Potential long-term risks associated with maternal aging (the role of the mitochondria)

Martin Wilding, Ph.D.

CREATE Fertility, London, United Kingdom

The mean age at which women create families in Western society is increasing. This is in spite of the fact that reproduction in later life is subject to various difficulties, such as the lower probability of conception in relation to maternal age, the increase in spontaneous pregnancy loss, and higher obstetric risk. In this review of recent data, we suggest that a fourth effect, the decrease in lifespan of children in relation to the age of conception of the mother, can be added to the list. We discuss this effect in relation to the transmission of the mitochondria exclusively through the female germ line and the effect of age on this organelle. Data from our own studies and the animal literature as a whole suggest that this effect could be due to the transmission of damaged mitochondrial DNA, and further indicate that the effect is more widespread than previously considered. (Fertil Steril® 2015;103:1397–401. ©2015 by American Society for Reproductive Medicine.)

Key Words: Maternal age, reproduction, mitochondria, mtDNA, lifespan

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/wildingm-maternal-aging-mitochondria/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

The trend in Western society is drifting toward an increase in the mean age at which females choose to conceive. This seems to be due at least in part to the fact that people have to make the difficult choice between following a career and childbirth, and these two are often fairly incompatible. The introduction of birth control methods enables women to decide when to have children, and this tends to lead to them delaying childbirth until later in life.

One of the problems with delaying childbirth is that the efficiency of reproduction decreases with respect to maternal age. This is combined with an increase in the rate of spontaneous pregnancy loss and may also be associated with higher obstetric risk during pregnancy and increase in the level of early pregnancy loss after IVF (1, 2). So what can cause the loss in reproductive efficiency with respect to maternal age, and are there long-term effects associated with later-life childbearing?

WHAT UNDERLIES THE RELATIONSHIP?

The relationship between age and reproductive efficiency seems to be a predominantly maternal one. The relationship could be due to an increase in errors in the oocyte and developing embryo, which would lead to a decrease in the implantation rate. Alternatively, the efficiency of the uterus in accepting the implantation embryo could decrease. In practice, clinical results with egg donation support the hypothesis that it is egg quality that determines the probability of successfully reproducing (1).

Egg quality seems to affect the ability of the embryo to implant and form a viable fetus through abnormalities in embryo development. The first data pointing to a high frequency of natural pregnancy wastage through abnormalities in the fertilized embryo were gathered by the embryologist Hertig, who collected 34 human embryos aged 1–17 days; 8 were considered from the preimplantation stage, and the others came from the first 2 weeks after implantation (3). Hertig observed that 50% of the preimplantation embryos presented such profound anomalies to force the conclusion that pregnancy could not have proceeded to term. Of the 26 remaining embryos, 6 (23%) also presented major anomalies incompatible with normal development. The study provided the first strong evidence that spontaneous loss of early human embryos by far exceeded clinically evident pregnancy losses. Since these tests, one of the major causes of embryo loss before or soon after implantation has been found

Received February 18, 2015; revised March 18, 2015; accepted March 27, 2015; Published online April 30, 2015.
M.W. has nothing to disclose.
Reprint requests: Martin Wilding, Ph.D., CREATE Fertility, 3-5 Pepys Road, London SW20 8NJ, United Kingdom (E-mail: martinwilding@hotmail.com).

Fertility and Sterility® Vol. 103, No. 6, June 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.03.034

to be aneuploidy in the egg (4). Clinically relevant aneuploidies during reproduction are caused by nondisjunction in the oocyte during meiosis and are related to maternal age (4–8). Simple mosaicisms (i.e., nondisjunction during mitosis) are probably related to this and may be a spontaneous occurrence (9, 10). More serious defects in the oocyte originate from the complete disruption of the meiotic and mitotic apparatus and lead to the chaotic segregation of chromosomes between cells and the complete loss of reproductive potential in the embryo (10).

The above data suggest two ways in which embryo loss occurs before or soon after implantation. First, small errors in chromosome alignment during meiosis cause missegregation of chromosomes and lead to aneuploidies that may be lethal. Evidence suggests that this has a nuclear-derived mechanism (11). Second, complete disruption of the meiotic apparatus (and presumably the mitotic apparatus) leads to random segregation of chromosomes and the impossibility of the embryo to form a viable being. Many experiments point to the role of the mitochondria in the cause of chaotic mosaicism (10).

WHY MITOCHONDRIA?

Mitochondria are the most abundant cell organelle. Mitochondria are also unique in that they are the only organelle outside of the nucleus that contains DNA. The number of mitochondria in a single human egg is estimated through the copies of mitochondrial DNA (mtDNA) present and is considered to be between 20,000 and 800,000 copies (12–14). The principle role of the mitochondrion is in the production of the cells' energy source, adenosine trisphosphate (ATP), through aerobic respiration, although many secondary functions have been ascribed to this organelle, such as calcium storage, steroid synthesis, and cell senescence (15). All cells need ATP for energy, and oocytes are no exception to this rule. In fact, a positive correlation between ATP levels in blastomeres and embryo development has been shown to exist in humans (16). Mitochondrial DNA consists of approximately 16,600 bases and codes for a total of 37 genes, including some vital proteins and transfer RNA species (15). The proteins encoded by mtDNA include metabolic enzymes required for the energy production (15, 17). The genes for most mitochondrial proteins, however, exist within the nucleus, and the current theory is that all mitochondrial proteins are being slowly transferred to the nucleus, but it is also possible that the mtDNA codes for proteins that are rapidly made and destroyed and therefore the DNA is required "on site."

ROLE OF MITOCHONDRIA IN THE MATERNAL AGE EFFECT

The fact that mtDNA is contained within the mitochondria themselves leads to a possible theory for the mechanism of the "maternal age effect." In fact, energy production and mtDNA do not coexist in a particularly healthy relationship. Mitochondrial energy production is very efficient but highly damaging to the immediate environment of the organelle. This is because the mechanism of energy production involves the release of oxygen free radicals. These are short-lived but very powerful oxidizing agents, meaning that all material in the vicinity of these agents is a target for oxidation. Material near the site of release of oxygen free radicals includes the proteins of the oxidative phosphorylation complex (these are replaceable) but also the mtDNA. A further problem with mtDNA is that little or no mechanisms for DNA repair exist within the mitochondria. Gross levels of damage may lead to the inactivation of the DNA and the senescence of single organelles; however, minor levels could lead to mutations within the DNA sequence of mtDNA and the production of inefficient proteins.

WHY IS THIS IMPORTANT TO REPRODUCTION?

In most parts of the body, cells with defective mitochondria obviously do not survive and are replaced by new cells. The problem with reproduction is that the primordial follicles are formed within the ovary before birth and are not replaced. These data suggest that the cells within the primordial follicle are subject to aging. Because life is a continuum, mtDNA would accumulate mutations and degenerate to the point where life was impossible without a resetting mechanism. Fortunately, the "mitochondrial bottleneck" hypothesis (whereby the mtDNA pool is reduced to a few copies in the primordial oocyte) acts as this reset mechanism by naturally redistributing mtDNA species (18–20). This evolutionary mechanism obviously enables the production of the best-quality eggs by detecting those with a substandard mtDNA content; however, it does not prevent the degeneration of these copies over time. In fact, the oocyte content of the female is fully determined at birth. Primordial oocytes are in a near-inactive state until adolescence; however, low levels of metabolism may occur, although data from the jellyfish *Aurelia aurita* suggest that no mitochondrial activity is present in the eggs themselves (21). Even if primordial oocytes have no metabolism as proposed, the mechanism of progressive damage of mtDNA still applies to the cumulus cells, suggesting that damage to these helper cells could lead to inefficient oogenesis in the egg (21). Either of these two mechanisms would probably lead to mistakes during meiosis and the increase in the number of eggs with chaotic mosaicism. This is in contrast to the sperm, which is continually produced from adolescence to death from meiosis in the testicle, and in fact is characterized by low levels of aneuploidy (22, 23). This theory is very similar in fact to the free-radical theory of aging (24, 25), whereby free radicals progressively degenerate nonreplicating cells in the body (such as the brain and nervous system). This theory has more recently developed into a mitochondria-based theory (26–28).

EVIDENCE FOR THE ROLE OF MITOCHONDRIA IN REPRODUCTIVE EFFICIENCY

Surprisingly little evidence for the relationship between mitochondrial mutations or indeed the resulting effect of these mutations on mitochondrial physiology exists. A correlation between mtDNA deletions and maternal age was found in granulosa cells (29), suggesting that defects in the nutrition of the oocyte during oogenesis could influence reproductive efficiency. In horses, the mtDNA copy number was found to