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Sex Hormones across the Menstrual Cycle in Pulmonary Arterial Hypertension: Adding a New Layer of Complexity

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One of our most recent diagnoses is a 9-year-old male with heritable pulmonary arterial hypertension (PAH) owing to a known rare variant (mutation) in a PAH-related gene. I ached for his family during a call last night, as we discussed a new result—his currently healthy younger sister shares the same pathogenic genetic variant. Their parents described it as a "gut punch," amplified because they know that females have a 42% lifetime risk of developing PAH among those with a genetic risk (1). Males develop PAH, no doubt. However, the strongest nongenetic risk factor for PAH, a progressively fatal pulmonary vascular disease, is female sex (2–4). Although the female predominance dates back at least to the initial reports of "primary pulmonary hypertension" by Dresdale and colleagues in the 1950s, we still do not know why incident case numbers skew toward female individuals over males (5).

But our field is making progress (please see the recent comprehensive review on this topic by Hester and colleagues [6]). Female enrichment suggests sex hormone effects, sex chromosome influences, or both contribute to PAH pathogenesis. The numerous human studies over the past decade exploring the association between PAH and variations in circulating sex hormones, with a particular focus on parent compound estrogens (estradiol [E2] and estrone [E1]), generally support the finding that individuals with PAH have higher estrogen levels. This is the case for both females and males with PAH compared with healthy subjects. Recent detailed efforts to explore not only E2 and E1 levels but also estrogen metabolites suggest that a global burden of active estrogens and associated downstream signaling are likely important.

In addition, a focus only on estrogens is likely too narrow. Recent work supports the concept that androgens are relevant to the PAH phenotype as well. In fact, androgens may contribute to, or perhaps antagonize, the PAH phenotype, with lower levels associated with not only disease but also functional outcomes (7, 8). The association of androgens appears applicable to women as well as men. Although less comprehensively studied, progesterone may also be relevant, with low progesterone levels recently associated with PAH and reduced survival among premenopausal adult females with idiopathic pulmonary arterial hypertension (IPAH); in contrast, high follicle-stimulating hormone levels were associated with IPAH status and reduced survival in that cohort (9).

However, a major challenge of studying sex hormones, particularly among women of reproductive age, is the potential variation in sex hormone levels in a given individual both in the short and long term. For example, in women of reproductive age (but not postmenopausal women), endogenous levels of estrogens fluctuate in response to the menstrual cycle. The menstrual cycle, in fact, is a crucial variable to consider: female sex hormone production and activity varies tremendously across the four phases of a typical 28-day cycle (menstrual, follicular [proliferative], ovulation, and luteal phases). Interestingly, however, estrogen levels are fairly constant for an individual woman of reproductive age when drawn at the same phase in the menstrual cycle in a given individual over 2–3 years; but, they do alter over the lifespan and with changes in body constitution (10). With regard to androgens, circulating levels of testosterone and androstenedione vary with a person's age, body mass index, and (for women) stage of menstrual cycle in a given month (although these androgens do not vary substantially in a given day) (11, 12). For these and other reasons, the study of humans with PAH, particularly females, and other conditions with regard to sex hormones is a challenging endeavor.

In this issue of *AnnalsATS*, Baird and colleagues (pp. 218–228) provide the first study published investigating the issue of sex hormone variation over the course of a menstrual cycle in women of reproductive age with PAH (13). The authors provide a detailed look at a small cohort of PAH patients and controls, associating variations in sex hormones with phenotypic changes relevant to the PAH condition (13). In this small study of 28 women (8 with PAH; 20 healthy control subjects) over the course of a menstrual cycle, they reproduced many of the previously known data concerning sex hormone levels in premenopausal women with PAH (e.g., higher E2 levels and lower dehydroepiandrosterone-sulfate [DHEA-S]

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levels among patients with PAH) while also advancing our understanding of the complex relationship between sex hormone levels and the cardiopulmonary condition. Cyclic variation in E2, however, was lower in patients with PAH than in control subjects, such that at one time point, patient and control subject E2 levels (visit 3) actually were not different; this likely corresponded to approximately 2 days postovulation, when E2, luteinizing hormone, and follicle-stimulating hormone (FSH) should be near their lowest cyclic levels (14). Patient E2 levels were associated with indices of cardiopulmonary function, with higher E2 levels correlating with lower 6-minute-walk test distance and higher N-terminal (NT)-pro hormone BNP (NT-proBNP) levels, although there was some variation according to menstrual phase. Although less straightforward, right ventricular function as estimated by tricuspid annular plane systolic excursion tracked with E2 levels at some phases.

Not surprisingly, the androgen DHEA-S levels did not display the same degree of variation across the menstrual cycle phases, with consistent reductions in patients versus control subjects. As with E2, DHEA-S was associated with indices of cardiopulmonary status, including a striking linear relationship between DHEA-S and 6-minute-walk test distance regardless of menstrual phase. In contrast, NT-proBNP levels generally had an inverse relationship with DHEA-S levels, although this was less prominent during visit 3, which presumably occurred just after ovulation. Evaluations of additional hormone levels, such as luteinizing hormone, did not substantially differ between groups or associate with functional metrics. Explorations of microRNA (miRNA) levels relevant to PAH (e.g., miRNA-29 family) demonstrated interesting but complicated results with some modification of levels of sex hormones with variability according to menstrual phase; future studies will be warranted.

Although small, this study by Baird and colleagues is an important advance for our field. Human studies in PAH are difficult in general, overcoming issues such as reduced physical health and vigor, accessibility, willingness to participate in additional studies on top of patients' large clinical demands, and other challenges. The additional pressure of timed study visits linked to the menstrual cycle at enhanced frequency further adds complexity. This work is an important reminder that no human is static, and for females of reproductive age, the study of sex hormones must take this into account.

But this study is not without limitations, many of which were addressed by the authors. First, circulating levels may not accurately reflect tissue-level activity, although the associations with functional parameters and miRNAs are suggestive. Second, as mentioned, accurate relay of the start of menstruation was crucial to activate study visit 1 and designation of phases, particularly in the absence of metrics to confirm the ovulatory phase; however, the graphic demonstration of E2 levels across study visits (Figure 1 of Baird and colleagues) did generally match the expected pattern of E2 across a standard 28-day menstrual cycle. Third, as a small study with several PAH subtypes, subtype differences, variations in therapeutic exposure, and the influence of time since diagnosis could not be explored. Fourth, cases had a substantially higher body mass index and report of irregular menstrual periods than control subjects. Finally, in-depth evaluations of right ventricular function, such as by cardiac magnetic resonance imaging, were not available.

Regardless, the current study advances our understanding of the interaction of sex hormones and PAH, including potential modulation of the clinical condition over the course of a menstrual cycle. And it is an important reminder that studies of sex hormone associations in PAH must account for expected cyclic variations among women of reproductive age. Whether the ratio of sex hormones, including sex hormone metabolites, corrects for this variation to some degree remains to be seen. Also, if cyclic variations modify response to therapy, such as in ongoing clinical trials of sex hormone modification involving women of reproductive age (NCT03528902 and NCT03648385), will be another important question to explore moving forward as we strive to determine the relationship between sex, sex hormones, and the PAH phenotype. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Community-acquired Pneumonia Owing to Multidrug-Resistant Pathogens: A Step toward an Early Identification

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Community-acquired pneumonia (CAP) continues to be one of the leading causes of hospitalization and is associated with a high risk of morbidity and mortality, particularly in elderly patients with multiple comorbidities (1–3). Historically, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Legionella* spp. have accounted for the main causes of CAP in patients presenting to the emergency department (4). However, over the past decades, some organisms traditionally associated with the healthcare setting, such as *Pseudomonas aeruginosa*, extended-spectrum β-lactamase–producing *Enterobacterales*, and methicillin-resistant *Staphylococcus aureus* (PES pathogens), have emerged as causes of pneumonia in the community (5). Moreover, the diffusion of multidrug-resistant (MDR) bacteria in the community became an important public health threat (6): nowadays, carbapenem-resistant *Enterobacterales*, MDR *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* are increasingly isolated in patients living at home or in long-term care facilities and represent a considerable challenge for clinicians because of the high mortality rates and limited available treatment options (7).

Since the delay in appropriate therapy may lead to worsened outcome, the identification of patients with CAP at high risk for resistant etiology is of outstanding clinical interest. The concept of healthcare-associated pneumonia (HCAP) was created to identify pneumonia in nonhospitalized patients who had significant experience with the healthcare system (8). However, this classification is not without limitations and may be overly sensitive, leading to inappropriately broad antibiotic use. On one hand, the incidence of MDR organisms among patients who meet criteria for HCAP ranges from 10% to 30% (5). On the other hand, about 30% of patients with pneumonia caused by MDR organisms are classified as CAP and not as HCAP (5). It appears clear that the HCAP definition does not completely mirror the probability of resistant etiology in patients with pneumonia living in the community.

To assist clinicians to select patients who need antibiotics active against nosocomial organisms, some tools have been proposed to replace the HCAP label (5, 9–11). The application in clinical practice of these risk scores could help in developing strategies to balance the need to treat infections appropriately while avoiding the overuse of broad-spectrum antibiotics. Ideally, a risk score that identifies patients with CAP who need antibiotic coverage against nosocomial pathogens should be easy to be applied in the emergency department, rapidly calculable from all physicians, and replicable and generalizable to settings with incidence of different MDR organisms. None of the currently available scores have all these features simultaneously. The ARUC score needs imaging and blood gas analysis to detect bilateral pulmonary infiltration or pleural effusion and partial pressure arterial oxygen/fraction of inspired oxygen ratio <200, respectively (5). The Aliberti score requires an in-depth medical history and also takes into account patients from nursing homes or those who receive immunosuppressive therapy (9). The tool by Shorr and colleagues was derived and validated more than 10 years ago and includes the intensive care unit (ICU) admission, which may be considered an outcome rather than a surrogate predictor of MDR etiology (10). Finally, the drug resistance in pneumonia (DRIP) score considers anamnestic risk factors but not severity of pneumonia (11).

In this issue of *AnnalsATS*, the study by Ceccato and colleagues (pp. 257–265) tried to validate a score for predicting PES microorganisms in patients with CAP (12). This score has some differences compared with the previous ones. First, it has been validated in two different cohorts of patients (Valencia and Mataro) with different disease severity. Compared with the Valencia cohort (the non-ICU cohort), the Mataro group (ICU cohort) had a higher proportion of severe CAP, with 53% of patients presenting with septic shock and 62% needing invasive mechanical ventilation. Nevertheless, the PES score retained a negative predictive value above 95% in both cohorts. This may indicate a good applicability of PES score in patients with CAP hospitalized in medical wards or in the ICU. Second, the PES score aimed to identify CAP by three specific pathogens (PES), narrowing the spectrum of causative strains to the most

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