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Is age-related decline in female fertility a mitochondrial dysfunction?

Abstract

The research question: Whether mitochondrial dysfunction might be responsible for age-related decline in female fertility.

Study design: Review of the literature on decline in fertility with advanced female age, and relation between ageing and mitochondrial dysfunction was performed in 2000 when the idea was conceived.

Findings: In humans, the fertility in female declines slowly from the age of 30 years Embryo implanting ability and survival start declining gradually after 30 years of age, but by more than two thirds after 40 years and in younger women with reduced ovarian reserve. While decline in the frequency of intercourse is one of the reasons, reduction in the quality of either the embryos arising from ageing oocytes due to higher incidence of oocyte aneuploidy or the older uterus have been implicated as the probable causes. Controversy still exists about which one of these is the main cause or whether both of them play a role together. While the suboptimal quality of the ageing oocytes and/or older uterus may be responsible for the age-related decline in female fertility, it is not clear why the functional quality of the uterus or the oocytes declines with increasing age. Recent researches have indicated the role of oxygen radical damage to the mitochondria in the somatic cells leading to mitochondrial dysfunction as the possible cause of the ageing process. In this article, a possible role of age-related mitochondrial dysfunction in the ageing oocytes and/or the uterus has been proposed as the cause of age-related decline in female fertility.

Implications: Research in to this area would be useful to explore the possibility. If decline in fertility with advanced female age is found to be associated with mitochondrial dysfunction preventive measures that might retard the process of mitochondrial dysfunction associated with ageing could be taken in advance. N. B. The hypothesis was originally conceived and the article was written by the author in 2000 and has been included here as it was written in 2000.

Keywords: female fertility, ageing oocyte, mitochondrial dysfunction

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Sudipta Paul
Department of Gynecology, Salford Royal Hospital, UK

Correspondence: Sudipta Paul, Consultant Obstetrician & Gynecologist, Freelance author and researcher, Department of Gynecology, Salford Royal Hospital, Salford, UK, Email medidea@hotmail.com

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Introduction

In humans, the fertility in female declines slowly from the age of 30 years.[1,2] Embryo implanting ability and survival start declining gradually after 30 years of age, but by more than two thirds after 40 years and in younger women with reduced ovarian reserve.[3] While decline in the frequency of intercourse is one of the reasons, reduction in the quality of either the embryos arising from ageing oocytes due to higher incidence of oocyte aneuploidy or the older uterus have been implicated as the probable causes. Controversy still exists about which one of these is the main cause or whether both of them play a role together.[1–6] While the suboptimal quality of the ageing oocytes and/or older uterus may be responsible for the age-related decline in female fertility, it is not clear why the functional quality of the uterus or the oocytes declines with increasing age. Recent researches have indicated the role of oxygen radical damage to the mitochondria in the somatic cells leading to mitochondrial dysfunction as the possible cause of the ageing process. In this article, a possible role of age-related mitochondrial dysfunction in the ageing oocytes and/or the uterus has been proposed to be the cause of the age-related decline in female fertility.

Older uterus or ageing oocytes

A substantial drop in the ongoing pregnancy rate per embryo transfer has been observed in women undergoing assisted reproduction, 48.8% in women aged <30 years to 13.6% in women aged >42 years). Embryo implantation rate also declines in a linear fashion, from 29% in women <34 years to approximately 5% at age 42. The reduced implantation rate in older women is apparently independent of the magnitude of their stimulation response. Though oocyte factors are held primarily responsible for the decline in fertility in older women, diminished endometrial receptivity has also been suggested as a contributor.[7] It has been suggested from studies performed in women undergoing *in vitro* fertilisation (IVF) treatment and IVF with oocyte donation, that senescence affects both the ovary (oocytes and granulosa cells) and the uterus.[1,8] A defective vasculature of the uterus has been indicated as the possible cause of an increased miscarriage rate in women aged ≥40 years.[1] With ovum donation, an increased rate of pregnancy loss after the completion of implantation has been observed in women >40 years. A retardation of steroid synthesis suggests that the mechanism(s) responsible for placenta formation and functioning in the uterus is affected by age.[9]

A negative correlation between age and fecundity has been shown in the mouse. It has been attributed to the appearance of amorphous material beneath the basal lamina of the endometrial epithelium that could impair implantation.[10] Elevated levels of epidermal growth factor might also have a physiological role in fertility decline in ageing mice possibly via uterine hypertrophy.[11] In cycling women >40 years, a disturbance in follicular recruitment but not in luteal function

or endometrial maturation has been observed and its possible role in the decline in fertility with ageing suggested.[12] Elsewhere, it has been suggested that age-related changes in the ovary account for most of the decline in fertility. Oocytes, which originate in the fetal life, decline in numbers and quality with age. The endocrine function of the ovary also declines with age leading to dysfunction of the neuro endocrine axis. The latter may be further affected by primary changes in the hypothalamus and pituitary due to ageing, although there is no such evidence in humans. The uterine vasculature may change due to the age-related endocrine dysfunction thereby losing its ability to support implantation and growth of the embryo.[13] The frequency of chromosomal anomalies in abortuses increases in parallel with the age-related rise in the incidence of spontaneous abortions.[14] That oocyte aneuploidy is one major reason for low pregnancy rates in older women, is suggested by the higher pregnancy rate in this group where young donor oocytes are used.[15] Majority of the studies support this view.

Degenerative changes and chromosomal abnormalities in the ageing oocyte have been implicated as the causes of the decline in female fertility with age.[4–22] A study, performed on women undergoing IVF, concluded that the reduction in quality of the embryos arising from ageing oocytes is the cause for age-related decline in female fertility. The blastocyst formation rate ([blastocysts/embryos on day 2] 100) and the blastocyst expansion rate ([expanded blastocysts/blastocysts] 100) according to the woman's age on the day of IVF were determined. With increase in age, the number of retrieved oocytes decreased, without alteration of the cleavage rate. In women above age 30 years, preimplantation development to blastocysts declined due to an arrest at the morula stage. A negative linear relationship between blastocyst expansion rate and woman's age was found, where the blastocyst stage was reached. Increasing age led to a drastic decrease in women having at least one expanded blastocyst (<30 years, 82%; ≥40 years, 36%) because of reduction in gamete production and embryo development. A high delivery rate per oocyte retrieval (25.8%) was found in women above age 40 years after embryo transfer at the blastocyst stage.[5] This study indicated a poor quality embryo up to the stage of blastocyst as the cause of reduction in fertility with increasing age. Although majority of the studies have suggested a decrease in the quality of the oocytes as the main cause of the age-related decline in female fertility, contribution by the uterus also remains a possibility.

Embryonic development and the mitochondria

Normal mitochondrial function in the embryo to produce adequate energy is essential for mitochondrial protein synthesis, DNA synthesis and embryonic growth.[23] In a study to determine the actual and potential activities of the cytochrome system in cleavage-stage mouse embryos, three major shifts in the mode of ATP production during preimplantation stages were detected. The first, between the two-cell and late four-cell stages; the second, between the eight-cell and late morula stages; and the third, between the late morula and late blastocyst stages.[24] The importance of ooplasmic factors has been postulated for the continued development of the zygote, particularly during early cleavage, when transcription of the embryonic genome is minimal.[25,26] In recent years, mitochondrial DNA (mtDNA) has been a subject of interest due to the subtle role it may have in early development.[27] Sperm mitochondria, carrying potentially harmful paternal mtDNA are eliminated from the embryo at an early stage, probably by a ubiquitin-dependent mechanism.[28,29] Therefore the mtDNA in the fetus comes from the oocyte.[27–31] As a consequence, any dysfunction of the oocyte mitochondria may have profound detrimental effects on the development of the embryo.

Ageing and mitochondrial dysfunction

Mitochondrial dysfunction has been attributed as the cause of the ageing process.[32,33] Oxidative damage appears to play a critical role in causing mitochondrial dysfunction of ageing.[34] The contributing factors include the intrinsic rate of proton leakage across the inner mitochondrial membrane (a correlate of oxidant formation), reduced membrane fluidity, and decreased levels and function of cardiolipin, which supports the function of many of the proteins of the inner mitochondrial membrane. Acetyl-L-carnitine, a high-energy mitochondrial substrate, appears to reverse many age-associated cellular dysfunctions, partly by increasing cellular ATP production.[35] With increasing age the mitochondrial function declines with an increase in the production of reactive oxygen species (ROS) and free radicals in the mitochondria. Up to a concentration range ROS may induce stress responses of the cell by altering genetic expression in order to increase energy metabolism to rescue the cell. However beyond this threshold, ROS may elicit apoptosis by induction of mitochondrial membrane permeability transition and release of cytochrome c. Recent researches have established a pivotal role of mitochondria in the early phase of apoptosis in mammalian cells.[36] Observations in transgenic Drosophila melanogaster support the hypothesis that oxidative injury might directly cause the ageing process.[37] The "free radical production hypothesis of aging" states that a decrease in oxygen radical production per unit of oxygen consumption near critical DNA targets (mitochondria or nucleus) increases the maximum life span of extraordinarily long-lived species like birds, primates and man.[38] It has been hypothesized that oxygen free radicals may damage the mtDNA thereby inhibiting mitochondrial division leading to age-related reduction in mitochondrial numbers, a deficient energy production with decrease in protein synthesis and deterioration of physiological performance.[37–41] mtDNA is 20 times more susceptible to mutation than nuclear DNA[42] due to its location close to the site of reactive oxidative species production, and a lack of protective histones in mtDNA.[43] Contrary to the popular belief, mitochondria can efficiently repair oxidative damage to their DNA.[44]

Ageing oocyte - a mitochondrial dysfunction?

Each mitochondrion contains 2-10 copies of mtDNA in all human tissues, except oocytes and platelets, which contain only one copy per mitochondrion.[42] During germ-line development in early bovine embryogenesis, the number of mitochondria increases 100-fold, from 1000 per oogonium to 100 000 per oocyte, while the number of mtDNA increases only 10-fold, from 10 000 to 100 000.[45] As a result each mitochondrion contains 1 mtDNA, instead of the usual 5-10.[45,46] Only a small number of mtDNA molecules replicate and give rise to the whole cytoplasmic genotype during the late stage of oogenesis.[47] This bottleneck may be a cause of the accumulation of oxidative damage to mtDNA during the ageing process,[48] which also occurs in oocytes.[45] Ageing of the ooplasm has been considered to be responsible for producing an abnormal meiotic spindle[17] with spindle abnormalities as the source of incorrect seggregation of chromosomes/chromatids at meiosis I.[4] To overcome this problem, the possibility of using manufactured oocytes is being investigated, where the nucleus of immature oocyte from an older woman is transplanted into the cytoplast of a younger woman.[49,50] The oocytes originate in the fetal life and enter the first meiotic division that remains arrested until ovulation. In contrast to the continuous production of primary spermatocytes in the male after puberty, no primary oocytes form after birth. The first meiotic division in the primary oocytes completes just before ovulation, forming secondary oocytes.[51] Therefore the age of the secondary oocytes in a woman above 40 years will be just above the woman's age, as these were originated before her birth. This means

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that the oocytes would have been exposed to the ageing process for that period, during which oxidative damage to the oocyte mitochondria might lead to mitochondrial dysfunction. This may affect the functional quality of the oocyte or cause oocyte aneuploidy due to interference with the meiosis, which would have profound detrimental effect on fertilisation, protein synthesis and cell division in the fertilised ovum, migration of the fertilised ovum to the uterine cavity, implantation and subsequent development of the embryo. As normal mitochondrial function is essential for embryonic development, dysfunction of the oocyte mitochondria may be responsible for the age-related decline in female fertility. Mitochondrial dysfunction may also lead to suboptimal quality of the uterus, thereby decreasing fertility.

Conclusion

Fertility in the female declines with age. This has been attributed to the decrease in frequency of intercourse, and reduction in the quality of an older uterus or the embryos resulting from ageing oocytes. Although an older uterus may impair implantation or increase miscarriage rates due to a decreased receptivity of the endometrium or defective vasculature, majority of the studies indicated ageing oocytes as the main contributing factor. The etiology for the suboptimal function of the older uterus or ageing oocytes is not clear. Oxidative damage to mitochondria leading to mitochondrial dysfunction is considered to be the cause of age-related changes in somatic cells. The latter are associated with a decrease in protein synthesis and deterioration in physiological performance. There is evidence that age-related changes also occur in the oocyte mitochondria. The mtDNA in the embryo is inherited from the oocyte mitochondria, any dysfunction of which might have profound detrimental effect on the embryonic development. Therefore, mitochondrial dysfunction associated with increase in age might have a role for the age-related decline in female fertility.

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Conflicts of interest

The authors declare there is no conflict of interests.

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