently (e.g. three times per week) throughout the cycle [66–68]. Interestingly, each of these training studies used a lower body hypertrophy protocol of 8–12 repetitions at ~ 80% 1 RM, with appropriate overload progressively implemented. In contrast, one study found no effect of menstrual cycle-based training frequency on strength or hypertrophy using an upper body protocol [69]. Importantly, while Wikstrom-Frisen et al. [66] included a control group who trained with constant frequency throughout the menstrual cycle, each of the studies discussed had a number of limitations in their design or implementation, indicating that the results should be taken with caution. Further research is needed to understand how menstrual cycle-based periodisation for hypertrophy training could be a feasible approach for females performing resistance training.

Several authors have suggested that estrogens may influence skeletal muscle hypertrophy [42, 70, 71]. When bound to its receptors, estrogen upregulates intracellular signalling pathways that stimulate skeletal muscle protein synthesis, such as the Akt/mechanistic target of rapamycin pathway (mTOR) [72]. Circulating estrogen enhances myoblast proliferation in vitro [73] and muscle size in rodents in vivo [74]. Estrogen may also play a key role in muscle repair and regeneration through the activation and proliferation of satellite cells [75, 76]. The administration of estrogen might

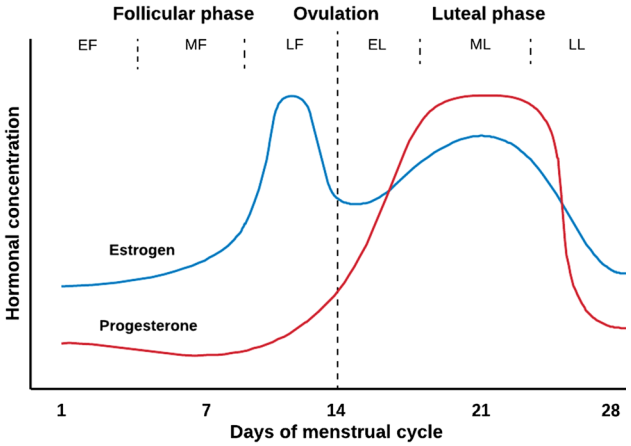

Fig. 1 Hormonal fluctuation with a eumenorrheic menstrual cycle (based on a 28-day cycle with ovulation occurring at day 14). *EF* early follicular, *EL* early luteal, *LF* late follicular, *LL* late luteal, *MF* mid-follicular, *ML* mid-luteal

reduce protein catabolism in males [77] and post-menopausal females [78]. Hormone replacement therapy using an estrogen-only [79] or combined estrogen-progesterone [80, 81] supplement in post-menopausal females has demonstrated increases in muscle mass and/or strength, possibly owing to an increase in estradiol by up to 50% with supplementation [80, 81]. Multiple comprehensive reviews detail the impact of estrogen on the skeletal muscle of early- and post-menopausal females [42, 70, 71], which may be relevant in understanding the role of estrogen in young females. However, it is also important to consider that the reduction in muscle strength in the early-mid luteal phase (i.e. post-ovulation) coincides with reduced maximal motor unit discharge rates, which may be influenced by the drop in estrogen and increase in progesterone in this phase [82]. Certainly, the effects of estrogen on skeletal muscle are promising, yet there remains a need to determine how young females (i.e. of menstruating age) performing resistance training can exploit naturally occurring surges in endogenous estrogen to maximise skeletal muscle strength and hypertrophy.

Progesterone may also play a role in skeletal muscle metabolism. Progesterone increases immediately following resistance exercise in the mid-luteal phase, but not in the early-follicular phase, and remains elevated up to 30 min post-resistance exercise [64]. Smith et al. [83] found that progesterone administration increases skeletal muscle protein synthesis rate, albeit in post-menopausal sedentary females. In contrast, some authors propose a catabolic effect of progesterone [84–86]. Landau and Poulos [86] reported that a large dose of progesterone (equivalent to that excreted in the first trimester of pregnancy) is associated with reduced serum amino acid levels, indicating an increase in protein degradation. To date, only one study of young females has

tested protein myofibrillar rates following a resistance exercise session performed in the follicular and luteal phases of the menstrual cycle, with no difference found between phases [38]. Importantly, Miller et al. [38] conducted testing in the early-follicular phase and the early- to mid-luteal phase, when the ratio of estrogen to progesterone secretion is small. It has been suggested that the individual effects of endogenous progesterone and estrogen may counteract each other when produced at a similar rate [42]. The estrogen-progesterone ratio is largest (i.e. the difference between estrogen and progesterone secretion is large) during the late-follicular phase [58, 59]. Importantly, emphasising training frequency during the follicular phase coincides with greater strength and hypertrophy improvements over time [66–68]. Therefore, resistance exercise in the late-follicular phase of the menstrual cycle could potentially promote greater skeletal muscle protein synthesis than in other phases. Previous authors have highlighted that research is needed to compare muscle protein synthesis rates between the early and late follicular phases to understand the effect of estrogen independent of progesterone [42]. However, until research in this space is available, we have recommended (Sect. 5) for researchers to avoid exercise testing in the late-follicular phase because of potential changes in strength or muscle protein synthesis rates. These recommendations also warrant further research.

3.2 Endogenous Non-Sex Hormones in Young Females

Growth hormone (GH), insulin-like growth factor 1 (IGF-1) and cortisol are non-sex hormones that play an important role in resistance training-induced skeletal muscle protein metabolism [37, 87]. Growth hormone regulates carbohydrate, lipid and protein metabolism in a number of tissues, with a key role in promoting the release of IGF-1 from the liver [88]. In turn, IGF-1 directly upregulates skeletal muscle protein synthesis by activating the PI3k/Akt/mTOR pathway [88]. Resistance exercise stimulates large bursts of GH in males and females [89]. However, there is mixed evidence to support a correlation between the acute resistance exercise-induced GH response with the magnitude of muscle hypertrophy in males [54, 89–91]. Interestingly, the area under the curve for GH-levels post-resistance exercise is greater in females than in males [37]. Further, the GH response in females is greater with high-volume short-rest resistance exercise compared with a low-volume high-rest prescription [54, 89, 92]. While basal GH and IGF-1 remain stable across the menstrual cycle [93], there is evidence that resistance training-induced GH secretion is greater during the mid-luteal phase than the early follicular phase [63, 64]. Despite a greater acute increase in circulating GH after resistance exercise in the mid-luteal phase compared with the early follicular phase, emphasising training frequency during the luteal phase does not result in greater increases in hypertrophy or strength over time [66]. Authors have suggested that this increased GH production during the luteal phase may arise from greater circulating estradiol because estrogen plays a role in GH axis neuro-regulation in both rodents and humans [94]. Growth hormone secretion also increases following hormone (estrogen) replacement therapy in post-menopausal females [95]. Further research is needed to determine if the peak of estrogen during the late-follicular phase may stimulate greater resistance exercise-induced GH, which could promote greater training adaptations during this phase.

In contrast to the anabolic hormones discussed so far, cortisol is a catabolic hormone that, among other roles, is upregulated in response to psychological and physiological stress [96]. Stress induced at the whole-body level and the skeletal-muscle level with resistance training can elicit an increase in cortisol [54]. In turn, supraphysiological levels of cortisol increase skeletal muscle protein degradation, as well as markers of protein degradation, in both human and rodent muscle cells [97, 98]. Further, findings demonstrate that cortisol decreases muscle protein synthesis in humans [99] and that a mix of catabolic hormones including cortisol increases muscle protein breakdown in humans [100]. The secretion of cortisol in response to resistance exercise is similar between males and females [37]. While it is unclear whether cortisol secretion remains consistent across the menstrual cycle [56, 101] or increases in the luteal/ovulatory phase [102], rodent models suggest that cortisol is downregulated by testosterone [103] and stimulated by estrogen [104]. Given that females secrete little, if any, testosterone in response to resistance exercise, these rodent models may explain why only males show a cortisol adaptation to long-term training [27] with a reduction in baseline serum levels that may aid their hypertrophic adaptation. Further research is needed to determine if an increase in cortisol with estrogen during the luteal phase [102] might counteract the beneficial GH profile during this phase [63, 64] and explain females' greater adaptation to resistance training performed in the follicular phase [66–68].

3.3 Hormonal Contraceptive Use

Another consideration for researchers and practitioners is hormonal contraceptive use. Many females use hormonal contraception to regulate their menstrual cycle or prevent pregnancy [105]. Hormonal contraceptives include the contraceptive pill, implant rod, contraceptive patch, progestogen injection, vaginal ring and the hormonal intrauterine device (IUD). While the most common methods for contraception vary regionally, use of oral contraceptive (OC) pills is more prevalent than other methods in Australia whereas the IUD is

more commonly used in European countries compared with other countries [106]. Studies conducted in the USA and Norway indicate that hormonal contraceptive use is particularly common amongst athletes, with up to 57% of female athletes using OC [107, 108] and 9% using an IUD [107]. The hormonal IUD (a progestogen-only device) has been shown to reduce muscle mass after 12 months [109]; however, confounding variables such as age and physical activity were not considered in the analyses. No other evidence exists regarding the effect of the IUD or implant rod on skeletal muscle strength, hypertrophy or protein metabolism with resistance training. In contrast, the combined OC pill, the most common form of OC, is more widely researched. The combined OC pill contains a synthetic estrogen (ethinylestradiol) and one of six synthetic progestogens [110]. The combined OC pill is also split into four generations dependent on their type of progesterone [111]. The OC pill reduces endogenous estrogen, progestogen and testosterone [110, 112] to low but consistent levels. Therefore, the level of circulating sex steroids is dependent on the dose of synthetic hormones delivered in each OC pill. The dose of synthetic hormone differs between monophasic, biphasic and triphasic OC, as well as the brand of pill [110]; a US study of female participants using OC pills found 67% used a monophasic pill and 88 different brands of OC pills were reportedly used [111]. As such, there may be a large variation in hormonal fluctuations between individuals taking the OC pill that could impact skeletal muscle strength, hypertrophy and protein metabolism.

Despite, or perhaps because of, potential hormonal variation, no differences in maximal strength have been found between resistance-trained females with or without OC during acute performance tests [113] or following up to 4 months of resistance training [66, 114]. Maximal strength is also unaffected by differences in monophasic OC androgenicity (i.e. the dose of synthetic progestogen), tested at various stages of the menstrual cycle [115]. Further, maximal strength does not differ during each phase of the OC cycle itself (including five brands of combined monophasic OC) [113, 115]. Interestingly, OC use increases sex hormone-binding globulin (more so in third- and fourth-generation OC pills), which has a high affinity for testosterone, binding it and making it inactive [112]. Further, OC administration may also increase GH levels but decrease IGF in second- and fourth-generation OC pills [116, 117]. A down-regulation of anabolic hormones could possibly play a role in changes in skeletal muscle protein balance with ingestion of OC pills. In support of this theory, the myofibrillar protein fractional synthesis rate was lower in female third-generation, but not second-generation, OC users compared with non-OC users following prolonged submaximal resistance exercise [118]. In this study, Hansen et al. [118] tested second- and third-generation OC users during days 18–21 of the pill cycle and non-OC users during days 3–6 of menstruation, therefore exposing all participants to low endogenous estradiol and progesterone, and highlighting the influence of high exogenous hormone levels on skeletal muscle protein synthesis. Interestingly, the authors suggest that the inhibiting effect of third-generation OC pills on myofibrillar protein synthesis may be due to the greater progesterone level compared with second-generation OC pills [118, 119]. However, this hypothesis and how it relates to muscle hypertrophy needs further research.

Collectively, the studies discussed have used a myriad of OC formulations, and it is therefore difficult to interpret the true impact of OC use on resistance training and skeletal muscle outcomes. Further, muscle protein metabolism in males is influenced by training status [120], therefore investigating the interaction between training status and OC is warranted. Research comparing the type, composition or generation of OC is needed to reliably understand the outcomes for female OC users performing resistance training.

4 Future Directions

Whilst the research investigating the interaction between resistance training and skeletal muscle protein metabolism in females is sparse, the different stages of the lifespan have hardly been considered. While the heavy resistance training typically performed by elite or recreational athletes is contraindicated during pregnancy, athletes who are pregnant or postnatal need specific exercise guidelines [121]. Estrogen and progesterone production markedly increase during pregnancy, and then rapidly decline in the immediate postpartum period [122]. Interestingly, acute maximal strength does not change in untrained females between trimesters, nor between in vitro fertilisation phases [123]. As low- to moderate-intensity resistance training is indicated during pregnancy and postpartum periods, further research is needed to understand the implications of hormonal changes on resistance exercise outcomes and skeletal muscle protein metabolism during these stages of life.

In contrast to pregnancy and the postnatal period, menopause is characterised by a reduction in estrogen by up to 67% and an accelerated loss of skeletal muscle mass by up to 1% per year after the onset of menopause [71, 124]. Acute muscle strength is lost during and after menopause; however, resistance training can attenuate this loss in strength and muscle mass [80, 124]. Notably, post-menopausal females have a faster post-absorptive muscle protein synthesis rate than pre-menopausal females over a 5-h period [83], although this response is reduced with feeding [125]. The upregulation of catabolic gene expression in post-menopausal females (without hormone replacement therapy) [83] may explain the loss of muscle mass despite upregulated

basal muscle protein synthesis. However, this hypothesis, as well as the role of resistance training in contributing to protein synthesis rates in post-menopausal females, requires further research. Understanding the outcomes associated with hormone replacement therapy in this population will also contribute to increasing our knowledge of the role of hormones in the maintenance of skeletal muscle mass in females in general.

Relative energy deficiency in sport (RED-S) is another potential concern for female athletes. RED-S is characterised by, but not limited to, impaired metabolic rate, muscle protein synthesis, menstrual function, bone health and immunity caused by relative energy deficiency [126]. Emerging literature suggests that the physiological impairments associated with RED-S may negatively impact muscle strength [126]. One study demonstrated that females with menstrual disturbances (i.e. low estradiol and progesterone) have an attenuated GH response to an acute bout of resistance exercise [64]. Further research is needed to understand the implications that an impaired anabolic hormone response may have on muscle protein synthesis. RED-S can develop from a reduction in energy intake, an increase in training load (intensity and/or volume), or a combination of both factors [126]. Athletes experiencing RED-S may therefore benefit from menstrual cycle-based periodised resistance training, given findings showing that when resistance training volume (frequency) is increased for 2 weeks during either the follicular or luteal phase, sex or other hormones such as cortisol and GH are not impaired [127]. Certainly, further research is needed to identify training methods that maximise performance and reduce negative exercise-related health problems in female athletes.

5 Implications for Research on Resistance Training in Females

Including female participants in resistance training research is essential to establish the associated health and performance outcomes for the female population. Additionally, there are some occupational settings, such as military positions or emergency services, where the physical strength requirements for males and females are equal [128], thus understanding the training outcomes for both sexes is critical. The following sections provide practical suggestions for researchers wanting to include females in research investigating the effect of resistance training. These suggestions may also be useful for researchers including female participants in other exercise physiology domains.

- It should first be determined whether the anticipated primary outcome is likely to be sex dependent and/or menstrual cycle dependent. Examples from this review show that some adaptations to strength training are influenced by the menstrual cycle, such as strength output [66, 67]. Other findings imply no change in muscle protein synthesis with menstrual cycle phase [38] but given that this was measured at only two time points, and not around ovulation, these findings should be taken with caution. When in doubt or if a pilot study cannot be performed, it is safe to assume that the primary outcome may be sex dependent and/or menstrual cycle dependent. While some sex differences are apparent (e.g. absolute strength, fatigability), researchers should remain confident that female and male participants who perform the same resistance training protocol are likely to have a similar relative acute muscle protein synthesis response to training along with similar relative hypertrophy and strength adaptation. For sex comparisons, it is therefore recommended that researchers present strength, hypertrophy and skeletal muscle protein metabolism data in relative values (i.e. the change from baseline) rather than absolute values.
- As best practice for both male and female cohorts, in a range of research domains, it is also important to consider and implement eligibility criteria specifying participants' training status and stage of growth across the lifespan (i.e. pubescent, young, pregnant, pre-menopausal, post-menopausal) to ensure a homogenous sample.
- The menstrual cycle typically ranges from 25 to 34 days [58]. Regardless of the duration of the intervention, researchers should collect a menstrual diary for at least two complete cycles prior to testing. This way, researchers can appropriately schedule laboratory visits or, when possible, moderate findings for hormonal variations across the cycle. Similarly, the menstrual diary should be completed for at least one cycle during and post-intervention, which will allow research teams to confirm the timing of particular testing sessions, relative to the menstrual cycle, and therefore contextualise unexpected individual findings. When possible, menstrual records should be supplemented by venous blood collection, urinary collection, or basal body temperature monitoring at key time points across the menstrual cycle and pre/post-intervention. For example, ovulation is expected to occur at or shortly following the nadir of basal body temperature, which is then followed by a steep rise in basal body temperature [129]. Measuring body temperature at waking each morning can be used to track this pattern.
- Importantly, the type of analyses required to moderate for hormone levels would only be possible in large studies with enough female participants with outcomes measured at different stages of the cycle, which greatly exceeds the typical cohort size used in laboratory-based exercise physiology research.

- While a homogenous sample is preferable, when testing both eumenorrheic and OC-using females, endogenous estrogen and progesterone levels in the early follicular phase are low for both groups and can therefore be considered alike when testing in this phase of the menstrual cycle [130]. Previous authors [110, 130] have recommended that inclusion criteria for OC users should be limited to a single brand, type and generation of OC to reduce hormonal variation. However, this approach is considered difficult to practically implement given the wide range of OC brands used by females. Therefore, it is recommended that for OC and other contraceptive methods, that researchers control for a single type of contraception (e.g. monophasic OC or hormonal IUD) and set limits about the acceptable dosage of synthetic progesterone and/or estradiol, which will in turn limit the number of brands included. While not the perfect approach, this may be a practical strategy to account for exogenous and endogenous hormone production between participants.
- For 'acute interventions', with a duration less than one phase (i.e. 4 days):
  - The ideal approach is a cross-over design where each participant acts as her own control and all interventions are tested during the same phase of the cycle.
  - When a cross-over design is not possible, all women should be tested in the same stage of their menstrual cycle.
  - When neither option is available, it is recommended that participants are tested during the early follicular and mid-late luteal phase when the ratio between estrogen and progesterone is small (see Sect. 3.1 for background detail).
- For non-acute interventions, with a duration less than one complete cycle:
  - If feasible, we recommend using a cross-over design where each participant acts as their own control and to follow the recommendations above.
  - When not possible to use a cross-over design, the start of the intervention should occur in the same phase for each participant. The ovulation phase should be avoided to rule out the potential impact of excessive differences in the oestrogen/progesterone ratio.
- For long-term interventions, with a duration of more than one complete cycle:
  - Intervention testing, as well as pre- and post-intervention testing, should start in the same phase for each participant. The ovulation phase should be avoided to rule out the potential impact of excessive differences in the estrogen/progesterone ratio.

6 Practical Implications for Resistance Training in Females

While females and males performing the same resistance training protocols may have similar skeletal muscle protein synthesis responses [37] and performance adaptations [27–29], the differences in hormonal responses to resistance exercise suggest that there may be ways to optimise the training adaptations for females performing resistance training. The following points provide a summary of the current evidence for practitioners prescribing resistance training for female populations.

- Females may acquire strength more efficiently with low-volume high-intensity training (i.e. combined strength and power training) as opposed to high-volume moderate-intensity training (i.e. combined strength and hypertrophy training) [32]. However, high-volume moderate-intensity training elicits a greater GH response than low-volume high-intensity training in females, which may be more beneficial for obtaining hypertrophy goals [89]. While the nuances of the response may differ, these recommendations are the same as for males.
- Females may also achieve greater strength and hypertrophy gains by training with high frequency in the follicular phase of their menstrual cycle (e.g. five times per week in the follicular phase and two times per week in the luteal phase), compared to training with a high frequency in the luteal phase or with constant frequency throughout the entire menstrual cycle (e.g. three times per week) [66, 67]. This 2-week high-frequency training approach may be more feasible to implement for recreationally active females or individual sport athletes rather than team sport athletes whose menstrual cycles are unlikely to be synchronised with their team mates.
- Use of OC has been shown to have no impact on skeletal muscle strength [113] and no published data exist regarding the interaction between OC and muscle hypertrophy. Further research is needed to determine the impact of specific types and brands of OC on skeletal muscle adaptations. Importantly, the use of OC may have other performance-related benefits including the reduction of premenstrual symptoms that could negatively impact performance [105].
- Ultimately, it is important that females are provided with individualised and periodised resistance training programmes that consider their menstrual cycle and hormonal contraceptives, as well as amenorrhea, pregnancy or menopause, for optimal results wherever practical. The

Table 1 Effect of sex, menstrual cycle, contraceptive use and pregnancy on acute responses and adaptations to resistance training

	Acute response to resistance exercise			Adaptation to resistance training	
	Strength performance, e.g. 1 RM, MVC or training load output	Muscle protein metabolism	Hormonal response	Muscle strength	Muscle hypertrophy
Sex	↓ Absolute strength in females [17] ↓ Relative strength in females [17]	↔ Muscle protein synthesis rate [37]	↑ Testosterone in males [37] ↑ GH, cortisol in females [37] ↔ IGF-1 [37]	↔ Relative strength [27–29], some evidence of ↑ relative strength in females [30, 31]	↔ Muscle relative cross-sectional area [31, 40]
Menstrual cycle	↑ In FP compared to early LP [62]	↔ Between early FP and mid-LP [38]	↑ Estradiol, progesterone in mid-LP [64] ↔ Estradiol, progesterone in early FP [64] ↑ GH in mid-LP compared to early FP [63, 64] ↔ Or ↑ cortisol in LP [102] ↔ Testosterone, IGF-1 [56]	↑ With high frequency training in FP compared to LP [66, 67]	↑ Muscle diameter with high frequency training in FP compared to LP [66, 67]
Contraceptive use	↔ Between OC users and non-users [113, 115] ↔ OC androgenicity [113, 115] ↔ Monophasic OC phases [113, 115]	↓ Muscle protein FSR in third-generation OC users compared with non-users [118]	↑ GH in OC users compared to non-users [117]	↔ Between OC users and non-users [66, 114]	

FP follicular phase, *FSR* fractional synthesis rate, *GH* growth hormone, *IGF-1* insulin-like growth factor 1, *LP* luteal phase, *MVC* maximum voluntary contraction, *OC* oral contraceptive, *1 RM* one repetition maximum, ↑ significantly increased, ↓ significantly decreased, ↔ no significant difference

demand for female-specific programming is evident, with mobile applications that are supported by national sporting bodies already developed to provide females with personalised training recommendations tailored to their own menstrual cycle. Coaches and athletes are advised to consider periodising training using menstrual cycle data (i.e. from mobile applications) or by autoregulation, whereby athletes progressively overload resistance exercises based on how they feel on a daily or weekly basis [131].

7 Conclusions

This review has highlighted important differences in the resistance training performance, adaptation and skeletal muscle protein response to training between males and females, and amongst different female populations (Table 1). The findings have highlighted where researchers need to be vigilant to limit confounding physiological variables between and within female participants. However, the authors also caution against only testing female participants when endogenous or exogenous hormone levels are low and/or similar. Rather, it is important for future research to also investigate female participants across a range of time points (in the menstrual cycle, across stages of life), to understand the impact of hormonal variation on resistance exercise performance and skeletal muscle adaptation. The current landscape that encourages women's participation in recreational and elite exercise programmes demands an equal input from researchers into female exercise, health and performance. The authors advocate for researchers to invest in rigorous research that advances the current exercise prescription and training outcomes for females performing resistance training.

Compliance with Ethical Standards

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