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VIEWPOINT

Variation in physiological function within and between menstrual cycles: uncovering the contributing factors

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The menstrual cycle is a biological rhythm characterized by cyclical variations in endogenous hormone concentrations. The primary function of the menstrual cycle is to support reproductive function; however, it is well-established that changes in these endogenous sex hormone concentrations can affect biological tissues and systems containing the respective hormone receptor(s). Indeed, studies investigating hormonal influences at a cellular level demonstrate large, and often distinct effects of key sex hormones, such as oestrogen and progesterone, whereas in contrast, *in vivo* studies into physiological function across the menstrual cycle in humans often show heterogeneity in reported outcomes. One example of this is the assessment of vascular function via flow mediated dilatation (FMD), with a recent systematic review and meta-analysis by Williams et al. (2020) highlighting considerable heterogeneity between studies investigating the change in FMD across the menstrual cycle. In a recent issue of *Experimental Physiology*, Liu et al. (2021) aimed to explore the heterogeneity in FMD changes across the menstrual cycle, in an attempt to elucidate the contributing mechanisms.

Typically, it is thought that much of the heterogeneity in menstrual cycle research can be explained by methodological differences between studies. For example, Williams et al. (2020) observed great between-study variance which the authors concluded could be partially attributed to differences in menstrual cycle phase identification and verification. As such, guidelines exist to aid researchers with experimental design of studies investigating physiology and exercise performance across the menstrual cycle (Janse de Jonge et al., 2019). Specifically, a 'three-step method' has been advocated to identify and verify menstrual cycle phases, with this approach considered best practice for experimental design within this field. The intention of this experimental design is to reduce variability and heterogeneity in the literature by ensuring homogeneous hormonal profiles. This approach requires the concurrent use of menstrual cycle mapping and urinary ovulation kits to identify menstrual cycle phase and to confirm an ovulatory cycle, followed by serum measurement of both oestrogen and progesterone concentrations to retrospectively confirm menstrual cycle phase. In a recent systematic review and meta-analysis investigating the effects of menstrual cycle phase on exercise performance, we highlighted that few of the included studies used the trio of recommended methods to identify and verify menstrual cycle phases, which might partly explain the large between-study variance reported in the results (McNulty et al., 2020). However, the present paper by Liu et al. (2021) used this three-step method and still discovered substantial variability within and between menstrual cycles, demonstrating that the conflicting findings reported in the research to date might not be fully explained solely by methodological differences. Additionally, whilst the three-step method is suitable for identifying and verifying menstrual cycle phase, it might not be sufficient for eliminating heterogeneity within menstrual cycle research.

Liu et al. (2021) examined the group-level and intra-individual reproducibility of early follicular to late follicular changes in FMD across two consecutive menstrual cycles in healthy, eumenorrhoeic women. The authors used the established best practice three-step method for identifying and verifying menstrual cycle phases. The results revealed that at the group-level there was no effect of menstrual cycle phase on FMD. At the individual level, phase changes in FMD were inconsistent, with only 4 of the 14 participants displaying a directionally consistent change in FMD, which was greater than typical error, between two consecutive menstrual cycles. Therefore, despite the use of the recommended best practice, the change in FMD in cycle 1

did not predict the phase change in FMD in cycle 2. As such, the findings from Liu et al. (2021) suggest that in addition to experimental design, there are other mechanisms contributing to this heterogeneity.

Additional factors contributing to the observed heterogeneity in Liu et al. (2021) could be between-cycle variation in hormone concentrations, with many participants demonstrating considerable intra-individual variability in oestrogen concentrations between consecutive cycles. Additionally, within- and between-cycle hormone receptor activity and function in endothelial tissue might also be another mechanism that underpins variability in FMD responses (Gavin et al., 2009). Finally, the bi-directional relationship between female sex hormones and lifestyle factors (e.g., stress, sleep, nutrition and exercise) is known to alter physiology, and could conceivably contribute to the intra-individual variability in physiological function between menstrual cycles. Collectively, the results of Liu et al. (2021) demonstrate that physiological changes might not be the same across consecutive menstrual cycles. Therefore is it any wonder there is heterogeneity in the literature?

At present, it appears that even if we are to maximise the internal validity of studies with female participants through the use of the best practice experimental designs, there might still remain a substantial degree of heterogeneity in the literature, and therefore a lack of clarity on the effects of female sex hormones. The paper by Liu et al. (2021) goes some way in demonstrating the mechanisms that underpin the observed cycle-to-cycle variability and highlights the potential contributing factors. These conclusions would not have been possible without the use of the three-step method, which highlights the importance of rigorous experimental design in this area. The challenge now for physiologists is to be able to draw conclusions about potential differences within and between menstrual cycles. Studying the contributing factors to heterogeneity in this area will enable us to understand why interventions might have different efficacy in females, for instance. Therefore, it is paramount that the mechanisms contributing to the variability demonstrated by Liu et al. (2021) should be considered and investigated, and not used as an excuse to exclude females from physiological research.

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COMPETING INTERESTS

None.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of this article. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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