Chromosome biology

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Advances of aneuploidy research in the maternal germline

During human pregnancy, a large proportion of zygotes do not mature into blastocysts, and many that form blastocysts do not implant. Studies of pregnancies with a clinical diagnosis, usually achieved around 4 weeks after conception (about 6 weeks in the postmenstrual period), show that circa 10–15% will end in spontaneous pregnancy loss before the end of the first trimester. In the past, it was erroneously believed that the causes of spontaneous pregnancy loss were maternal, anatomical, endocrinological or due to infections. But it is now well established that the most frequent cause is genetic, more specifically cytogenetic, because of fetal chromosomal abnormalities. Chromosomal anomalies are diagnosed in more than 60% of first-trimester miscarriage samples that are tested. Spontaneous pregnancy loss thus constitutes the most common 'genetic disease' of humans.

Errors can occur during meiotic chromosome segregation that result in gametes with extra or missing chromosomes, leading to trisomy or monosomy, respectively, upon fertilization; the presence of an abnormal number of chromosomes is also known as aneuploidy. Advanced maternal age is the trait that correlates the most with fetal chromosomal abnormalities, specifically the autosomal trisomies, such as trisomy 21. Multiple studies suggest that the rate of aneuploidy is chromosome-specific. Cytogenetic analyses of preimplantation embryos show that most abnormal segregation events occur during the first meiotic division. The reported rates of aneuploidies in the first and the second meiotic divisions vary, and maternal age plays a role. Errors in the first segregation increase with age, but those of the second meiotic division seem to be less affected by it.

For a long time, the generally accepted mechanism of abnormal chromosome segregation in humans was believed to be the phenomenon of non-disjunction, with sister chromatids failing to separate during the second division. More recently, precocious separation of sister chromatids was also detected because of the presence of single chromatid errors in karyotypes of human eggs that had failed to fertilize during in vitro fertilization. Moreover, a third type of segregation error was identified in human oocytes, reverse segregation, which is characterized by the premature separation of both homologues at the first meiotic division, allowing for the presence of one chromatid from each homologue in both the egg and the polar body.

In 2019, a ground-breaking publication by Gruhn et al. found that oocytes from teenagers and very young women (<20 years) were more likely to be affected by non-disjunction events in the first meiotic division (35% of oocytes), with the largest chromosomes (chromosomes 1 to 5) most prone to aneuploidy. Segregation errors then decreased with age until increasing again in oocytes of women aged >35 years, which displayed significantly higher rates of precocious separation of sister chromatids (48%) and reverse segregation (43%) of the smaller acrocentric chromosomes.

This U-curve of the rate of aneuploidy along the reproductive life span of female individuals may underlie a biological clock for fertility, seemingly shaping it through the high incidences of aneuploidy at both ends of the spectrum, the very young and the more advanced maternal ages. This may provide an evolutionary protective mechanism against adverse outcomes during childbearing and child-rearing years. The study by Gruhn et al. emphasizes the need to better understand the distinct mechanisms that shape aneuploidy rates at both ends of the reproductive window. One of the most intriguing questions is how age-dependent mechanisms reduce chromosome segregation errors from young teenagers to young adult women (20–32 years).

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We face the challenge of integrating these newly identified genetic and non-genetic causes of aneuploidy into mechanistic working hypotheses. Then we will be able to understand how the improvement of the genetic quality of oocytes from teenage to young adult ages occurs and how these pathways can be harnessed clinically. These ground-breaking developments in reproduction knowledge could certainly have very substantial implications for the identification and treatment of different clinical fertility phenotypes.

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Original article: Gruhn, J. R. et al. Chromosome errors in human eggs shape natural fertility over reproductive life span. *Science* **365**, 1466–1469 (2019)

Related article: Gruhn, J. R. & Hoffman, E. R. Errors of the egg: the establishment and progress of human aneuploid research in the maternal germline. *Ann. Rev. Genet.* **56**, 369–390 (2022)

Competing interests

The author declares no competing interests.