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Variations in Plasma Proteome across the Menstrual Cycle

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INTRODUCTION

Menstrual cycles are a fundamental aspect of female reproductive health. However, variations in the plasma proteome across the menstrual cycle remain largely unknown. Previous studies suggest that these changes, along with menstrual irregularities associated with cycle length, may hold substantial diagnostic and prognostic value, not only for reproductive health conditions but also for broader health outcomes, including cardiovascular diseases [1, 2, 3, 4, 5].

OBJECTIVES

1. Do plasma proteins show phase-specific variation across the menstrual cycle?
2. Do trajectories differ by protein type or by women's characteristics?

METHODS

We analysed socio-demographic, health and proteomic data from a representative sample of 1,284 non-pregnant pre-menopausal women from a cohort of South Asian ancestry (2016-2019). Plasma proteins were measured with SomaScanAssay (v4.1, N=7k). To test for differences in protein levels, participants were categorized into eight groups based on the date of their last menstruation. A subset of 60 proteins was selected based on their association with menopause, divided into three groups: high association with menopause, medium association with menopause and low association with menopause. Statistical analyses were conducted accordingly: Welch's ANOVA was applied to the first set (20 proteins) due to unequal variances, followed by post-hoc analysis using the Games-Howell test to adjust for multiple comparisons; standard one-way ANOVA followed by Tukey's test was used for the second and third sets, where homogeneity of variance was met.

RESULTS

The first research question, which examined whether plasma proteins exhibit phase-specific variations during the menstrual cycle, identified significant changes for nine proteins in the first set (LHB, FSHB, CGA, CGB7, SFRP4, TFPI, HAMP, FTL, FCGRT), one protein in the second set (OXT), and four proteins in the third set (CHRDL2, BIN1, CREBBP, and SLC9A3R1).

Of these, twelve proteins (LHB, FSHB, CGA, CGB7, HAMP, FTL, FCGRT, SFRP4, TFPI in the first set; OXT in the second set; CHRDL2, and CREBBP in the third and last set) are linked to menstrual physiology or reproductive health through their function, tissue expression (e.g., endometrium, cervix, ovaries, placenta), or association with reproductive-related conditions or pregnancy. No significant differences were found when stratified by age, BMI, chewing tobacco use, type 2 diabetes, or oral contraceptive use.

CONCLUSIONS

Understanding how menstrual cycles influence circulating proteins could improve our knowledge of biomarker fluctuations and their role in predicting disease. This insight may help identify potential diagnostic and prognostic markers. The next

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step is to expand the analysis to all 7,000 available proteins to uncover associations with the menstrual cycle and validate significant variations across its phases.

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