Lead Author Q&A – Maria Cristina Guglielmo

Older paternal age linked to higher miscarriage risk and lower live birth rates in donor egg IVF cycles, new study finds

1. What motivated you to specifically investigate paternal age in the context of oocyte donation cycles?

   A strong motivation to specifically investigate paternal age in the context of oocyte donation cycles derives from the unique opportunity these cycles provide to isolate and examine the male partner's contribution to reproductive outcomes. In fact, in oocyte donation cycles, the oocytes come from young and healthy donors, which remove variability in egg quality and underlying diagnoses due to maternal age. This control allows us to examine more clearly how paternal age alone might affect ART outcomes such as fertilisation, embryo development and pregnancy outcomes.

2. In your opinion, why has male age received less attention compared to female age?

   There is a cultural perception that male fertility is relatively unaffected by age: that "men can stay fertile forever" and they can become fathers at any age without consequences.

   Even in reproductive clinical research, male age has historically received less attention than female age. Female reproductive biology is more time-sensitive: women have a finite ovarian reserve, a well-defined reproductive lifespan, and their fertility declines with advancing age. In contrast, men can remain fertile into much later stages of life, leading to a perception that paternal age is less critical. For these reasons, in assisted reproductive technologies, the success rates are mainly associated with the age of the female partner related to the availability of oocytes in quantity and of good quality, and male age is often treated as secondary or negligible.

3. Were you surprised by the effect paternal age had on miscarriage and live birth rates?

Yes, we were somewhat surprised by the impact of paternal age on miscarriage rates and live birth outcomes, especially in the context of oocyte donation cycles, where egg quality is uniformly high and maternal age is controlled.

Our findings challenge the traditional assumption that sperm from older men are adequate once fertilisation occurs and that paternal age has little relevance to reproductive outcomes. They highlight that paternal age plays a critical role, not only in conception, but also in pregnancy maintenance and the likelihood of live birth.

4. Did you observe any trends that suggest a specific age threshold where risks begin to increase more noticeably?

Several studies indicate that the impact of paternal age becomes more noticeable around the age of 40 to 45. While there is not a universal cut-off, this range consistently appears as a point where measurable changes in reproductive outcomes begin to emerge. For example, we already know that in autologous IVF cycles, live birth and pregnancy rates are decreasing significantly in men aged 45 and older, and that the frequency of chromosomal anomalies in embryos tends to increase starting around age 40.

Therefore, the age of 45 years may represent a practical threshold to take into consideration, especially in the context of assisted reproduction. However, it is important to consider paternal age as a continuum as associated risks tend to rise progressively, rather than manifest suddenly at a specific age.

5. Do you have any hypotheses about the biological mechanisms behind these outcomes?

Certainly - several biological mechanisms may explain the association between advanced paternal age and reduction of live birth rates, even in our oocyte donation cycles. As men age, spermatogonial stem cells divide continuously, leading to a higher chance of DNA replication errors, and so an increased number of de novo mutations and increased levels of sperm aneuploidy. Moreover, advanced paternal age is associated with the increment of sperm DNA fragmentation and changes in the epigenetic profile of sperms, such as DNA methylation.

Together, all these mechanisms suggest that paternal age influences not just the genetic content, but also epigenetic integrity and functional capacity of the sperm, which in turn may affect embryo quality and impair early embryonic development. These factors can explain the increased risk of miscarriage, resulting in reduced implantation rates and pregnancy outcomes, even when maternal factors are optimised through egg donation.

6. What are the broader clinical implications of your findings for fertility treatment practices, particularly in how clinics assess and counsel male patients regarding paternal age?

Understanding how paternal age impacts reproductive outcomes can improve clinical counselling and IVF strategy adjustments, particularly for older intended fathers.

Our results underscore the need for a more balanced and inclusive approach to fertility assessment that recognises paternal age as an important factor, even in settings like oocyte donation programmes. Clinics should counsel male patients, especially those over 45 years-old, about the potential impact of advancing paternal age on fertility potential, pregnancy success rates and miscarriage risk.

In addition to standard semen analysis, incorporating advanced tests, such as sperm DNA fragmentation and oxidative stress assessments, may offer a more comprehensive evaluation of male reproductive health and support more individualised treatment strategies.

Finally, clinics should also consider discussing sperm cryopreservation as a preventative option for younger men who plan to delay parenthood, particularly in light of the potential age-related decline in sperm quality.

7. What are the next steps for your research?

The next steps of our research will focus on understanding how paternal age affects reproductive and offspring outcomes and translating that knowledge into clinical practice.

Further research will focus on elucidating the underlying biological mechanisms, such as sperm DNA fragmentation, oxidative stress and epigenetic alterations, that may mediate the effects of advanced paternal age. This will involve the analysis of biological samples to better characterise these pathways.

Some studies show that the risk of neurodevelopmental disorders in offspring is statistically significantly rising with paternal age. Therefore, our future investigation will aim to assess the long-term health and developmental outcomes of children conceived with older paternal age in the context of oocyte donation programmes, where maternal factors are minimised.