Editorial

Sex Matters: The Importance of Generating Sex-Based Care Models

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Medical research and clinical care algorithms have a longstanding history of being based on data predominantly generated from male animal models[1] and white men.[2] The National Institutes of Health (NIH) only recently recognized this inherent bias and its impact on science, drug development, and treatment strategies. In 2015, the NIH mandated that all submitted proposals for preclinical and clinical studies account for sex as a biological variable as a prerequisite for application review and subsequent funding.[3] However, differences in health outcomes based on sex, ranging from survival at birth[4] to overall lifespan,[5] have long been known and rationalized. This sex-based rationalization of health outcomes has been particularly pronounced in the field of newborn medicine. The pervasive paradigm that male newborns are inherently at a disadvantage for overall survival and morbidities compared with their female counterparts has arguably resulted in a complacent acceptance, with limited attempts to modify outcomes with the development of targeted, sex-based treatments and therapies.

The National Institute of Child Health and Human Development (NICHD) began to report on the differential survival and developmental outcomes on the extreme premature neonatal population in 2008.[2] The NICHD Extremely Preterm (<28 weeks' gestation) Birth Outcome Tool (https://www.nichd.nih.gov/research/supported/EPBO/use) is generated by data collected nationwide from neonatal centers participating in the Neonatal Research Network, with findings confirmed based on outcomes from neonatal intensive care units participating within the Vermont Oxford Network, an ancillary neonatal database. Cumulative outcome data are then stratified based on sex, gestational age, weight, maternal corticosteroid administration given for lung, brain, and skin maturity, and singleton or multiple gestation. Data outcomes across all included gestational age groups within the tool reveal reduced survival and developmental outcomes for male infants, even when controlling for potential confounding variables. Since the tool's inception, a focus of interest has been given to the improvement in outcomes for extremely preterm infants based on timing of resuscitation, but limited research has been conducted to further our understanding of inherent biological differences between the sexes that result in survival and developmental discrepancies.

For nearly 15 years, my own research has focused on the interrogation of sex-specific outcomes of neonatal development and pathology at a molecular level. By exploring real-time gene expression in saliva samples collected throughout a neonate's hospitalization, our laboratory has identified biological pathways and networks that are differentially expressed between the sexes for a variety of neonatal conditions and morbidities, even after controlling for known confounders, including gestational and postmenstrual age.[6–8] These data suggest that not only are males and females developing along different age-dependent trajectories, but also they may in fact be developing completely separately. Lumping the sexes into singular treatment algorithms that do not account for these differences will undoubtedly continue to lead to stark discrepancies in outcomes. Rather, incorporating an improved understanding of the biological and developmental differences that differentially distinguish the sexes is likely our best path forward to narrowing the gap in survival rates that have simply been accepted as the norm for far too long.

To launch 2022, *Clinical Therapeutics* is highlighting the importance of recognizing sex and gender differences when developing treatment strategies and therapeutics. We are also releasing our journal policy statement regarding gender equity and inclusion of underrepresented minorities as reviewers of the journal and members of our board.[9] At first glance, these concepts may seem to be juxtaposed, with one arguing for equal treatment of all individuals and the other declaring the need to conduct well-designed clinical studies to better understand the individual biology that makes us unique. In fact, we are reinforcing and supporting the ideal that politics should never influence science. Our important social mandate to attain and maintain equity for all should not be convoluted or confused

with the equal need to ensure that therapies are developed based on our inherent differences. Although our Special Topic Update focuses on varying sex-based outcomes in cardiovascular disease, it should be contextualized across a variety of diseases that affect patients of all ages. Sex matters and plays an important role in response to treatment, metabolism, and clinical outcomes. We all share in the responsibility of moving beyond complacent acceptance of differential sex outcomes and working toward developing targeted approaches to treat our unique biology.

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