Human egg cells are imperfect surprisingly often

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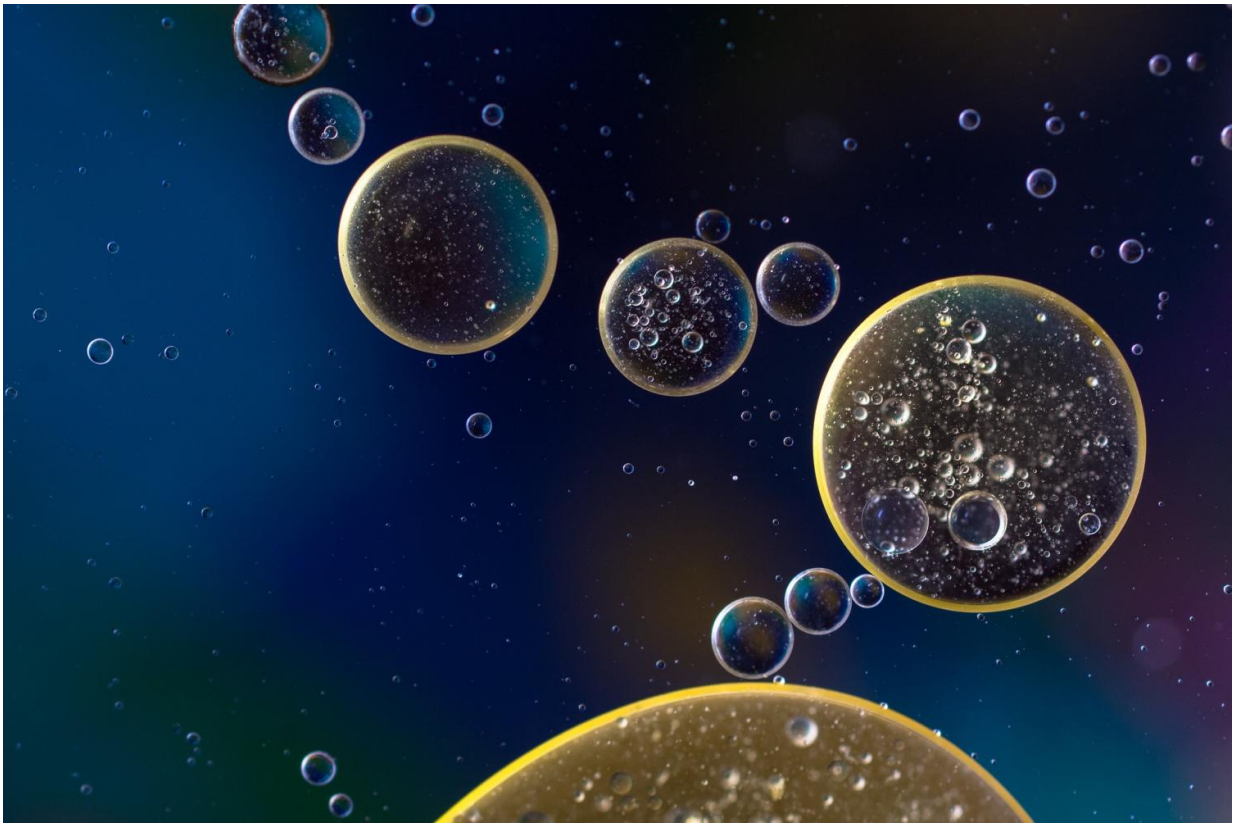

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More than 7% of human oocytes contain at least one exchangeless chromosome pair, demonstrating a remarkably high level of meiotic recombination failure, finds a study appearing December 10 in the

American Journal of Human Genetics. The findings suggest that right from the get-go of human egg cell development, a striking proportion of oocytes are predestined to be chromosomally abnormal. But the frequency of exchangeless chromosomes is not affected by maternal age.

"As much as anything else, this is a public service announcement," says first author Terry Hassold of Washington State University. "We have known for a long time that advancing maternal age increases the likelihood of chromosomally abnormal eggs, but this observation demonstrates that many chromosome errors have nothing to do with maternal age. They are, instead, errors that are extremely common in our species, for reasons that are unclear."

Meiosis is a type of cell division that produces egg and sperm cells. It involves two rounds of division that ultimately result in four cells with only one copy of each paternal and maternal chromosome. Prior to division, genetic material from the paternal and maternal copies of each chromosome is exchanged through a process called meiotic recombination or crossing over.

Recombination failure is a leading cause of aneuploidy, which is the presence of an abnormal number of chromosomes. But the magnitude of the effect has not been clear, because until now, there had been no attempt to directly measure the incidence of exchangeless chromosomes in a large series of human oocytes—immature egg cells.

To address this knowledge gap, Hassold and his collaborators conducted a large population-based analysis of exchangeless chromosomes in the fetal ovary. In total, they examined 7,396 oocytes from 160 tissue samples. To determine the overall proportion of human oocytes containing one or more exchangeless chromosomes, they counted chromosome pairs that lacked the crossover-associated protein MLH1.

The researchers found a surprisingly high level of recombination failure, with more than 7% of oocytes containing at least one exchangeless chromosome pair. According to the authors, this may be an underestimate of the real frequency of exchangeless chromosomes in human oocytes due to conservative analyses used, and the real value may be as high as 10%-15%.

The smallest autosomes (i.e., chromosomes 21 and 22) are most likely to exhibit recombination failure. There is also a subtle but statistically significant positive correlation between gestational age and the frequency of exchangeless chromosomes. The observations indicate a 1.6-fold increase in aneuploidy in the older gestational age group.

"Probably the most surprising observation was simply the high proportion of eggs that contained exchangeless chromosomes," Hassold says. "We had known from previous preliminary studies and from trisomic pregnancies that the value would be high, but seeing it directly in human eggs was still a little jarring."

Moving forward, the researchers will search for genetic variants that may affect the likelihood of having exchangeless chromosomes.

In the end, the new results may have considerable, practical clinical importance. "From our experience counseling couples who have experienced a miscarriage or the birth of a child with an extra or missing chromosome, it is clear that there is frequently accompanying guilt," Hassold says. "Our results indicate that quite the contrary, many of these chromosome errors are simply hardwired into human biology."

More information: *American Journal of Human Genetics*, Hassold et al.: "Failure to recombine is a common feature of human oogenesis" www.cell.com/ajhg/fulltext/S0002-9297(20)30407-9 , DOI: 10.1016/j.ajhg.2020.11.010

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