Commentary:

Female Physiology-Endocrinology: Education is Lacking and Innovation is Needed!

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Abstract

Women, throughout their lifespans, undergo unique endocrinological changes relative to their reproductive hormones. The influence of how the female sex steroid hormones have non-reproductive actions is a trending topic of great interest in the exercise-sports sciences, especially among women of reproductive age. Herein, we present several key points on our perspective for moving the study of this topic forward in the future. These are; *i*) encouraging researchers to pursue high-quality research on female physiology-endocrinology in the exercise-sports science setting, *ii*) the need for exercise-sports science educational curriculums at the university level to embrace the study of female physiology-endocrinology area, and *iii*) the need for innovation in the study of this topic and as such we propose using research design models involving supraphysiological hormonal states *in vivo*, i.e., pregnancy and IVF treatment, to gain new insights on sex steroid hormonal actions in women. Herein we provide the rationale for our recommendations as well as a brief physiological overview of these clinical states. Exercise sports sciences need more studies on women! But there is a need to "think outside the box" on this topic and we encourage researchers to be unconventional, be bold, think creatively, and contemplate whether these supraphysiological hormonal states might give them insightful information on female physiology and ovarian sex steroid hormones actions.

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1. Introduction – We need educations

In the last decade, there has been an exponential growth in research trying to understand how human female physiology varies from that of males, and the potential application of these variations to impact the exercise-sports training regimes and competitive performance of athletic women. It is about time!

Women make up half of the world's population and yet they have been, and still are, grossly under-studied in the exercise-sports sciences. There are several reasons for this occurrence, but in our opinion, one key reason is poor pedagogical approaches in the foundational education of exercise-sports scientists. That is, university exercise physiology curriculums are male-centric, and specific female physiology if discussed at all, is typically relegated to one chapter in a textbook (and, that chapter might not even be taught!). We are of the mindset that the unique aspects of female physiology have not been adequately emphasized in university programs and this error of omission has allowed exercise-sports scientists to be ill-prepared to research this topic.

We based these opinions on: 1) our experiences as academics who collectively have over 50 years of university teaching-research experience with more than 100 peer-reviewed research papers on female physiology, 2) our service-work to the field through professional organizations, and 3) dialogue with colleagues and associates across the broad spectrum of our discipline worldwide.

Perhaps the most pressing female physiology topic in the exercise-sport sciences revolves around the roles of the female sex steroid hormones to influence and modify the exercise physiology of women (Hackney 2021; Oothuyse et al. 2022). Estrogens and progesterone (ovarian sex hormones) not only regulate female reproduction but have been linked directly and indirectly to affecting metabolism, the cardiovascular system, thermoregulation, muscular function, as well as mood and perception across a woman's lifespan (Oothuyse et al. 2022). And, if pedagogy on female physiology is taught on a limited basis, exercise endocrinology is perhaps

even more rarely developed fully as a curricular topic. As a result, there is a lack of female endocrinology knowledge in exercise-sports scientists, and as such they are challenged to the ever-changing reproductive hormonal landscape in women in their research. Put simply, there are generations of researchers who do not know this specific topic well (or at all) and can be/are overwhelmed by its "complexity" (whether they admit it or not). It is our contention that this situation has led to the avoidance of studying female exercise physiology-endocrinology by many, or the study of it has utilized poor research design approaches as researchers "jump on the bandwagon" to study the new *hot topic* in the field. The latter has led to ambiguous or erroneous findings being reported in the literature on women and their hormones.

"Carpe diem" – it is time for university exercise-sports science curriculums to be revamped, revised, and fully embrace this topic. As girls' and women's sports participation continues to grow, we need well-prepared scientists who fully understand female physiology and endocrinology if we are to optimize their sporting potential and overall health and well-being.

2. Besides education, we need innovation

As alluded to prior, the impacts of the female sex steroid hormones on non-reproductive physiology can be associated with many aspects of exercise-sporting ability, such as training adaptation, injury rates, and competitive performance potential of girls and women (Elliott-Sale et al. 2020; McNulty et al. 2020). This latter point, performance, has generated tremendous contemporary public and media interest in whether female athletes of reproductive age should adjust their training-competitive regimes to accommodate for sex steroid hormone changes (whether the changes are of an endogenous [e.g., menstrual cycle] or exogenous [hormonal contraceptive use] nature). Whether such adjustments are warranted is an issue of debate in the scientific community as evidence "for" and "against" such practices exist. The entire issue is complicated by a lack of adequate high-quality research evidence from which to draw definitive conclusions (as noted earlier), and some voices in the sports-media communities "getting the cart

in front of the horse" and making claims of what women should do without having a sound foundation for their recommendations (Colenso-Semple et al. 2023: Elliott-Sale et al. 2021).

Debate, however, is not a bad word in science! Such lack of resolution on what should be done to aid sporting women and help them reach their optimal ability should be a driving force for investigators prompting them to pursue novel and innovative study approaches to research questions. To that end, in studying the roles and influences of female sex steroid hormones, it is our premise that the unique endocrinology experienced by many women in their lifespan provides some innovative and exceptional research approaches to be utilized for understanding the underlying mechanisms for the non-reproductive roles of sex steroid hormones.

As such, we propose one research approach for studying the physiological effects of sex steroids, i.e., specifically examining *in vivo* supraphysiological hormonal states in women. Herein we discuss the potential use of the states of pregnancy and *in vitro* fertilization (IVF) as potential research models. In so doing our overarching intent is to stimulate female physiology-endocrine researchers in the exercise-sports sciences to "*think outside the box*" in research study designs as they pursue understanding sex steroid hormonal effects and mechanisms.

Causality is the science of cause and effect and the ultimate goal in the pursuit of the research hierarchy in the context of the Scientific Method. However, much of the research conducted in the exercise-sports science area revolves around research designs that do not permit true "cause and effect" to be elucidated (e.g., observational, cross-sectional, quasi-experimental designs, etc.). A key premise in causality is understanding mechanisms of how effects are brought about and understanding the actions of female sex hormones is no different (Oothuyse et al. 2022).

It is our premise that to date, many approaches to understanding the non-reproductive role of these hormones have been too conservative and not innovative enough. The pursuit of new and innovative research designs may provide/allow greater elucidation of the mechanistic actions of estrogens and progesterone. Additionally, *in vivo* human research can be greatly

confounded by factors that are difficult to control in free-living research settings. As such any aspects of research designs that can mitigate aspects of the variance encountered in working with humans are advantageous. We feel utilizing the states of pregnancy and IVF as research design models can provide insight into hormonal mechanistic actions as well as alleviate some confounding variance in data outcomes. Table 1 provides a summary of the advantages of using each of these models. In theory, testing outcomes under these conditions could provide a more rigorous research design and as such provide data of a higher scientific caliber.

3. Physiology of the Pregnancy Model

To date, most of the research on the exercise physiology responses of healthy reproductive-age women has either ignored the non-reproductive role of sex steroid hormones or has used the fluctuations in their hormone levels as a research design manipulation. The former approach has led to some studies with poor scientific outcomes. The latter case has typically involved exercise assessments in separate phases of the menstrual cycle. That is experiments in the early follicular, late follicular (ovulation), or mid-luteal phases of their menstrual cycles creating differing sex steroid hormonal environments, e.g., low estrogens/progesterone, high estrogens/low progesterone, and high estrogen/progesterone (Elliott-Sale et al. 2021). To a much lesser extent, some researchers have studied the varying hormonal states of women on hormonal contraceptives (e.g., oral pills or hormonal intra-uterine devices), but this approach to studying female physiology has always been challenging due to the different pharmaceutical formulations of estrogens/progestins used in the contraceptive techniques (Elliott-Sale et al. 2020).

Perhaps the rarest of female physiology studies in the exercise-sports sciences has involved the exercise assessment of pregnant women. Most certainly from an ethical point of view, it is challenging to get such work approved by institutional review boards (i.e., ethics committees), as there is always a great concern for the health and safety of the mother as well as the fetus. Furthermore, the focus of much of this research is typically; *i*) on the feasibility and fitness efficacy of maternal exercise training throughout pregnancy, *ii*) the safety of such exercise

on the fetus, and/or *iii*) the implication of exercise on labour and delivery. These are all critically important issues to observe and understand, but the changes in the hormonal milieu of pregnant women through gestation are remarkable (Feldt-Rasmussen and Mathiesen 2011; Fotherby, 1984). Estrogen and progesterone are produced throughout the first trimester in similar quantities as those produced during the luteal phase of the menstrual cycle (both steroid hormones elevated). However, during the second trimester, secretion of progesterone increases rapidly, and then stabilizes or declines slightly during the final trimester. At term, maternal progesterone levels are approximately six times greater than during the late luteal phase of the menstrual cycle. Estrogen levels begin to rise early in the second trimester and continue to increase throughout pregnancy (Feldt-Rasmussen and Mathiesen 2011). These dramatic hormonal changes are depicted in Figure 1.

The magnitude of the sex steroid hormone changes from the first to second to the third trimester of a woman's pregnancy pattern that of a classic "dose-response experiment" one might observe in clinical pharmacology (Emmett et al. 2020). Furthermore, they truly represent supraphysiological levels versus those of the menstrual cycle and additionally represent a chronic exposure paradigm due to the gestational duration.

While maternal-fetal safety is and should be a paramount concern in exercise pregnancy studies, the potential for understanding how female physiology is altered when such hormonal change occurs is a fascinating research design opportunity and underutilized. Furthermore, this proposed approach, however, is not novel, as Elliott and associates (2005) used it in studying muscular maximum force production in women over 20 years ago.

4. Physiology of the IVF Treatment Model

In vitro fertilization treatment is an exaggerated model of the menstrual cycle. During the first phase of treatment, estrogen and progesterone concentrations are downregulated, to levels indicative of menses. Following downregulation, estrogen concentrations are increased to elevated physiological levels while progesterone concentrations stay low, a similar pattern but not

to the magnitude of the late follicular phase of the menstrual cycle, i.e., low progesterone and high estrogen. During the third phase, progesterone concentrations also are increased to supraphysiological levels; a similar pattern but not to the magnitude of the mid-luteal phase of the menstrual cycle, i.e., high progesterone and high estrogen (see Figure 1). Finally, estrogen levels are allowed to decline, while progesterone levels remain elevated. These hormonal changes are typically brought about by a cocktail of hormones being administered to a woman. Such as human chorionic gonadotrophin (hCG), gonadotrophins, and other hormonal analogs, including estrogen and progesterone (Choe and Shanks 2022; Lebovic et al. 2013). An IVF treatment may include a controlled ovarian hyperstimulation (COH) procedure. COH involves the administration of oral and/or injectable drugs (such as gonadotropin-releasing hormone antagonists) to induce ovulation in the anovulatory infertile patient, and superovulation in the ovulatory infertile patient (N.B., COH can also be used as an *in vivo* procedure uncoupled to IVF treatment) (Wang et al. 2011).

The magnitude of the hormonal change with IVF is not that typically seen in pregnancy and most certainly the exposure is of a more acute period (~3 weeks) but nonetheless can exceed 10 to 20 times that of the late-follicular (ovulation) and mid-luteal phase of the menstrual cycle. Although the specific hormone changes and levels are a function of the pharmaceutical approach used by the healthcare provider in treating women. Again, Elliott and associates (2005) as well as Greeves et al. (1997) successfully used this approach to examine sex steroid hormonal changes across separate phases of IVF treatment to determine the influence on muscular maximum force production ability in women.

5. Limitations and Design – Approaches Issues

The use of either a pregnancy or an IVF model to study sex steroid hormones is unique but has limitations. Firstly, researchers must be cognizant of the mental and emotional stress each of these situations presents for a woman (Glick & Bennett, 1981). As such, there is a strong likelihood that no matter how supportive a woman may be for wanting female physiology research

to be undertaken, they may still say no and not choose to participate. Or they may limit what measurement outcomes they are willing to have assessed, obviously impacting aspects of study protocols and evaluations. In addition, even if they are willing to take part, they may remain tentative in their approach to the research for fear of disrupting their treatment.

Secondly, physiological changes such as body composition (body mass and or percentage of body fat) can be confounding factors for the certain dependent variables being studied within a research paradigm. In each of these conditions (pregnancy-IVF) women undergo such compositional changes These concerns would be more so in pregnancy than in IVF. In a similar vein, the anatomical physique changes in pregnancy can create research challenges, e.g., the center of gravity shifts in a woman (hence biomechanical alterations occur), and internal organs are displaced perhaps affecting aspects of functionality.

Thirdly, either condition might have medical restrictions, voluntary or involuntary, on the levels of physical activity and what type of activity is and is not allowable. Again this creates a limitation on what type and to what extent an exercise research intervention/treatment may be utilized. However, this also presents an opportunity for creativity in determining means to exercise challenge (testing, training) a woman participant. But, most certainly recruitment of pregnant/IVF treatment women can be difficult as is the case with most clinical populations.

Finally, in much of the human-based exercise-sports science research, the “gold standard” for a research design is a repeated measures approach. The research participant in this way serves as their own control and the role of between-individual variability confounding results is mitigated. This preferred approach may not be possible for a variety of reasons (e.g., the timeline of pregnancy [9 months] just may not be possible for some research protocols). Alternatively, between groups (supraphysiological vs. normal status) cross-sectional type designs either at one phase of hormonal levels or multiple (longitudinal) might be necessary. Such designs have limitations relative to understanding cause and effect and typically require greater subject numbers for adequate statistical power.

6. Conclusions

The physiology of women and men is highly comparable, and yet sex differences exist. Women, throughout their lifespans, undergo unique endocrinological changes relative to their reproductive hormones. The influence of how the female sex steroid hormones have non-reproductive actions is a trending topic of great interest in the exercise-sports sciences. This is especially true for understanding exercise training responses and sports performance capabilities in women of reproductive age.

Herein, we note several main points on the aforementioned topic; *i)* additional high-quality research is needed on female physiology-endocrinology in the exercise-sports science setting, *ii*) exercise-sports science educational curriculums at the university level need to embrace the study of female physiology-endocrinology, and *iii*) innovation in the study of this topic is needed and we propose one such innovative approach – using research design models involving supraphysiological hormonal states, i.e., pregnancy and IVF treatment, to gain new insights.

Relative to the last point, we recognize in many settings there can be social sensitivities to doing research "experimentation" on women in these clinical states and hence may be viewed as taboo. But precedent exists for such research in the exercise-sports sciences, and we encourage researchers to nonetheless be unconventional, be bold, think creatively, and contemplate whether these supraphysiological hormonal states might give them insightful information on female physiology and sex steroid hormones actions.

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Table 1. Advantages to use of pregnancy and in vitro fertilization (IVF) conditions as research models to understand the roles and effects of female sex steroid hormone on exercise physiology.

Pregnancy Model
1. Overcomes the inter and intra-individual variability in ovarian hormone concentrations seen in eumenorrheic menstrual cycles
2. Overcomes the age-related effects seen in post-menopausal studies
3. More chronic and substantial changes in sex hormone levels than experienced during the menstrual cycle
4. Provides a longitudinal model that can be investigated across a broad hormonal spectrum - from menstrual cycles to supraphysiological, to lactational amenorrhea - within a calendar year
5. Unlike the menstrual cycle, pregnancy results in changes in bioavailable oestradiol and testosterone
IVF Model
1. 1-3 and 5 above
2. Allows the effects of estrogen to be independently studied from other reproductive hormones

Figure 1. Typical changes in key the reproductive hormones of women throughout pregnancy. Wikimedia Commons - This file is licensed under the Creative Commons Attribution-Share Alike 4.0 International license (https://creativecommons.org/licenses/by-sa/4.0/legalcode).

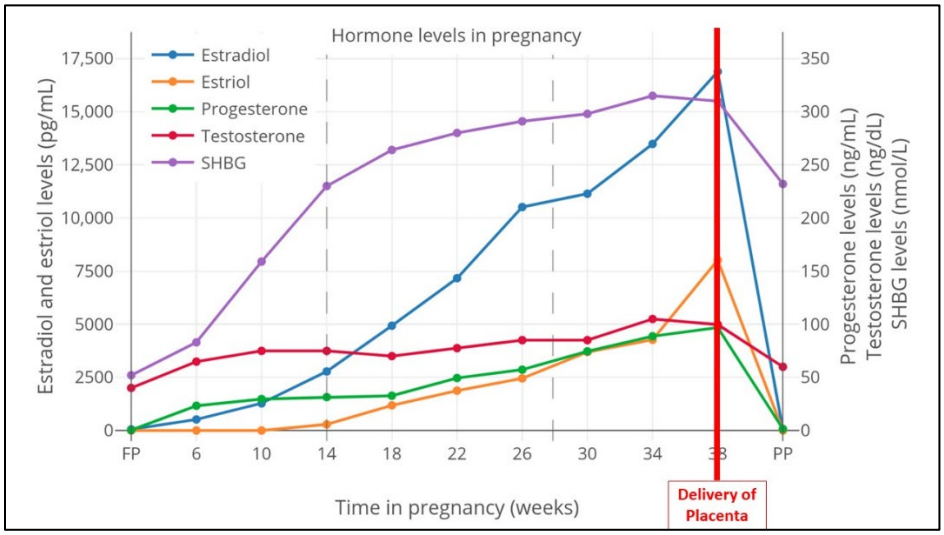

Figure 2. Typical hormonal levels during the eumenorrheic menstrual cycle, pregnancy, and IVF treatment of a woman (reproductive age) (Elliott et al. 2003, 2005).