Insights into fetal death—a patient resource

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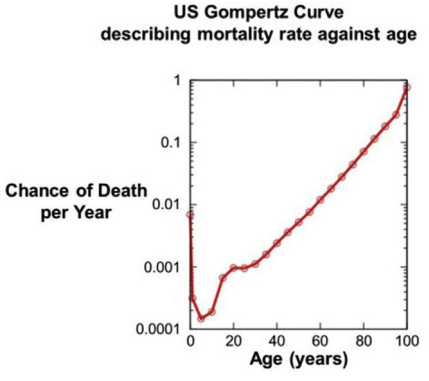
Evidence supports a role for placental aging in the etiology of the majority of fetal deaths. This knowledge may reduce maternal feelings of guilt following fetal death that frequently exacerbates the distress caused by grief. The accompanying video may be a useful resource for women who have experienced a fetal death.

Key words: aging, autophagy, mitochondria, messenger RNA translation, mammalian target of rapamycin complex, progeria, soluble fms-like tyrosine kinase-1, soluble vascular endothelial growth factor receptor 1, telomeres

Families who experience a fetal death or stillbirth are forever changed. Moreover, some parents exhibit long-lasting sadness and increased rates of marriage breakdown.[1,2] For women, feelings of guilt or self-blame are a major contributing factor to the long-term consequences of the death of the neonate.[3] Recent work strongly supports placental aging as an etiologic factor in most cases[4] Supporting this view, a histopathologic study of placentas associated with cases of unexplained intrauterine death at term revealed that 91% of cases showed thickening of the maternal spiral artery walls, 54% of cases contained placental infarcts, 10% of cases had calcified areas, and 13% of cases demonstrated vascular occlusion[5]; in contrast, other studies reported increased atherosclerosis.[6] Interestingly, all changes were associated with aging in other organs. Further supporting a link between placental aging and stillbirth, telomere length is reduced in placentas associated with stillbirth,[7] and fetal growth restriction is also associated with both stillbirth and telomere shortening.[8] To try to alleviate some of the maternal distress, we have created a brief educational video that uses the power of animation to explain that the placenta is an organ of the fetus, not the mother, and how aging of this fetal organ may lead to the death of an otherwise healthy fetus.

Aging is a difficult concept to define. We can all recognize it in our family members, friends, and colleagues, but defining it is less straightforward. Galileo has written that "the book of nature is written in the language of mathematics" and perhaps the most valuable definition of aging is the one proposed by the actuary Benjamin Gompertz in 1820, indicating that, after achieving sexual maturity, aging is the process whereby the probability of death increases with each point in time.[9] This is well illustrated with the Gompertz curve describing the mortality rate against age in the United States (Figure 1). The increasing rate of the probability of death implies the presence of interacting factors that provide initial resilience but progressively fail.[10] The shape of the curve illustrates the declining likelihood of death before sexual maturity. This occurs during the period of maturation, which is contrasted with the increasing likelihood of death after maturity is reached. There are parallels in obstetrical demise with a high rate of fetal loss early in gestation, which falls as gestation progresses only to rise in late gestation with increased rates of fetal death observed after maturation of the placenta (Figure 2).[11] Although these curves represent an observed empirical reality, the biology that underlies these equations has been more challenging to uncover. However, the increasing rates of fetal death in late gestation imply that a process of aging is implicated, likely in the placenta, which has completed its maturational process, but the fetus has not. Empirically, we know that different individuals age at different rates and some fetal deaths occur earlier in pregnancy, especially in association with growth restriction[12] and chromosomal anomalies. As an example, fetal death occurs more often in the presence of trisomy 21.[13] Interestingly, individuals with trisomy 21 exhibit progeria,[14] and it seems likely that there is also an increased rate of aging in the placenta. Fetal growth restriction has been linked to markers of senescence[15] and is associated with an increased risk of fetal death.

FIGURE 1
Estimated probability of a person dying at each age



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R.S. and K.M. are seeking to develop diagnostics to predict risk of stillbirth. The other authors report no conflict of interest.

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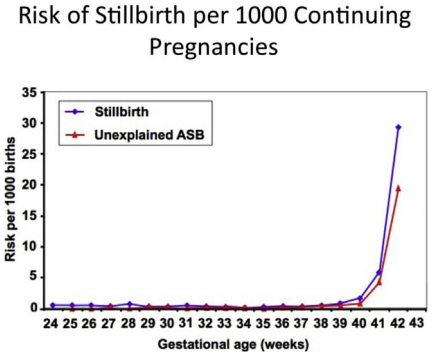
FIGURE 2
Risk of explained and unexplained ASB per 1000 continuing pregnancies



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ASB, antepartum stillbirth.

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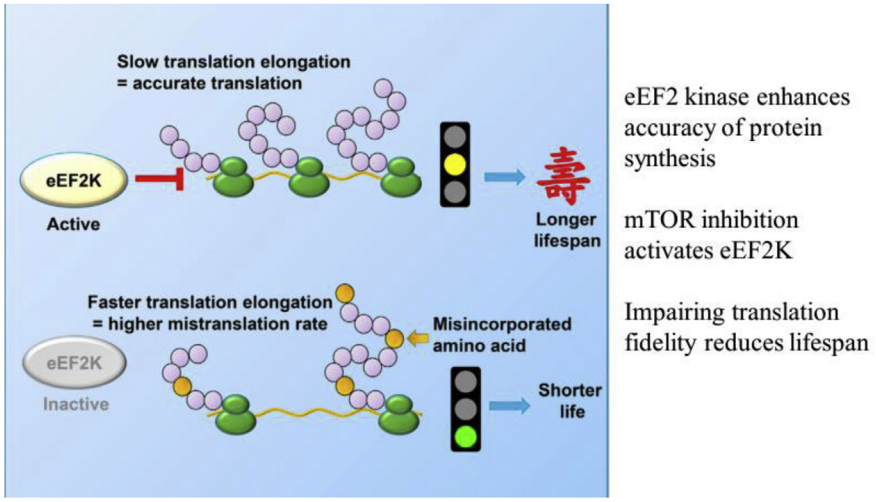
Data have recently been provided from several different groups on the biological mechanisms that underlie aging. Chris Proud's laboratory in South Australia has uncovered evidence that animals with a long life-span translate messenger RNA into protein more slowly and more accurately than those with a shorter life span (Figure 3).[16] Such carefully constructed proteins are more likely to retain their function for longer, as they are built to last. This process is regulated by the mammalian target of rapamycin (mTOR) complex, which inhibits the eukaryotic elongation factor 2 kinase (eEF2K) that slows the ribosomal process of protein synthesis, allowing more accurate translation. Intriguingly, we observed increased mTOR activity in late gestation placentas, which would be expected to lead to inhibition of eEF2K and faster but less accurate protein synthesis, likely to progress to abnormal protein folding.[4] Moreover, rapid turnover of protein has been identified by Matsuda et al,[17] as linked to life span, with animals with short life span showing rapid turnover leading to short "clock" processes and slow turnover linked to slow clocks and long life span. In addition, evidence for disturbances in protein turnover exists in the late gestation placenta where we have demonstrated enlarged autophagosomes, the organelles responsible for the degradation of abnormally folded proteins and deteriorating mitochondria. Deteriorating mitochondria produce increased free radicals, which oxidize DNA and increase lipid peroxidation, both of which have been observed in the late gestation placenta and placentas associated with fetal death.[4] The high ratio of guanosine and cytosine in the telomeres at the ends of the chromosome makes them vulnerable to oxidative damage, and shortening of telomeres has been reported in placentas associated with stillbirth.[7] Last, Grunewald et al[18] have linked increased circulating soluble vascular endothelial growth factor receptor 1 (sVEGFr1 or soluble fms-like tyrosine kinase-1) to decreasing vascular perfusion and aging in general. This is an area in which obstetrical research has been at the forefront, with increased circulating sVEGFr1 linked to fetal death in several publications.[19,20]

The biology of aging is finally catching up with the empirical observations of Gompertz, potentially allowing the development of assays to predict fetal death and, perhaps in the future, to delay placental aging. In the meantime, making this new knowledge available to families who have experienced stillbirth may provide some explanation for their pain and reduce the likelihood that inappropriate guilt exacerbates maternal distress. ■

FIGURE 3
eEF2K controls the accuracy of translation and lifespan



The inhibition of mTOR leads to the activation of eEF2K, which slows the translation elongation process, resulting in more accurate translation and longer life span[16]

eEF2K, eukaryotic elongation factor 2 kinase; *mTOR*, mammalian target of rapamycin; *mTORC1*, mammalian target of rapamycin complex 1.

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GLOSSARY

eEF2K: eukaryotic elongation factor 2 kinase
mTOR: mammalian target of rapamycin complex
sVEGFr1: soluble vascular endothelial growth factor receptor 1

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