

# Abstract

Reprod Fertil Dev. 2009;21(1):10-4.

## Telomeres and reproductive aging.

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**BACKGROUND:** Infertility, miscarriage and aneuploid offspring increase with age in women, and meiotic dysfunction underlies reproductive aging. How aging disrupts meiotic function in women remains unclear, but as women increasingly delay having children, solving this problem becomes an urgent priority. Telomeres consist of a (TTAGGG)(n) repeated sequence and associated proteins at chromosome ends, mediate aging in mitotic cells and may also mediate aging during meiosis. Telomeres shorten both during DNA replication and from the response to oxidative DNA damage. Oocytes do not divide in adult mammals, but their precursors do replicate during fetal oogenesis; eggs ovulated from older females have traversed more mitotic cell cycles before entering meiosis during fetal oogenesis than eggs ovulated from younger females. Telomeres also would be expected to shorten from inefficient DNA repair of oxidative damage, because the interval between fetal oogenesis and ovulation is exceptionally prolonged in women.

**RESULTS AND DISCUSSION:** We have tested the hypothesis that telomere shortening disrupts meiosis by shortening telomeres experimentally in mice, which normally do not exhibit age-related meiotic dysfunction. Interestingly, mouse telomeres are much longer than human telomeres, but genetic or pharmacological shortening of mouse telomeres recapitulates in mice the human reproductive aging phenotype as the mouse telomeres reach the length of telomeres from older women. These observations led us to propose a telomere theory of reproductive aging. Moreover, chronological oxidative stress increases with reproductive aging, leading to DNA damage preferentially at (TTAGGG)(n) repeats. Finally, if telomeres shorten with aging, how do they reset across generations? Telomerase could not play a significant role in telomere elongation during early development, because this enzyme is not active until the blastocyst stage, well after the stage when telomere elongation takes place. Rather, telomeres lengthen during the early cell cycles of development by a novel mechanism involving recombination and sister chromatid exchange.

**CONCLUSION:** Telomere dysfunction resulting from oxidative stress, a DNA damage response or aberrant telomere recombination may contribute to reproductive aging-associated meiotic defects, miscarriage and infertility.

PMID: 19152740