Extended fertility and longevity: the genetic and epigenetic link

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Many women now choose to develop their careers before having children. Thus, it is becoming increasingly important to assess a woman's potential for extended fertility and to understand the health consequences of having children at a late age. In particular, there is a striking positive correlation between extended fertility and longevity in women, which poses important implications for medicine, biology, and evolution. In this article we review the diverse epidemiologic evidence for the link between fertility potential, age of menopause, and women's lifespan. Then we discuss the recent advances using genomic technology to better understand biological mechanisms driving this association. At the genetic level, there are polymorphisms that may be driving both extended fertility and longevity. At the cellular and molecular levels, changes in the genome (both nuclear and mitochondrial), epigenome, and transcriptome during oocyte aging have important implications for fertility. By synthesizing results from diverse domains, we hope to provide a genomic-era conceptual framework in which this important connection can be investigated and understood. (Fertil Steril® 2015;103:1117–24. ©2015 by American Society for Reproductive Medicine.)

Key Words: Transcriptomics, DNA array, genome-wide association study, mitochondrial genome, telomeres

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Diverse epidemiologic evidence shows that women who have children at late age are more likely to live longer. However, the genetic connection remains obscure. In this article we summarize and discuss the current understanding of the biological mechanisms underlying this link, many of which were recently uncovered using genomic technologies. This raises a set of questions that are relevant for both basic research and clinical practice: [1] Do women with extended fertility really live longer? [2] To what extent is this phenomenon explainable in genetics terms? Are there mutations/genomic variations that increase fertility? [3] What are the molecular mechanisms behind the convergence of fertility and longevity? [4] How can the resulting insights on genomic, epigenetic, and gene expression data impact medical practice?

We present information to address these questions under two contexts: [1] the genetic context in which stable and heritable polymorphisms in the DNA affect extended fertility and longevity; and [2] a complementary cellular view that describes the age-dependent, functional profiles of the cell. The conceptual framework of the study is presented in Figure 1. The bulk of the relevant literature comes from genetic analysis of cohorts of women and high-throughput studies of epigenetics (Table 1) and gene expression of oocytes and related cells.

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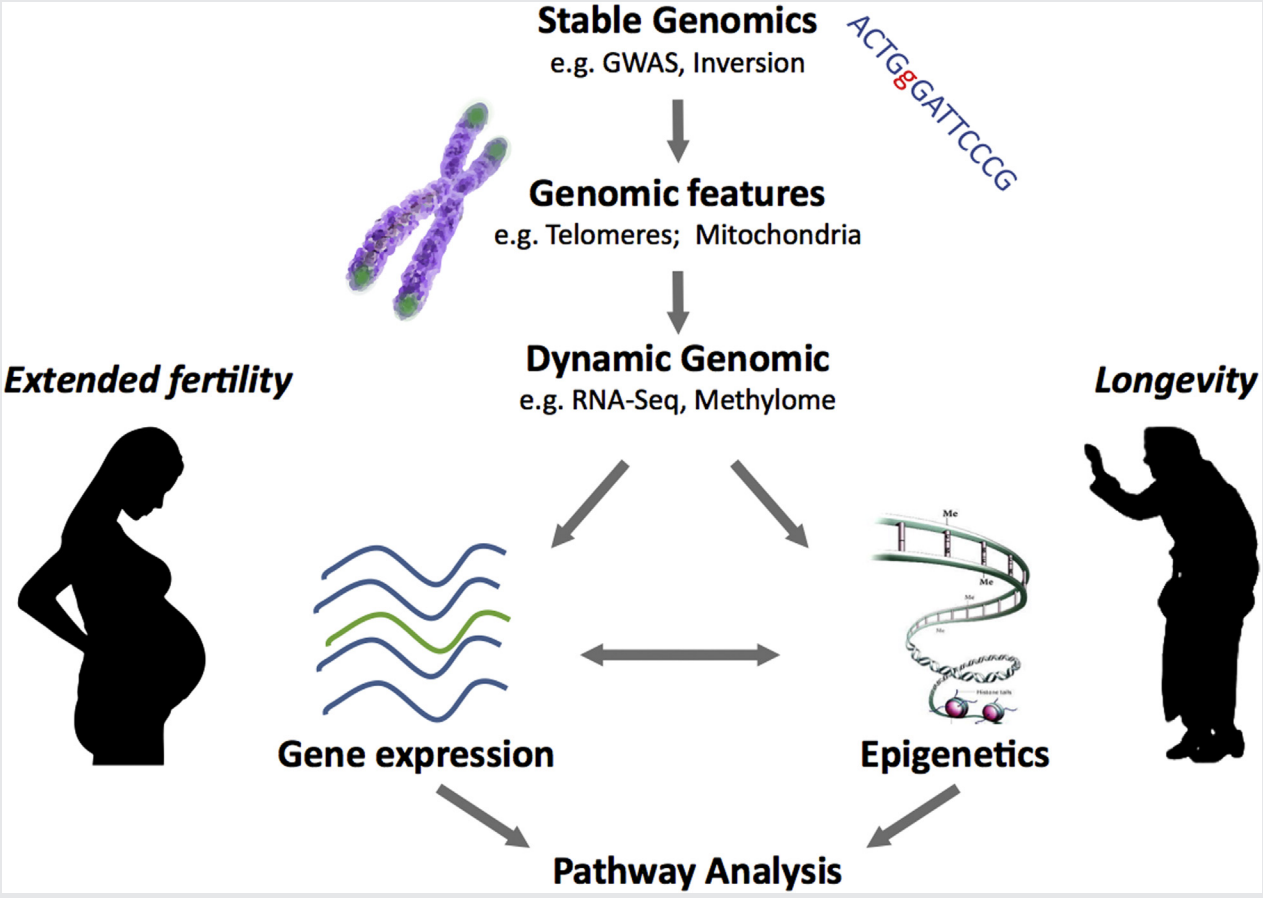
EVOLUTIONARY THEORIES FOR THE ROLE OF THE POSTFERTILITY LIFESPAN

Females of most animal species reproduce throughout life until they die (1). This is consistent with one of the basic tenets of evolution, which equates the fitness of a species with the number of successful offspring. Humans are different from most animals and primates in this regard; women live approximately half of their lives in the postproductive phase.

Researchers propose that the extended postfertility lifespan in humans confers evolutionary advantage because substantially more resources are channeled for the success of the offspring (2). This is formulated as the "grandmother hypothesis." A study across several geographically diverse populations shows that women with longer postreproduction span improve the reproductive success of their children and have more grandchildren, thus increasing the fitness of their own genes. Furthermore, the mortality

FIGURE 1



Schematic showing the molecular components connecting extended fertility in women with longevity.

Wainer-Katsir. Genetic basis for extended fertility. Fertil Steril 2015.

rates of the mothers accelerate from the time when their own offspring begin to terminate reproduction (1).

EPIDEMIOLOGIC LINK BETWEEN WOMEN FERTILITY AND LONGEVITY

Genealogic records are the best resource for the phenomenologic trends on extended fertility and longevity. A key factor in many of the large population analyses is the need to remove the socioeconomic covariates from the genetic component (3). Moreover, it is important to note that there are multiple definitions for fertility potential and aging. Menopause age, the number of children, and the ability to have children in the fifth decade are all indirect manifestations of fertility. Similarly, loss of cognitive and physical capabilities, onset of neurodegenerative diseases, and mortality serve as sign posts to the processes of aging.

The rapid drop in female fertility at age 40 years has been documented and extensively studied. It is largely explained by an age-related increase in chromosomal aneuploidy (Table 1) that results in early pregnancy loss (4). Nevertheless, fertility at a late age has been shown to positively correlate with longevity (5–7). For example, on the basis of approximately 2,600 women, it was shown that women with two to three children had significantly lower mortality (a hazard ratio of 0.82 at 95% confidence) compared with women with no children (5). Another study (of approximately 5,300 white women, aged 55–100 years) showed that women with natural menopause before age 40 years had an odds ratio of death of 1.95 (95% confidence interval) compared with natural menopause at ages 50 to 54 years (8, 9). Extensive genealogic records for approximately 2,000 women and thousands of birth records from the Amish community for 150 years (8) also revealed that a later age at last birth was associated with longer lifespan. A similar trend was confirmed for cohorts from different geographic locations and ethnic groups (e.g., the Netherlands, United States, Canada, and Finland) (1, 5, 9, 10).

The correlation between extended fertility and longevity is not limited to modern cohorts. Historical support comes from analysis of a cohort of women born in the year 1896. Only 5% gave birth after age 40 years. However, among the centenarian women in this cohort, this fraction reaches 20% (6). Additional historical records include more than 1,600 French-Canadian women from the 17th and 18th century who lived at least 50 years. Quantitatively, 50-year-old