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Gaining insights into reproductive health from historical events

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Maternal exposures may affect offspring reproductive health, but these effects are likely small, requiring large samples, or large changes in the exposure to detect. Also, enough time must pass to allow the offspring to reach an age at which the health endpoints of interest are observable. Drastic historical events that affect large numbers of people and are discrete in their time period of occurrence, provide an opportunity to examine how the maternal prenatal experience influences the reproductive health of the offspring.

The current paper, by Zhang et al. (BJOG 2020;127:39–45) is the largest study to examine this question, with over 58,000 women included. The authors report an elevated risk of still birth, but not spontaneous miscarriage, in women exposed to the famine prenatally and in infancy.

This contrasts slightly with the Dutch Hunger Winter cohort which examined the effects of the approximate 7 month period in which Germany blockaded all food supplies into the occupied region of the Netherlands leading to widespread famine. The Dutch cohort found no association between famine exposure and pregnancy loss or infertility (Yarde, Hum Reprod. 2013 Dec; 28(12): 3328–3336), although this study was much smaller (~1000 women). In the Dutch Hunger Winter study an association was found with age of menopause, which might indicate that famine exposure alters ovarian reserve. Ovarian reserve was not examined in the current study. Moreover, the Dutch Hunger Winter study included both men and women, while the current study of the Great Chinese Famine did not. These may be important avenues of future research.

The study of the Great Chinese Famine involves an extended exposure time frame, the famine lasted at least two years while the Dutch Hunger Winter was a shorter period, from approximately October until May. While this finite exposure period allows for the identification of trimester-specific exposure, it is possible that the shorter exposure period does not result in the same effects on the offspring.

Studies of historical events face important challenges. First, who is the appropriate unexposed comparison group? Comparison groups from the same time period typically differ in geography which may be related to other socioeconomic characteristics or health care access, and which in turn could influence reproductive outcomes. Comparison groups from different time periods but the same place may be affected by the continuing

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repercussions of the previous event, and they are systematically older or younger than their exposed counterparts. A second challenge is the extended time between exposure and the reproductive outcomes of interest. The outcomes are often collected retrospectively themselves, and with little to no information about exposures that may have occurred between the in utero period and adulthood. Third, famine may have coincided with other important influences on offspring health, such as violence, trauma, political upheaval, increased infections and illness, and/or socioeconomic depression. These exposures make it difficult to isolate the effect of famine as they may also have important influences on the reproductive development and health of the child.

Important insights can be gained from examining large-scale population exposure events. While there are methodological challenges for these studies, they are uniquely positioned to address difficult scientific questions.