Let's get loud: Amplifying female voices in sepsis research

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Disparities of female participation in sepsis research, as both subjects and researchers, continue to impact this important critical illness. The systematic under-representation of females has led to less generalisable data, unexplored sex differences in sepsis host response, and limitations in clinical translation. Closing the gap on this sex disparity could lead to new insights into sepsis pathophysiology and treatment.

Female under-representation affects both preclinical and clinical research. Preclinical animal models of sepsis typically use only animals of one sex, and one systematic review screened 176 studies and identified only two evaluating the impact of biological sex on fluid and antibiotic administration in infectious animal models of sepsis.[1] A global study of sepsis incidence data, from 2017, reported 26.2 million cases of sepsis in females compared to 22.7 million cases in males, with a higher age-standardised sepsis incidence in females than in males.[2] The report also showed that maternal sepsis accounted for over 20% of female sepsis cases. Despite this unequal global burden of sepsis, female subjects constituted only 40% of all cohorts of published randomised and quasirandomised trials and observational studies, dated 1973 to 2017, based on a bibliometric analysis.[3] Approximately 10% of studies in this analysis accounted for sex in the study design and reported sex-disaggregated data for the main outcome measures.

Concerted efforts to recruit female participants in sepsis studies and to study sex differences in sepsis are beneficial for multiple reasons. First, pregnancy is often an exclusion criterion for trial participation, yet maternal sepsis makes up a substantial proportion of sepsis in females[2] and is the third leading cause of maternal mortality globally.[4] Second, the key insights into underlying mechanisms, treatment effects, and new therapeutic targets may be revealed by studying sex differences in sepsis. Estrogen receptors are present in multiple organs and immune cells. Estrogen has cardioprotective and immunoprotective effects, while testosterone has vasodilatory and immunosuppressive effects.[1,5] Female mice have greater diversity in their peripheral blood immunophenotype and microbiome, differences in microRNA expression that downregulate TNA-α, and differences in histone methylation, all of which could impact host response in sepsis.[1] Sex differences also exist in pharmacokinetics, volume of distribution, and responses to medications.[1] A rat sepsis model investigating beta blocker therapy showed increased stroke volume in male rats but decreased left ventricle ejection fraction in female rats.[1] A sex-disaggregated analysis of the Adjunctive Corticosteroid Treatment in Critically ill Patients with Septic Shock (ADRENAL) trial suggested that hydrocortisone may decrease time to ICU discharge in males, but not in females, and may increase risk of shock recurrence in females.[6] Third, delivery of care for females could be improved as evidence suggests the presence of unconscious bias and differential care delivery to females with sepsis. In regard to care, males are more likely to be admitted to the ICU, utilise more ICU resources, and receive more aggressive care, while females more commonly have orders for limitations in care.[5] This is also the case in sepsis, although data is conflicting about different outcomes for females with sepsis.[5] Additionally, five studies have reported decreased sepsis bundle compliance or longer time to antibiotic administration in females, demonstrating opportunities for improvement in care delivery for females.[5]

Disparities also exist with regard to females as sepsis researchers. Females continue to be under-represented as physicians in the field of critical care, and disproportionately so as academic leaders, conference speakers, and editorial board members. This extends to inclusion in sepsis research design, authorship, and guideline development. In a bibliometric analysis of sepsis trials by Antequera and colleagues, only 13% of first or last authors across all studies were females.[3] Moreover, the 2016 Sepsis III definitions publication had no female representative in the nineteen member authorship.[7] These observed patterns may be partly due to the fact that many important contributions by females fall under the banner of quality improvement or clinical operations, an artificial distinction from research that leads to under-recognition in a traditional research and academic promotion structure.[8] However, nuanced semantics is not the only explanation for the wide-reaching imbalance we have noted, in which disparities persist even for females performing "traditional" sepsis research.

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Looking forward, how can we address these disparities and improve sepsis research and patient outcomes? Starting with pre-clinical animal models, study designs should include animals of both sexes and *a priori* plans to analyse outcomes and mechanisms by sex. In humans, the hormonal milieu of the individual participant is seldom accounted for in analyses. Data should be collected not only on whether a female patient is pre-pubertal, pregnant, or pre- or post-menopausal, but also on phase of the estrous cycle and exogenous sex hormone administration, exposures which confound most literature. Improved definitions of maternal sepsis and implementation of obstetrical sepsis warning systems will address the challenge of delayed recognition of maternal sepsis. Enrolment of pregnant females in clinical trials will lead to standardised and optimised management of maternal sepsis. Sepsis clinical trial design should include consideration of 1) stratified randomization to ensure balance across phases of the reproductive cycle, 2) reporting data by sex regardless of whether a difference is seen, and 3) testing interactions between sex and the main outcome measure. Testing for effect modification by sex requires a much larger sample size to adequately power a trial, but sex-disaggregated analyses may allow for hypothesis generation and the ability to include data in subsequent meta-analyses.[9] Finally, there is evidence that forming research groups with representation from both sexes improves the quality of science produced.[10] When developing research teams, guidelines panels, and scientific conferences, invited participants should speak up if contributors are not diverse and balanced. Inclusion of females, as research subjects and research leaders, is key to maximising innovation, productivity, impact, and improving care for all patients.

Contributors

Dr. Fitzgerald contributed by performing literature search, writing of the original draft, and review and editing of the manuscript. Dr. Reddy contributed by performing literature search and review and editing of the manuscript. Dr. Woods-Hill contributed by performing literature search, writing, and editing and revising the manuscript. All authors read and approved the final version of the manuscript.

Declaration of interests

Authors declare no competing interests exist.

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