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Subtle changes in menstrual cycle function – pieces of the puzzle

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Reproductive health has been shown to be an important window for long-term health and is a critical piece of the puzzle as we seek to understand pathophysiologic processes important for fertility and chronic disease. Special attention has been given to the thyroid, as thyroid dysfunction is prevalent among the general population and has been associated with various short- and long-term health outcomes in women. It is estimated that approximately 20 million Americans (12% of the US population) have thyroid disease and up to 60% of those with disease are unaware of their condition.[1] Hyper- and hypo-thyroidism have been associated with adverse reproductive outcomes, including menstrual disturbances,[2] infertility,[3] and hormone-related chronic conditions.[4] Thyroid problems are also more common in women, suggesting important connections between thyroid function and cyclic reproductive hormones.

In this issue of *Paediatric and Perinatal Epidemiology*, Jacobson and colleagues[5] report relationships between thyroid hormones and reproductive hormone metabolites and cycle characteristics across the menstrual cycle in a small prospective cohort of euthyroid premenopausal women. They observed that serum total thyroxine (T_4) concentrations were associated with small increases in urinary estrogen and progesterone metabolites. Though there was a suggestion that lower free T_4 was associated with a small decrease in cycle length compared to higher free T_4, overall thyroid hormone levels were not associated with cycle, phase, or bleed lengths.

Very little is known about the links between thyroid hormones and reproductive hormones among euthyroid women. In that regard, this study provides critical insights for understanding how the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-thyroid axes interact on menstrual function. Their study suggests that even within normal ranges, thyroid hormones could be related to small changes in menstrual cycle characteristics, perhaps through mechanisms involving gonadotropins and steroid hormones, specifically estrogens and progesterone. This research is especially important as it contributes to our

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understanding of the potential underlying mechanisms between thyroid hormones and other reproductive endpoints.

Jacobson and colleagues are to be commended for this study as it is difficult to study female reproductive health and menstrual cycle function. Menstrual cycle studies require complex prospective study designs to capture time-varying hormones and time-varying confounders and very willing participants. Given the dynamics of reproductive hormones and varying cycle lengths, timing is of the essence. Their study rigorously assesses steroid hormone changes based on daily urine samples over multiple cycles, whereas most studies of menstrual function rely on markers such as average menstrual cycle length or regularity, often via self-reported data. These markers are collected for convenience in place of hormone assessment which is really the outcome of interest. With such rich and complex data, the authors importantly accounted for random effects for cycles and woman to account for the nesting of days within cycles and cycles within women, respectively, an important consideration combining biological knowledge of the menstrual cycle with appropriate analytic techniques. Cycles were also aligned by the estimated day of ovulation to help with cycle phase comparisons.

As noted by the authors, however, thyroid hormones were measured only at a single time prior to follow-up of cycle characteristics and the authors assumed that thyroid hormones influence steroid hormones. It is also possible though that thyroid hormones may be affected by other steroid hormones in a cyclic fashion. For example, in early pregnancy β-hCG is elevated, and as it is chemically similar to thyroid stimulating hormone (TSH), β-hCG can bind to TSH receptors[6] and cause elevations in free T_4.[7] It is therefore possible that even in the setting of normal thyroid function, variations in estrogen and progesterone (or more likely fluctuations in gonadotropins, which are structurally similar to TSH), could cause subtle changes in some of the thyroid hormones. As there may be some biological feedback between thyroid and reproductive hormones, there is a need for future studies to assess both thyroid hormones and steroid hormones prospectively with appropriate statistical methods to account for potential time-varying confounding. The reproductive system is beautifully choreographed and multiple measures of thyroid function within each cycle would help to tease out the complicated interactions between thyroid and reproductive hormones. Further, missing data issues are common, and especially so in studies of this nature which require daily samples or multiple samples timed to specific cycle phases. The authors considered only cycles with complete data in assessing these biological relationships. It will be important in future work to consider alternative analytic approaches to deal with missing data in menstrual cycle studies to ensure the missingness does not bias the findings. This study included women across a large age range (18–54) and a couple of the women were potentially peri-menopausal. The authors showed it did not influence the findings here; however, including only premenopausal women is an important consideration for the design of future work of normal menstrual function as well.

The findings of their study suggest subtle changes in reproductive hormones in relation to thyroid hormones in premenopausal women. However, it is not yet clear how these findings can be translated to other outcomes of interest, such as anovulation, hormone-related reproductive disorders, or fecundability. What are the clinical implications and how do these

subtle changes impact reproductive health and long-term health down the road? Though menstrual cycle length is commonly used as a proxy for the hormonal milieu, the small changes in reproductive hormones they observed did not translate into differing cycle lengths, and anovulation was not able to be assessed due to small numbers. It is unknown whether these hormonal changes may influence other outcomes such as infertility, and in fact, a study among healthy women with thyroid hormone levels in the normal range suggests no associations between subclinical hypothyroidism and fecundability, pregnancy loss, and live birth.[8] While the evidence suggests an interplay between thyroid hormones and menstrual cycle physiology, particularly an altered hormonal milieu, direct causal relationships are not clear from this study, nor are effects on other downstream reproductive endpoints, particularly given the potential feedback between the two.

This snapshot of the relation between thyroid and reproductive hormones is an important piece of the puzzle, though future work disentangling the potential feedback mechanisms is needed to fully understand the broader picture and how these subtle changes may influence downstream reproductive outcomes.

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Biography

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