

The relationship between oestrogen and muscle strength: a current perspective

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Kirsty Jayne ELLIOTT-SALE*

*School of Science and Technology, Nottingham Trent University - Nottingham - United Kingdom.

Abstract

The relationship between muscle strength and oestrogen is ambiguous and is still largely unresolved. The evidence for and against an effect of oestradiol on determinants of muscle function is equivocal and often contradictory. The bulk of the research in this area was performed during the eighties and nineties, using models of reproductive functioning such as; the menstrual cycle, the menopause and hormone replacement therapy, oral contraceptives and in vitro fertilisation treatment, to alter the female hormonal milieu. In the last decade, approximately 15 papers have demonstrated a relationship, both positive and negative, between the concentration of oestrogen and skeletal muscle strength. Conversely, around 20 articles have not shown any influence of oestrogen on a number of strength measures. The majority of these studies were performed using post-menopausal and eumenorrhic females. Most current studies use hormonal assays to confirm oestrogen status, however no recent studies have reported the bioavailable concentration of oestradiol. Similarly, no research in the last 10 years has used in vitro fertilisation treatment or pregnancy as acute and chronic models of supra-physiological changes in sex hormone concentration. Future work should focus on performing meta-analyses on each of the key components of muscle strength in an attempt to elucidate a causal relationship. In addition, models of reproductive functioning that cause the greatest magnitude of change to oestrogen concentration should be used, while controlling as many confounding factors as possible.

KEY WORDS: Oestradiol; Reproductive hormones; Muscular system; Females; Performance.

Introduction

During the eighties and nineties there was much debate and controversy about the effects of ovarian hormones on muscle strength in females¹⁻⁵. Researchers used various models of reproductive functioning to investigate this relationship including; the menstrual cycle⁶, the menopause⁷, in vitro fertilisation (IVF) treatment⁸, pregnancy⁹, oral contraceptives¹⁰ (OC's) and hormone replacement therapies¹¹ (HRT's). Since then, numerous review papers¹²⁻¹⁴ have been published, yet the number of original research outputs has declined. To date, there is still no consensus regarding the role of oestrogen in force production or universal guidelines for advising females about reproductive status and skeletal muscle function. This review will consider data from the last ten years examining the relationship between oestrogen and muscle strength. It is important to study this relationship as the female hormonal milieu changes across the lifespan and muscle strength

is an enabling factor which facilitates functional independence and athletic performance.

Interestingly, the association between sex hormones and the muscular system was first noted almost 100 years before the majority of research in this field was conducted: JACOBI¹⁵ observed periodic changes in muscle strength during the menstrual cycle. Since then, several authors have linked cyclical changes in muscle strength, in eumenorrhic females, with fluctuations in ovarian hormone levels across the menstrual cycle^{3,4,10,16-17}. However, there is also substantial evidence to the contrary^{1,5,18-20}. During the same period, numerous authors have reported a notable reduction in strength at the onset on the menopause that can be preserved by HRT^{11,21-23}. In contrast, a similar number of reports have contradicted this evidence and have shown no relationship^{2,7,24-25}. The influence of OC's on muscle function is also confusing with some authors^{16,26} suggesting an

effect and others showing no difference^{4,10}. For a comprehensive review of the literature published between 1980 and 2000 see CABLE and ELLIOTT¹².

Data from this era was impaired by a variety of design issues such as; inconsistent terminologies (e.g. menstrual cycle phase and postmenopausal status), inaccurate methods (e.g. basal body temperature assessment to confirm ovulation), subjective measures (e.g. retrospective questionnaires to establish menstrual cycle phase), grouping non-homogenous participants (e.g. using OC and

HRT users on different brands and types of exogenous steroid supplementation) and comparing incompatible strength measures (e.g. different test modalities and muscle types). For a detailed summary of these and other issues see CABLE and ELLIOTT¹², ELLIOTT-SALE et al.²⁷ and ELLIOTT-SALE and Martin²⁸. The purpose of this current perspective is to summarise the research published since 2004 and to critically evaluate if the research from the eighties and nineties has influenced and informed the research design of recent studies.

The evidence for an effect of oestrogen on muscle strength

During the last ten years approximately 15 papers have shown an effect of oestrogen on muscle strength or determinants of muscle strength (TABLE 1). Three studies used the menstrual cycle as a model of reproductive functioning²⁹, while two further studies combined the menstrual cycle with OC use³²⁻³³. One report examined the effects of OC consumption and withdrawal on strength³⁴ and one combined previous OC use with a control group that had never used OC's³⁵. Undoubtedly, the most common reproductive functioning models used in the literature in the last decade were the menopause and HRT³⁶⁻⁴⁴. These models were used to investigate numerous facets of muscle strength including; muscle stiffness³⁰ and soreness²⁹, dynamic and isometric force

production^{38,43}, power⁴¹, endurance³², performance³³, functional capacity³⁹ and gene expression³⁷. Generally, the relationship between oestrogen and muscle strength was positive; high concentrations of oestradiol were associated with the preservation of muscle strength and mass in addition to mobility and function³⁶⁻⁴⁴. However, one study showed a negative relationship between oestrogen concentrations and muscle function; ALLALI et al.³⁵ showed increased performance in a number of functional tests in previous OC users. Only one study showed a detrimental effect of high concentrations of oestrogen on muscle function; NICOLAY et al.³² found that static handgrip endurance was reduced in the late-follicular phase of the menstrual cycle when oestrogen levels are high.

TABLE 1 - Studies showing an effect of oestrogen on muscle strength or determinants of muscle strength.

Authors	Reproductive status	Strength tests	Conclusions
BELL et al. ³⁰	Eumenorrheic females (3-5 days after the onset of menses) & men.	Hamstring neuromechanical variables; hamstring musculotendinous stiffness, rate of force production, time to 50% peak torque, & electromechanical delay	Correlations exist between muscle properties & reproductive hormones. Females, however, may be more sensitive to reproductive hormones & their fluctuations.
DIELI-CONWRIGHT et al. ⁴⁴	Post-menopausal; HRT & non-HRT users.	10 sets of 10 maximal eccentric repetitions of single-leg extension on a dynamometer.	Data suggest that postmenopausal women using HRT express greater myostatin-related gene expression, which may reflect a mechanism by which oestrogen influences the preservation of muscle mass. Further, postmenopausal women using HRT experienced a profoundly greater myostatin-related response to maximal eccentric exercise.

continue

TABLE 1 - Studies showing an effect of oestrogen on muscle strength or determinants of muscle strength (continuation).

Authors	Reproductive status	Strength tests	Conclusions
SAKAMAKI et al. ³¹	Eumenorrheic females (follicular [FP] & luteal phase [LP]) & men.	MRI-measured biceps muscle volume (MV) & isometric elbow flexion strength.	Results indicate that muscle hypertrophy & strength gain are higher in the LP than in the FP following 6 days of blood flow restriction training, although the sex difference in the training response is non-existent.
BRYANT et al. ³³	Monophasic OC pill users and eumenorrheic females.	Leg stiffness and foot centre of pressure during hopping.	Consistent lower limb dynamics of monophasic OC users demands less reliance on acutely modified neuromuscular control strategies during dynamic tasks and may explain the lower rate of lower limb musculoskeletal injuries in this population compared with non-OC users.
FINNI et al. ⁴³	Post-menopausal monozygotic twin pairs discordant for HRT.	Maximal voluntary torque & twitch characteristics using electrical stimulation before & after intermittent dynamic plantarflexor exercise until exhaustion.	In early postmenopausal women, involuntary but not voluntary force-generating mechanisms of the plantarflexors are augmented by the use of HRT.
ALLALI et al. ³⁵	Pre & post-menopausal; who were either (1) previous OC's users or (2) never used OC's.	Timed get-up-and-go test, five-times-sit-to-stand test & 8-feet speed walk.	OC past users had significantly greater performance, on three strength-related tests than the never used group.
DIELI-CONWRIGHT et al. ⁴⁰	Post-menopausal; HRT & non-HRT users.	10 sets of 10 maximal eccentric repetitions of single-leg extension on a dynamometer at 60 degrees /s with 20-s rest periods between sets.	Postmenopausal women not using HRT experienced greater muscle damage after maximal eccentric exercise, indicating a possible protective effect of HRT against exercise-induced skeletal muscle damage.
RECHICHI & DAWSON ³⁴	Three time points of a single OC cycle; during consumption phase, early & late withdrawal phase.	Drop jumps (30cm and 45cm heights), a counter movement jump, a 10s cycle sprint test & a 5x 6s repeated sprint cycle test.	Reactive strength varied significantly throughout an OC cycle, possibly due to the action of hormones on neuromuscular timing & the stretch-shortening cycle.
RONKAINEN et al. ⁴¹	Post-menopausal monozygotic female twin pairs discordant for HRT.	Habitual & maximal walking speeds over 10 m, thigh muscle composition, lower body muscle power assessed as vertical jumping height, and maximal isometric hand grip and knee extension strength.	Long-term HRT was associated with better mobility, greater muscle power, & favourable body & muscle composition among 54- to 62-yr-old women. HRT is a potential agent in preventing muscle weakness & mobility limitation in older women.
VAN GEEL et al. ⁴²	Post-menopausal.	Maximum quadriceps extension strength (MES) & maximum handgrip strength, timed up-and-go test.	Age-related loss of MES in postmenopausal women is partly dependent on the presence of endogenous bioavailable testosterone and oestrogen.

continue

TABLE 1 - Studies showing an effect of oestrogen on muscle strength or determinants of muscle strength (continuation).

Authors	Reproductive status	Strength tests	Conclusions
NICOLAY et al. ³²	Eumenorrheic & OC users; tested early-follicular (day 4-6), late-follicular (day 11-13), & luteal (day 20-23) phases of the menstrual cycle. Male control participants also.	Grip strength; single repetition maximum voluntary contraction, 20-repetition grip test, & a 30-s static (continual) hold.	Menstrual cycle phase did not have a detectable effect on any measure of strength (absolute force production) in eumenorrheic women or women taking chemical contraceptives. However, static endurance (percent change in force throughout the 30-s hold) was significantly reduced during the late-follicular phase in the eumenorrheic women, when levels of oestrogen are expected to be elevated. The women using OC's did not experience any similar fluctuation in static endurance across the three phases; however the static endurance of the contraceptive group was significantly lower than the eumenorrheic women during both the early-follicular and luteal phases.
POLLANEN et al. ³⁷	Post-menopausal; HRT & non-HRT users.	Explorative microarray experiment to characterize possible effects of continuous, combined HRT & oestrogen deprivation on skeletal muscle.	During the early postmenopausal years, when there is no counteracting medication available, muscle transcriptome changes notably, whereas HRT appears to slow down this phenomenon & could therefore aid in maintaining proper muscle mass & function after menopause.
ROLLAND et al. ³⁸	Post-menopausal.	Percentage of loss per year of isometric knee extensor strength.	Loss of muscle strength was positively correlated with oestrone ($r = 0.29$) and was significantly predicted by oestrone (0.32; 6%).
SOWERS et al. ³⁹	Midlife women.	2-lb lift, sit-to-stand, timed stair climb, timed walk, velocity & hand grip.	Hysterectomy, even with availability of an oestrogen source, seems to be a "risk" state for diminishing physical function at midlife, & this may initiate a vulnerable stage for future compromised quality of life.
KERKSICK et al. ²⁹	Men & women (eumenorrheic; midluteal phase of menstrual cycle).	Knee extensor strength & soreness.	Strength changes were similar among genders, however in females 17 β -oestradiol provided some protection against muscle injury, oxidative stress, & apoptosis. Differences between genders may provide greater endogenous protection against oxidative stress and apoptosis.
ONAMBELE et al. ³⁶	Pre-menopausal, post-menopausal with HRT use & post-menopausal without HRT use.	Size, strength, voluntary activation capacity & index of crossbridge force state in the thumb adductor muscles.	The presence, rather than absence of oestrogen, is associated with relatively higher muscle function, which limits the potential for any further training-induced increments in muscle performance. They proposed that this would be expected if the muscle strengthening actions of training and oestrogen share a common, partially saturable physiological pathway. Furthermore they suggested that the mechanism that is involved in the early training-induced strength increment cannot be due to increased size or recruitment & would appear instead to be due to increased motor unit firing frequency.

The evidence against an effect of oestrogen on muscle strength

Since 2004, approximately 20 studies have not shown any relationship between oestrogen and muscle strength (TABLE 2). Of these studies, nine employed a menopause model with and without HRT⁴⁵⁻⁵³, while six used the menstrual cycle⁵⁴⁻⁶⁰. One study used a pubertal model⁵⁹ and the remaining studies used OC's⁶¹⁻⁶³. Muscle function was assessed through a variety of measures including; maximal dynamic⁵³ and isometric⁵⁸ strength, endurance⁴⁶, performance⁶⁰, power⁴⁵ and functional capacity⁴⁸. Despite significant changes in oestrogen concentration, none of these studies were able to demonstrate the putative role of oestrogen in determining muscle strength.

TABLE 2 - Studies showing no effect of oestrogen on muscle strength or determinants of muscle strength.

Authors	Reproductive status	Strength tests	Conclusions
CHOQUETTE et al. ⁵³	Overweight-to-obese post-menopausal women; divided into 4 groups: (1) placebo, (2) isoflavones, (3) exercise & placebo & (4) exercise & isoflavone.	Maximal muscle strength at the leg press & the bench press, muscle mass index, muscle quality in the legs & relative strength.	Isoflavones, irrespective of exercise, did not produce changes in any strength related variables.
EKENROS et al. ⁶³	Same woman at 3 specific phases of an OC cycle, as well as during a menstrual cycle of the corresponding cycle days (non-OC cycle).	Maximal isokinetic muscle strength of knee extensors, isometric handgrip strength, & 1-leg hop test for distance.	No support for any significant influence of OC use on muscle strength & hop performance in healthy moderately active women.
WILD et al. ⁵⁹	Pubertal girls, in Tanner stage II & 4-6 months from their peak height velocity. Tested 4 times during the 12 months of their growth spurt, according to the timing of their maturity offset (test 1: maturity offset = -6 to -4 months; test 2: maturity offset = 0 months; test 3: maturity offset = +4 months; test 4: maturity offset = +8 months).	Anterior knee laxity, lower limb flexibility, & isokinetic strength.	A significant effect of time on anterior knee laxity was shown from the time of peak height velocity, although no changes in oestradiol concentration were displayed over time. Participants displayed a significant increase in isokinetic quadriceps strength over time, with no apparent increase in isokinetic hamstring strength.
JACOBSEN et al. ⁵²	Women aged >70 were randomized; 290 received the allocated intervention: 97 placebo, 101 raloxifene, & 92 tibolone.	Handgrip strength.	In women >70 years old, raloxifene and tibolone significantly & similarly increased body mass density but not muscle strength.
RIBOM et al. ⁵¹	Post-menopausal.	The stand-up test was used to assess leg muscle strength & balance. Handgrip & leg muscle strength were measured using JAMAR & modified Cybex dynamometers.	Short-term treatment with low-dose tibolone (1.25 mg/d) seems not to affect muscle strength in older women.
BURGESS et al. ⁵⁷	Eumenorrheic; days 3 +/- 0.4, 13 +/- 0.2, and 21 +/- 0.3.	In vivo patellar tendon properties assessed by dynamometry.	In terms of tendon properties, menstrual cycle phase does not necessarily need to be considered when organizing training and competition schedules.

continue

TABLE 2 - Studies showing no effect of oestrogen on muscle strength or determinants of muscle strength (continuation).

Authors	Reproductive status	Strength tests	Conclusions
MONTGOMERY & SHULTZ ⁵⁸	Eumenorrheic; early follicular and either the early luteal or midluteal phases.	Maximal voluntary isometric contraction (MVIC) torque of the knee flexors and extensors.	Thigh MVIC torque did not change from time of menses (when oestradiol & progesterone were lowest) to time in the luteal phase after an unopposed oestradiol rise or combined oestradiol & progesterone rise.
TSAMPOUKOS et al. ⁶⁰	Three phases of the menstrual cycle; follicular, just prior to ovulation & luteal.	Repeated 30-s sprint on a non-motorised treadmill interspersed with a 2-min rest, peak power output & mean power output.	Hormonal fluctuations due to menstrual cycle phase do not interfere with maximal intensity whole body sprinting & the metabolic responses to such exercise.
NICHOLS et al. ⁶²	Premenopausal; OC & non-OC users.	One-repetition maximum bench press, 10-repetition maximum leg extension, isokinetic peak torque bench press, & isokinetic peak torque leg extension.	The use of combination OCAs did not provide sufficient androgenic effect to increase strength gains beyond the stimulus of the training protocol.
ABT et al. ⁵⁶	Pre-menopausal; eumenorrheic (menses, post-ovulatory, & mid-luteal phases of the menstrual cycle).	Fine motor coordination, postural stability, knee strength, & knee joint kinematics and kinetics.	Neuromuscular & biomechanical characteristics are not influenced by fluctuation in oestradiol and progesterone. All neuromuscular & biomechanical characteristics remained invariable between testing sessions despite concentration changes in oestradiol and progesterone.
HERTEL et al. ⁵⁵	Eumenorrheic; mid-follicular, ovulatory, & mid-luteal stages.	Knee flexion & extension peak torque, passive knee joint position sense, & postural control in single leg stance.	Neuromuscular control & knee joint laxity do not change substantially across the menstrual cycle of females despite varying oestrogen & progesterone levels.
LEBRUN et al. ⁴⁹	Women aged 56-73 years, 8-30 years postmenopausal.	Muscle strength was measured using dynamometry.	No consistent relation was found between serum levels of hormones measured & strength. In the elderly & late postmenopausal women hormonal factors do not predict quality of life.
SIPILA et al. ⁵⁰	Post-menopausal women.	Isometric muscle strength.	Higher serum oestradiol concentration & greater muscle strength were independently associated with a low incidence of fall-related limb fractures even after adjustment for bone density. Hormonal status & muscle strength have their own separate mechanisms protecting from fall-related fractures.
DAYAL et al. ⁴⁶	Postmenopausal women randomized to (1) hydroepiandrosterone (DHEA) 50 mg daily, (2) conjugated equine oestrogen (CEE) 0.625 mg daily, (3) DHEA 50 mg+CEE 0.625 mg daily, or (4) placebo.	Muscle mass, muscle strength & muscle endurance.	Compared with no hormone therapy, none of the supplemental hormone groups caused significant changes in muscle mass, muscle strength & muscle endurance. Androgen replacement therapy, with DHEA, to menopausal women increases serum androgen levels without any appreciable effect on muscle cross-sectional area, muscle strength, muscle function, or improvement in health-related QOL.

continue

TABLE 2 - Studies showing no effect of oestrogen on muscle strength or determinants of muscle strength (continuation).

Authors	Reproductive status	Strength tests	Conclusions
ELLIOTT et al. ⁶¹	Pre-menopausal; OC & non-OC users (days 7 & 14 of pill consumption & day 5 of pill withdrawal & days 2 & 21 of the menstrual cycle).	Maximum dynamic & isometric leg strength & maximum isometric strength of the first dorsal interosseus muscle.	Oral contraceptive use does not significantly affect muscle strength. Moreover, oral contraceptive users are not stronger or weaker than their eumenorrhic counterparts.
GRUNDBERG et al. ⁵⁴	Pre-menopausal.	Quadriceps, hamstring & grip strength.	The TA-repeat in the human ERalpha gene does not correlate with muscle strength or body mass measurements, indicating that body composition is not as sensitive to genetic variation in this receptor as other target organs for oestrogen.
SCHAAP et al. ⁴⁷	Men & women aged 65-88 years.	Physical performance, functional limitations & muscle strength.	Low levels of sex hormones were associated with impaired mobility and low muscle strength in men, but not in women. Levels of sex hormones were not associated with the incidence of falls neither in men, nor in women.
TAAFFE et al. ⁴⁸	Post-menopausal; current estrogen replacement therapy (ERT) users & nonusers	Isometric hand grip & isokinetic knee extensor strength assessed by dynamometry. Physical function assessed using 6-m walk & narrow walk speed, repeated chair stands, & standing balance.	The associations between ERT & muscle composition & strength were minor & did not translate into improved physical function. Initiation of ERT for preservation of muscle composition & function may not be indicated.
MADDALOZZO et al. ⁴⁵	Non-randomized [self-selected HRT and non-HRT replaced] post-menopausal women.	Upper- & lower-body peak force by isokinetic dynamometry & leg power by the Bassey Power Rig.	HRT does not play a role in either increasing or maintaining strength, lean muscle mass, lower limb power, or the attenuation of increases in total body or abdominal fat, at least in this group of postmenopausal women during the initial years of menopause.

Methodological issues and advancements

The menopause and the menstrual cycle remain the most popular models for investigating the effects of oestrogen on muscle strength; accounting for more than two thirds of recent publications. Surprisingly, the IVF model has not been used 2004, despite providing acute supra-physiological changes in oestradiol concentration without the confounding factors associated with the menopause and the menstrual cycle: notably age and inter and intra-individual variability in hormone secretion. In addition, both puberty and pregnancy have been under-utilised, even though they provide substantial chronic natural changes in the female hormonal milieu⁹.

It is encouraging to note that the majority of recent studies have used blood samples to confirm

reproductive status; post-menopausal^{38,50}, menstrual cycle phase^{29,30} and OC use^{9,34}. However, no studies have specifically measured the bioavailable concentration of oestradiol, which may be of particular interest for studies using post-menopausal groups; previous work has shown that the bioavailability of oestradiol did not significantly differ between two phases of the menstrual cycle⁶⁴. The bioavailable part of oestrogen is not a set proportion of the total concentration and is dependent on its affinity to and concentration of its binding protein. Therefore, models of reproductive functioning, such as the menopause, might influence the bioavailable concentration of oestradiol and subsequently its relationship with muscle strength. Moreover, there are

still a number of publications that have used a variety of types and brands of OC's^{33,63} and HRT's^{39,41}, which can lead to extremely large variation in hormone concentration when grouped together and may ultimately lead to type II errors²⁷.

The term "muscle strength" is too ambiguous and makes comparing studies and drawing any conclusions very difficult. In the last decade, over 20 indices of muscle strength or determinants of muscle

strength have been investigated (see TABLES 1 and 2 for exact tests). It would be judicious to perform a meta-analysis on each of the main components of strength (dynamic, isometric, endurance, power) in relation to oestrogen status. It is interesting to note that recently several studies have investigated the effect of oestrogen on the gene expression influencing muscle strength and hypertrophy^{37,44}, indicating a new direction for this type of research.

Conclusions

To date, there is still no unanimous consensus regarding the effect of oestrogen on muscle strength. There is almost the same number of papers supporting an effect of oestrogen on skeletal muscle function as there are showing no effect. Moreover, both positive and negative correlations have been reported when an effect was evident. Future work should focus on discrete elements of muscle strength and use the

best and most appropriate models of reproductive functioning available; i.e. models that cause the greatest magnitude of change in sex hormone concentration (e.g. IVF). In addition, future work should aim to control as many confounding factors as possible (e.g. age, smoking, exercise status etc.). Moreover, there is a need to conduct meta-analyses on previous research in order to move towards a conclusion on this topic.

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ENDEREÇO

Kirsty Elliott-Sale
Sport, Health and Performance Enhancement (SHAPE)
Research Group
School of Science and Technology
Nottingham Trent University
Clifton Lane
Clifton - Nottingham - NG11 8NS - UK
e-mail: kirsty.elliottsale@ntu.ac.uk

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