Journal of Fertilization: In Vitro - IVF-Worldwide, Reproductive Medicine, Genetics & Stem Cell Biology

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Opinion Article

Influence of Advanced Paternal Age on Early Embryonic Gene Activation during *In Vitro* Fertilization

Isabelle Fournier*

Department of Developmental Reproductive Biology, Nouvelle Santé University, Lyon, France

DESCRIPTION

The influence of maternal age on reproductive outcome has been widely investigated for many years, particularly because advancing female age strongly affects oocyte quality and chromosomal stability. In contrast, the role of paternal age in embryo development received less attention until recent decades. Increasing numbers of couples now pursue parenthood later in life due to educational, social, and economic factors, leading to growing interest in age-related male reproductive changes. Although men maintain sperm production throughout adulthood, aging influences hormonal regulation, Deoxyribonucleic Acid (DNA) integrity, mitochondrial activity, and epigenetic signaling within spermatozoa. These changes may affect embryonic development after fertilization, including the period of early embryonic gene activation during in vitro fertilization cycles.

Early embryogenesis initially depends on maternal messenger Ribonucleic Acid (RNA) and proteins stored within the oocyte before fertilization. During the first cleavage divisions, the embryonic genome remains relatively inactive while maternal transcripts support cellular metabolism and division. Subsequently, embryonic gene activation occurs as the developing embryo begins transcribing its own genetic material. In humans, this transition becomes prominent between the four-cell and eight-cell stages. Proper activation of embryonic genes is essential for blastocyst formation, cellular differentiation, and implantation competence. Researchers have therefore examined whether paternal age influences this critical developmental period.

Sperm cells contribute more than paternal DNA to the embryo. They also deliver centrioles, messenger RNA fragments, microRNA molecules, and epigenetic modifications capable of influencing gene expression after fertilization. Aging spermatozoa frequently display increased oxidative stress, reduced chromatin packaging quality, and higher rates of DNA fragmentation. Such abnormalities may interfere with accurate replication and transcription during early embryogenesis. Although fertilization itself may still occur successfully, subsequent developmental arrest becomes more common in some cases involving older paternal age.

Several clinical studies have reported reduced blastocyst formation rates among couples with advanced paternal age, even when maternal age remains relatively controlled. Delayed embryo cleavage, lower embryo quality scores, and increased miscarriage rates have also been observed in certain populations. However, findings remain inconsistent because male aging often coincides with female aging, making independent paternal effects difficult to isolate. Variability in laboratory techniques, lifestyle factors, and semen preparation methods further complicates interpretation.

DNA fragmentation has emerged as one of the most studied age-related sperm abnormalities. Reactive oxygen species generated during aging can damage sperm DNA through strand breaks and base modification. Unlike most somatic cells, mature spermatozoa possess limited DNA repair capacity due to highly condensed chromatin structure and minimal cytoplasm. Following fertilization, the oocyte attempts to repair paternal DNA damage before embryonic genome activation occurs. Excessive damage may overwhelm this repair system, leading to abnormal transcription patterns and impaired embryonic development.

Mitochondrial dysfunction may also contribute to age-related sperm alterations. Although paternal mitochondria are generally degraded after fertilization, mitochondrial activity remains important for sperm motility and fertilization competence. Aging sperm often display reduced mitochondrial membrane potential and increased oxidative metabolism abnormalities. These changes may influence calcium signaling, Adenosine Triphosphate (ATP) production, and chromatin stability during fertilization and pronuclear formation.

Epigenetic modifications within spermatozoa have attracted increasing scientific attention in reproductive genetics. DNA methylation patterns and histone retention sites influence regulation of developmental genes after fertilization. Aging appears associated with altered methylation profiles in sperm cells, particularly in genes involved in neurodevelopment,

Correspondence to: Isabelle Fournier, Department of Developmental Reproductive Biology, Nouvelle Santé University, Lyon, France, E-mail: isabelle.fournier.nsu@eurobiomail.org

Received: 01-Sep-2025, Manuscript No. JFIV-25-41839; **Editor assigned:** 03-Sep-2025, PreQC No. JFIV-25-41839 (PQ); **Reviewed:** 17-Sep-2025, QC No. JFIV-25-41839; **Revised:** 24-Sep-2025, Manuscript No. JFIV-25-41839 (R); **Published:** 01-Oct-2025, DOI: 10.35841/2375-4508.25.13.423

Citation: Fournier I (2025). Influence of Advanced Paternal Age on Early Embryonic Gene Activation during *In Vitro* Fertilization. J Fertil *In Vitro* IVF World w Reprod Med Gent Stem Cell Biol. 13:423.

metabolism, and cellular differentiation. Some researchers propose that these epigenetic changes may affect embryonic gene activation timing and developmental programming during early cleavage stages.

Animal studies have provided additional insight into paternal age effects on embryogenesis. Experiments involving aged male mice have demonstrated altered embryo metabolism, delayed blastocyst development, and differences in gene expression related to cell cycle regulation. Some offspring produced from older male animals also exhibit behavioral and metabolic abnormalities later in life. While direct comparison to human reproduction remains limited, these findings support further investigation into paternal aging within assisted reproductive medicine.

CONCLUSION

The growing trend toward delayed parenthood ensures that paternal aging will remain an important topic within reproductive medicine. Current evidence indicates that advanced paternal age may influence embryonic gene activation through mechanisms involving DNA fragmentation, oxidative stress, mitochondrial dysfunction, and epigenetic alteration. Continued investigation combining embryology, molecular genetics, and developmental biology may improve understanding of paternal contributions to early embryogenesis and support development of refined fertility treatment strategies for aging couples undergoing assisted conception.