

## Does my father have higher sperm counts than me?

Eat. Survive. Reproduce. These are the fundamental functions of all species, including humans. More specifically, we eat to survive, and we survive to reproduce and spread our DNA. However, there exist data that suggest that human reproduction is in peril. The total fertility rates (defined as births per woman over her lifetime) continue to decline and are projected to decline further worldwide (1, 2). Such declines have a profound impact on society because a birth rate of 2.1 is required for a nation to maintain a stable population. If the fertility rate were to fall below such a value (as it has for many countries in the developed world), the economic implications are enormous in terms of the workforce and ultimately tax base for social programs (which are compounded as lifespans increase). Thus, in addition to an academic question, a declining fertility rate has existential implications for a society.

It is important to be precise with definitions. Distinct from fertility, fecundity is the biologic capacity to reproduce. Therefore, when examining declines in fertility rates, we must recognize that declines in fertility may or may not involve changes in fecundity. The reasons for the decline in fertility are likely mixed because of both biology and behavior. As our species and society have developed, the number of children desired has decreased. In addition, effective contraception and career opportunities have resulted in individuals delaying childrearing. Indeed, the average age of parents has increased with time. However, given that the world has not remained static over the past 50 years, many scientists have also explored whether environmental factors may also contribute to changes in fecundity.

Fecundity, specifically, or reproductive health more broadly, can be measured in different ways. For couples, investigators have explored time to pregnancy. For women, investigators have examined hormone profiles and the timing of menstruation and ovulation. For men, semen quality or the rates of genital malformations/genital cancers have been explored. The registries of infertility treatment, birth rates, genital cancers and genitourinary malformations, and nationally representative surveys of reproductive health have been studied to help identify trends. However, many of these lack granular data regarding pregnancy intentions, exposures, or population-based study design.

Investigators have explored changes in our lives and how that may impact fertility. The consumption of high-calorie/processed foods, obesity, higher daily temperatures, and sedentary lifestyle have all become more common with each passing decade. Studies suggest that such factors could lead to changes in human fecundity.

Two of the most significant articles in the fecundity decline research sphere deal with declines in sperm count.

The first was published in 1992 by Carlsen et al. (3) and has come to be known as the Carlsen paper. In the study, the investigators reviewed data on 14,947 men included in a total of 61 articles from around the world that were published between 1938 and 1991 (3). The investigators identified a significant decline in sperm count from  $113 \times 10^6/\text{mL}$  in 1940 to  $66 \times 10^6/\text{mL}$  in 1990. Although the study was met with worldwide attention and ushered in additional focus on the question, some investigators scrutinized the methodology. Questions about combining and comparing studies from different populations worldwide, the selected/nongeneralizable nature of men with semen data available for study, and changes in analytic techniques over time arose. Subsequent studies questioned whether a temporal decline in semen quality exists (4). As such, Levine et al. (5) attempted to address several concerns of the Carlsen paper. A comprehensive meta-analysis was published in 2018; this study examined the sperm count from 185 studies of 42,935 men who provided semen samples between 1973 and 2011. Overall, the investigators reported a decline in the sperm count from  $99 \times 10^6/\text{mL}$  in 1973 to  $47 \times 10^6/\text{mL}$  in 2011 (a 52.4% decline). To address several concerns of the Carlsen paper, the investigators restricted the included studies on the basis of the population and laboratory criteria and performed several subanalyses restricted to men from distinct regions of the world or with known fertility status ("Unselected" for fertility status or "Fertile"). The study region was stratified into "Western" (North America, Europe, Australia, and New Zealand) and "Other" (South America, Asia, and Africa). The investigators reported significant declines for Western Unselected and Western Fertile populations, whereas no significant association was identified for Other Unselected or Other Fertile men. The investigators hypothesized that differences in the exposomes between the regional strata could explain the reported differences.

Although the methodology did address many concerns of prior analyses, the study still lacks data from a systematic, population-based semen quality surveillance similar to how the Centers for Disease Control and Prevention monitors obesity or blood pressure in the United States through the National Health and Nutrition Examination Survey. To date, the question of changes in semen quality remains controversial. This issue's *Fertile Battle* seeks to address the fundamental questions surrounding sperm decline from thought leaders on both sides of the debate.

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