2020 IMPACT CIRCLE

Intergenerational Effects of Advanced Parental Age on Reproductive and General Health Outcomes

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Unmet Need: Men and women worldwide are delaying childbearing, meaning that children are being born to increasingly older parents. While the evidence is clear in females, and emerging in males, that advanced reproductive age can negatively impact an individual's *ability to have* a child, the intergenerational impact of advanced parental age on the reproductive potential and general health of the children is unknown.

Background: The female reproductive system is unique in that it is the first in the human body to show overt signs of aging, with a dramatic decline in egg quality and quantity beginning when women reach their mid-thirties. Reproductive aging in the female is associated with adverse outcomes including infertility, miscarriages, and birth defects. One of the most significant recent discoveries in reproductive science is that environmental exposures (chemicals and diet) at critical windows of susceptibility in one generation can impact reproductive health across multiple generations. But whether or how having one or both parents of advanced age affects reproductive function and general health in the next generation has never been explored.

Novel Hypothesis: We hypothesize that the aging environment associated with having a mother, a father, or both parents of advanced reproductive age at the time of conception will affect reproductive potential and general health endpoints in the next generation.

Proposal: We have coalesced an innovative team, including a reproductive biologist (Duncan) and an aging researcher (Garrison), who will use a physiologic aging mouse model 1) to determine the effect of male and female reproductive aging on fertility and pregnancy outcomes and 2) to assess whether having a mother, a father, or both parents of advanced reproductive age at the time of conception impacts reproductive and general health outcomes in male and female offspring.

Impact: Understanding intergenerational consequences of reproductive aging is critical because both the male and female reproductive systems are susceptible to multigenerational and transgenerational effects of environmental chemicals and diet. Advanced parental age

results in cumulative exposures that impact reproductive function, and thus will undoubtedly have an impact across generations. As far as we are aware, this study is the first of its kind and will have significant translational application to the human population where delayed childbearing is fundamentally changing the reproductive landscape. Impact Circle funding will allow us to generate preliminary data that will serve as the foundation for a future larger collaborative NIH grant application.