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Caffeine therapy for apnoea of prematurity: Wake up to the fact that sex matters.

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The developmental continuum of multiple physiological systems in preparation for uterine to neonatal transition is abruptly interrupted by preterm birth. The immature choreography of sensory reflexes, central respiratory rhythm and pattern generation, and respiratory mechanics is such that preterm infants struggle to establish and maintain smooth airflow in and out of the lungs, a critical function required to achieve sufficient blood oxygenation and excretion of carbon dioxide. Advances in prenatal and postnatal care, including administration of antenatal corticosteroids, and enhancements in delivery room respiratory support, postnatal monitoring and nutritional management have collectively contributed to improved survival rates for preterm infants, especially the extreme preterm infant. The focus of neonatal care has now progressed towards reducing infant morbidity, thus maximising the quality of life of the vulnerable neonate both in the immediate and longer term.

Apnoea of prematurity (AOP) remains a significant problem in the neonatal intensive care unit. AOP is characterised by intermittent cessations of respiratory airflow due to periodic central inspiratory neural quiescence, arising from brainstem network underdevelopment. Moreover, preterm infants have immature respiratory muscle composition and compliant lungs with little functional reserve capacity. Apnoeas are clinically significant events often accompanied by intermittent hypoxic and bradycardic episodes, requiring varying levels of intervention. Greater immaturity translates into greater incidence of apnoeas. Clinical studies of early life adversity and animal models employing exposures to chronic intermittent hypoxia, a cardinal feature of recurrent apnoea, have reported long-term deleterious effects on cardiorespiratory function and adverse long-term neurocognitive outcome. Male sex is associated with a higher incidence of preterm birth, higher mortality rate at the extremes of preterm gestation, and higher morbidity as determined by increased rates of brain injury, bronchopulomonary dysplasia, necrotising enterocolitis and poorer neurocognitive scores at follow up at 24 months. However, the influence of sex on AOP has not been adequately studied in the clinical setting.

In this issue of *Experimental Physiology*, Bairam et al. 2018 retrospectively examined the records of over 24,000 infants delivered between 24-34 weeks' gestational age, admitted to 30 tertiary neonatal centres participating in the Canadian Neonatal Network between January 2011 and December 2015. The main aim of the study was to investigate putative sex differences in the incidence of AOP and compare interventional treatment duration between male and female infants. Bairam et al. 2018 report that AOP was more likely in infants born

to mothers with significant clinical intervention including delivered by caesarean section, and/or receiving antenatal steroids and $MgSO_4$ administration. The infants with AOP were born earlier, weighed less, had lower Apgar scores at five minutes and had significantly more morbidity than infants without AOP. These results suggest that infants with AOP are more immature and are exposed to a more stressful neonatal transitional period. Of interest, this is the first clinical study to reveal a small but significant increase in the incidence of AOP in females at 26-27 weeks' gestational age compared with age-matched males, although this may relate to diagnosis in the context of multi-morbidity. Male sex is a risk factor for preterm respiratory distress syndrome, bronchopulmonary dysplasia, chronic lung disease, and lower respiratory tract infections. Physiologically, compared with females, males have: less fetal breathing movements *in utero*; delayed lung development, surfactant production and sodium transport efficiency prior to 32 weeks' gestational age; larger lungs with lower peak flow rates; longer latencies to achieve SpO_2 >90% after birth; and deficient antioxidant status. Despite the use of antenatal steroids to promote lung development, intrinsic sex differences confer increased vulnerability in males, whom traditionally require more supplemental oxygen, ventilatory support and surfactant use than preterm females.

Caffeine administration is the main therapeutic strategy for the treatment of AOP. Almost 90% of the cohort with AOP were treated with caffeine. Caffeine cessation was used as a proxy for the resolution of AOP. Interestingly, despite the higher incidence of AOP in extreme preterm females, Bairam et al. 2018 report prolonged administration of caffeine in males born less than 28 weeks' gestational age. Although this study did not standardise criteria for the diagnosis of AOP, or caffeine initiation or discontinuation, it nevertheless suggests important sex differences both in extreme preterm and also late preterm infants, which have a relatively low incidence of chronic lung disease. The authors reasonably posit that the data are supportive of more rapid respiratory maturation in females compared with males.

Clinically, respiratory support with prolonged caffeine administration may be warranted in males to limit further stress exposure. Remarkably, 64% of preterm infants ≤33 weeks' gestational age at birth had pathological apnoeas seven days after caffeine discontinuation (Doyle et al., 2016); importantly, extended caffeine administration minimised intermittent hypoxia exposure in a similar cohort (Rhein et al., 2014). In future studies, examination of the relationship between sex, caffeine concentrations and durations of use, and intermittent oxygen desaturations are warranted to support evidence-based standardisation of caffeine initiation, dosage and withdrawal in the treatment of AOP. Perhaps caffeine does not serve extreme preterm male infants as well as their female counterparts and adjuvant therapies such as antioxidants (Lavoie and Tremblay, 2018) and/or sex hormones (Joseph et al., 2018) should be explored.

The causal factors precipitating intrinsic male vulnerability are not understood; however, there is evidence of sexual disparity in genetics, sex steroid hormone concentrations and receptor expression, and metabolism. Animal studies also provide evidence of respiratory vulnerability in males such as exaggerated hypoxia-induced blood oxygen desaturation, post-

hypoxia respiratory depression and higher free-radical production in rat pups, and hypercapnic acidosis and prolonged oxygen supplementation requirement in preterm lambs. These studies illustrate greater respiratory depression and increased oxidative stress in males compared with females during early life. Based on the evidence from their translational animal models, Bairam et al. 2018 suggest that enhanced GABAergic inhibition of the central respiratory network is a plausible factor underpinning male vulnerability. In addition, sex steroid hormones likely play a pivotal role; males lack oestrogenic protection, while androgens can affect respiratory control and plasticity. Bairam et al. 2018 propose that perinatal stress increases testosterone in males, which compromises respiratory development.

Despite male sex being repeatedly highlighted as a significant risk factor for poorer outcomes following preterm birth, there is a paucity of clinical information on the mechanisms underlying this risk and little sex-specific management in the neonatal intensive care unit. It is time that sex is routinely incorporated into clinical and basic neonatal research study designs, which may in time inform stratified approaches to the treatment of AOP. An improved understanding of sex-specific requirements of preterm infants may lead to optimised strategies to better support ventilation, avoid the long-term harmful sequelae of early life oxidative stress and inflammation, and ensure that male and female infants not only survive, but thrive.

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