Effect of fertility and infertility on longevity

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Changing demographic trends and projections of the survival and fertility rates of each generation have been a topic of great interest to not only demographers and epidemiologists but also to evolutionary biologists and reproductive endocrinologists. Compelling evolutionary theories suggest that there is an inverse association between fertility and longevity. Multiple historic, demographic, and current studies have since been conducted to test this theory, but the results have been inconclusive. The average number of children born to each woman has been declining progressively in developed countries during recent decades. This is in part due to changes in the behavior of couples but also to environmental factors. While improved accessibility to assisted reproductive technology can relieve some of the burden of infertility on these couples and lessen the problem of low total fertility rates in many developed countries, it is not enough to overcome the overall decrease in total fertility rates that we have witnessed in recent decades. This article critically reviews some important studies and provides an overview of this ongoing debate, while highlighting the relevance of trying to understand the possible mechanisms that may link fertility and infertility to longevity. (Fertil Steril® 2015;103:1129–35. ©2015 by American Society for Reproductive Medicine.)

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The average number of children born to each woman has been declining in developed countries during the last few decades, and it is in part due to changes in the behavior of couples. Having children is often seen today as competing with women's career development and couples' aspirations. The increased cost of living and of raising children has also led couples to opt in favor of postponing starting a family until later in life, when they will have more financial security and professional stability. Effective contraceptive methods have provided couples with the possibility to plan how many children they would like to have and when. As a result, couples are having fewer children than in previous generations and the birth of the first child is consequently being delayed to a later age, resulting in an increase in the mean age at first birth by 2–4 years over the last 30–40 years (1). The mean age at childbearing has exceeded 30 years of age in some Western European and Scandinavian countries (2). Postponing childbearing can, however, result in infertility, particularly if delayed to the mid to late 30s when ovarian reserve and fertility potential begin to decline at an exponential rate (3). Other important contributors to the increase in infertility are general health issues, such as obesity, the rise in sexually transmitted diseases, and environmental exposure to ubiquitous endocrine-disrupting chemicals, such as phthalates, bisphenol A, parabens, and others, that have been associated with both poor semen quality and adverse female reproductive outcomes (4–8). While improved accessibility to assisted reproductive technology (ART) can relieve some of the burden of infertility on these couples and lessen the problem of low total fertility rates in many developed countries, it is not enough to overcome the overall decrease in total fertility rates that we have witnessed in recent decades (9). In this paper, the term fertility is used synonymously with the number of births per woman (10, 11). The combination of decreased fertility and increased life expectancy over time has resulted in an aging population and major demographic changes, and the link between fertility and longevity, and ultimately the fate of future generations, has been questioned and extensively debated for more than half a century. Compelling evolutionary theories have been formulated that suggest an inverse association between fertility and longevity (12, 13). Multiple studies, historic, demographic, and also current, have since been conducted to

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test this theory, however, results have been conflicting and, at best, inconclusive. The question that remains, and is perhaps more relevant now than ever before, is, how does infertility affect longevity?

Evolutionary Theory: Trade-off between Fertility and Longevity

Evolutionary theories state that reproduction comes at a cost to an individual's life span. The early theory of antagonistic pleiotropy postulates a trade-off between fertility and longevity that is genetic in origin. Pleiotropic genes are said to have a positive effect on vigor and fertility earlier in life and, conversely, a negative effect later in life, when reproductive potential is low, leading to more rapid deterioration of individual fitness. The rate of senescence/aging is the balance of these two opposing forces whereby increased fertility potential early in life is at the cost of longevity (12).

The disposable soma (DS) theory (13) proposes a similar trade-off, but its mechanism is metabolic rather than genetic. Under DS theory, longevity involves a direct trade-off between energy investments in somatic maintenance and resources available for reproduction (14, 15). The large expenditure involved in pregnancy and lactation is the proposed root cause of accelerated senescence, and individuals who bear fewer children are predicted to live longer than those who bear many children. Attempts have been made to substantiate these evolutionary theories, mainly through the analyses of demographic and historical data from natural conception cohorts (before birth control was practiced).

Westendorp and Kirkwood Study: Fertility is Associated with Decreased Longevity

A landmark and controversial paper by Westendorp and Kirkwood (15) examined the association between parents' longevity and fertility, using as their source a historical database of British aristocratic married women born before 1875 and whose family histories dated back to as early as the year 740. The advantages of using a historical database are [1] natural fertility cohorts where biologically maximal fertility conditions were the norm and [2] the fact that all women in the database have already died so full reproductive histories are known as well as age at death (longevity). It was possible to perform subanalyses including only those women who had surpassed the age of menopause and, by doing so, prevent cases of premature deaths from complications of pregnancy and/or childbirth from being misclassified as post-reproductive deaths.

On the flipside, these historical data come from a time period when the demographic trends were very different from what we know today. Fertility rates were high, contraception was not practiced, and average life expectancy was shorter owing to poorer medical care and precarious living conditions among lower social class families as compared with the aristocracy. To minimize confounding by socioeconomic status, the study was thus restricted to the British upper class/aristocracy. In accordance with the DS theory, increased parity was found to be associated with decreased longevity. Conversely, bearing fewer children was associated with increased longevity: almost 50% of women who lived to over 80 years of age were childless (15).

Replicating the Westendorp and Kirkwood Study: No Association between Fertility and Longevity

Gavrilova and Gavrilov (16) conducted a validation study on historical databases from European aristocratic families, including the British (Bloore) database used in the Westendorp and Kirkwood study (15). All cases of reported childlessness were cross checked with at least two different sources for quality control, and 32% ($n = 107$) of childlessness claims ($n = 335$) were found to be false-negative claims that generated a spurious increase in the prevalence of childless women who lived long lives. After correcting inaccuracies resulting from overestimated reported prevalence of elderly women and underreporting of the number of children each older woman gave birth to, Gavrilova and Gavrilov (16) reanalyzed the data, and the new findings revealed that longevity was not at the cost of infertility and the association between childlessness in women of extreme longevity (over 80 years) disappeared (16). Another possible critique of the Westendorp and Kirkwood study was the inappropriate use of a Poisson regression for the statistical analyses as opposed to a simple linear regression (17). A prerequisite for the use of a Poisson regression is the assumption that the dependent variable (number of children born to a woman) follows a Poisson distribution. The Poisson distribution assumption, however, did not hold true. Consequently, the women at the higher extremity of the distribution had an overinflated influence on the effect estimate. After reanalyses of the data, the association became insignificant (17).

Other Historical Cohort Studies: Fertility is Associated with Increased Longevity

This debate prompted other similar studies on natural fertility cohorts around the world. A study that was conducted on the Amish (18), including subjects born between the mid 18 century and early 20 century who lived to at least the age of 50 years and were dead at the time of analyses, showed a positive association between fertility in men and women with a longevity advantage of 2–3 months for each extra child until 14 children. After 14 children, the direction of the association was reversed and a strong trade-off for each additional child born was observed. This threshold effect of 14 children may have been the breaking point after which there was metabolic trade-off for each additional child born, as proposed by the DS theory (13). A later age at last birth was also associated with a longer lifespan. In this context, one could argue that the association is due to reverse causation where increased longevity is associated with increased parity and later age at last birth, simply because women who live longer have more opportunities to conceive multiple times. Since all women in the study lived to age 50 years and beyond, this does not seem like a plausible explanation. A later age of menopause, however, may have been a contributing factor to increased longevity.

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