# Meiotic errors in oocytes of young and advanced maternal age women: the U-curve of fertility

Giulia Fiorentino[1], Tamara Canosi[1], Laura Rienzi[2,3], Filippo Maria Ubaldi[2], Maurizio Zuccotti[1], Danilo Cimadomo[2], Federica Innocenti[2]

[1] Department of Biology and Biotechnology "Lazzaro Spallanzani", University of Pavia, Pavia, Italy; [2] IVIRMA Global Research Alliance, GENERA, Clinica Valle Giulia, Rome, Italy; [3] Department of Biomolecular Sciences, University of Urbino "Carlo Bo", Urbino, Italy

**ABSTRACT**

Italy is currently one of the countries most affected by declining birth rates, a negative trend mainly determined by several socio-economic factors that lead women to postpone pregnancy. The use of in vitro fertilization techniques cannot counteract the natural decline in fertility that accompanies advancing maternal age. This decline is associated with an increase in chromosomal aneuploidy in oocytes that, if fertilized, could result in aneuploid embryos that are often miscarried. Here, we discuss the "molecular clock hypothesis" proposed by Hoffmann's lab, which suggests a U-shaped trend of female fertility. The high rates of chromosomal aneuploidy observed at the two "ends of the curve" may represent an evolutionary mechanism of protection that exists to balance the risks associated with pregnancy. This hypothesis lays the foundations for debating the idea that very young women are free from the risk of aneuploidy, and also suggests the existence of a safety mechanism that "protects" against possibly complicated pregnancies both after the age of 40 years and in very young women. The U-shape hypothesis described in humans will be discussed in a comparison with the fertility trends of other mammalian species.

**KEYWORDS**

Fertility, aneuploidy, advanced maternal age, IVF.

## Chromosomal mis-segregation as a cause of reduced fertility

Italy is currently one of the countries most affected by declining birth rates [1], a negative trend mainly determined by socio-economic factors that lead women to postpone pregnancy pending greater economic and social stability [2]. The main biological cause of this fertility decline is the increase in meiotic chromosome segregation errors, and therefore in aneuploid oocytes, that accompanies maternal aging [3]. Chromosome segregation occurs during both the first and the second meiotic division (MI and MII) and it is a finely regulated process prone to mistakes that may result in the formation of oocytes containing two copies of a chromosome (disomic gamete) or lacking a chromosome following a non-disjunction event (nullisomic gamete) [4]. These chromosomal abnormalities affect 30–80% of oocytes, depending on the woman's age [5], and have a substantial impact on preimplantation embryos [6,7].

In the period between fetal development and menarche, oocytes are arrested at the dictyate stage in the prophase of MI [8]. A prolonged period of quiescence, as observed in women of advanced maternal age (AMA, ≥35 years), may compromise the genetic stability of oocytes and increase the risk of mis-segregation [3]; in fact, AMA is associated with a wide range of adverse pregnancy outcomes, including a higher incidence of implantation failures, chromosomal abnormalities, and miscarriages [9,10]. The incidence of aneuploidy-related pregnancy losses is lower in women aged <40 years than in those >40 years of age (65% vs. 82%) [11].

Evidence suggests that multiple factors, including cohesin dysfunction, spindle instability, and alterations in chromosome telomere length, may increase the likelihood of age-dependent mis-segregation [12]. Alterations in the activity of cohesins (i.e., proteins involved in the separation of homologous chromosomes during MI and sister chromatids in MII) can cause segregation errors during oogenesis. In this regard, mouse model studies highlighted an association between alterations in chromosome cohesion and oocyte aging [13,14]. Furthermore, an imbalance in the process of chromosome cohesion often results in a high incidence of premature separation of sister chromatids (PSSC) in AMA women [15].

Accurate chromosome segregation also requires specific

**Article history**
Received 4 Oct 2023 – Accepted 22 Dec 2023

**Contact**
Federica Innocenti; innocenti@generapma.it
*IVIRMA Global Research Alliance, GENERA, Clinica Valle Giulia, Rome, Italy*
*Via Giuseppe De Notaris, 2b, 00197, Rome, Italy*

spindle configuration and dynamics [16]. Recent studies indicate a decreasing number of proteins involved in spindle assembly in both mouse and human aged oocytes [17-21].

In addition, progressive shortening of telomeres (i.e., structures consisting of repeated nucleotide sequences which protect the ends of chromosomes) occurs at each cell division and may lead to meiotic dysfunction, morphological alterations of the spindle, as well as subsequent embryo fragmentation [13]. This hallmark of aging has been observed in both human and mouse AMA oocytes [22,23]. In particular, short telomeres have been found to be characteristic of oocytes from patients who have had recurrent in vitro fertilization (IVF) failures or fragmented or aneuploid embryos [24].

Alongside these events, associated with nuclear maturation and cell division, the reduction of women's reproductive potential with aging is also due to other cytological aspects [13].

Cytoplasmic maturation, involving organelle reorganization and storage of transcripts and proteins, is essential to support the entire oocyte maturation process, fertilization, and early embryogenesis [25,26]. In this regard, it has been found that mitochondria with structural alterations or impaired metabolic activity characterize "elderly" oocytes [27,28], and that poor-quality mitochondria may lead to early arrest of embryonic development in AMA women [29]. In particular, high mitochondrial production of reactive oxygen species in mammalian oocytes correlates with premature loss of chromosomal cohesion, segregation defects and aneuploidy [30-33]. Some studies indicate that long-term supplementation with antioxidants reduces aneuploidy in oocytes from older mice [34] and humans [30].

## Comparison of aneuploidy frequencies among mammalian species

In several mammals besides humans, AMA is associated with an increase in aneuploidy incidence, with most of the regulatory cellular processes conserved across species [35]. However, only a few studies have been performed in in vivo ovulated MII oocytes. In the mouse, the frequency of aneuploidy in MII oocytes is 3-10% in young animals (1–3 months) [36-41], rising to 12.5% in 9-month-old adults [37], and to 30-37.5% in 12-month-old mice [37,38,40]; instead, very-old (15-19 months) mouse oocytes display a 25% rate of aneuploidy [39,41]. In the monkey, two studies report an aneuploidy incidence of 0-5% in *in vivo* ovulated oocytes from young females aged 4-15 years versus 14.3% in oldest monkeys aged 16-26 years [42,43]. Additionally, in vitro matured MII mare oocytes showed a frequency ranging from 15.6% in young (<14 years old) to 55.6% in old (>16 years old) individuals [44]. In cattle, the overall rate of aneuploidy was found to be between 3% and 7% [45,46].

Overall, these studies show an increase in aneuploidy rate with AMA, similar to that found in women. On the contrary, a couple of studies in in vitro matured MII porcine oocytes indicated no increase in the prevalence of aneuploidy, which ranged from 11-12% [47,48] in young animals aged <15 months to 8.7% in old animals (7-8 years) [47]. Overall, due to differences between the various techniques used for scoring oocyte aneuploidy, the reported frequencies are sometimes highly heterogeneous [49-51]. Importantly, however, the use of these mammalian model organisms has facilitated the identification of key mechanisms associated with the development of aneuploidy which are also conserved in human oocytes. Nevertheless, some specific spindle dynamics predispose the human oocyte to the occurrence of chromosomal segregation errors [52]. In contrast to the mouse, which shows an acentriolar microtubule-organizing center (aMTOC)-mediated spindle assembly, human oocytes lack aMTOCs and instead show Ras-related nuclear protein-guanosine triphosphate (RAN-GTP)-driven microtubule formation. A mutation in the RAN gene prevents spindle assembly in human oocytes [52,53]. In addition, unlike oocytes of other mammals, human oocytes are deficient in the microtubule motor protein kinesin superfamily protein C1 (KIFC1), which stabilizes the spindle [54-57]. Supplementation with exogenous KIFC1 was proposed as a promising strategy to reduce spindle instability and the risk of aneuploidy in human oocytes [56]. Considering the large difference in lifespan between humans and other mammals, it is plausible that human oocytes are more susceptible to error-causing factors which, accumulated throughout the reproductive years, contribute to aneuploidy [6].

## The U-shaped curve of fertility

In recent years, the incidence of meiotic aneuploidy in human oocytes has been carefully investigated.

A better understanding of the maternal aging-related mechanisms leading to aneuploidy is essential for the development of intervention strategies that may reduce its occurrence and detrimental effects, thus preventing abnormal reproductive outcomes. Human females are among the few mammals that experience menopause [58]. According to the most supported hypothesis, named the "molecular clock hypothesis" [59], the occurrence of aneuploidy may be a protective mechanism for restricting fertility, and possible gestations, to a specific period in a woman's life. Indeed, it is thought to be an evolutionary adaptation whose purpose is to minimize risky pregnancies in very young and, especially, in AMA women. Indeed, on examining the chromosome arrangement of oocytes from very young, adult and AMA women, chromosomal aneuploidy is seen show a U-shaped trend, with a high incidence from puberty to <20 years, a decrease at the ideal reproductive age (20-34 years), and a rapid increase from 35 years to menopause [59]. As oocyte aneuploidy is one of the main causes of infertility, this phenomenon is reflected in the fertility curve, which also follows a U-shaped trend, albeit an inverted one, given that fertility is higher in adult life, when the occurrence of chromosomal errors during meiosis is lower [59] (Figure 1A).

Recent evidence indicates that the U-shaped trend shown by the occurrence of chromosomal errors is associated with different segregation error mechanisms. In oocytes during the GV-to-MII transition taken from young (ideal reproductive age) and AMA women, a single nucleotide polymorphism analysis of the pericentromeric chromosomal region (closely linked to segregation events during meiosis) revealed that three different main types of errors, occurring in a temporal sequence

during aging [59,60], underlie the U-curve of aneuploidy [4]: (i) non-disjunction of homologous chromosomes during MI (MI NDJ), when the gain or loss of an entire chromosome occurs; (ii) PSSC, in which the sister chromatids of a homologous chromosome separate during MI; and (iii) reverse segregation (RS), in which the sister chromatids of both homologous chromosomes already separate during MI. Looking at these meiotic anomalies individually, MI NDJ is the most frequent alteration in women under 20 years of age and progressively decreases with increasing maternal age; PSSC, instead, increases with age; while RS is significantly higher in AMA patients (Figure 1B).

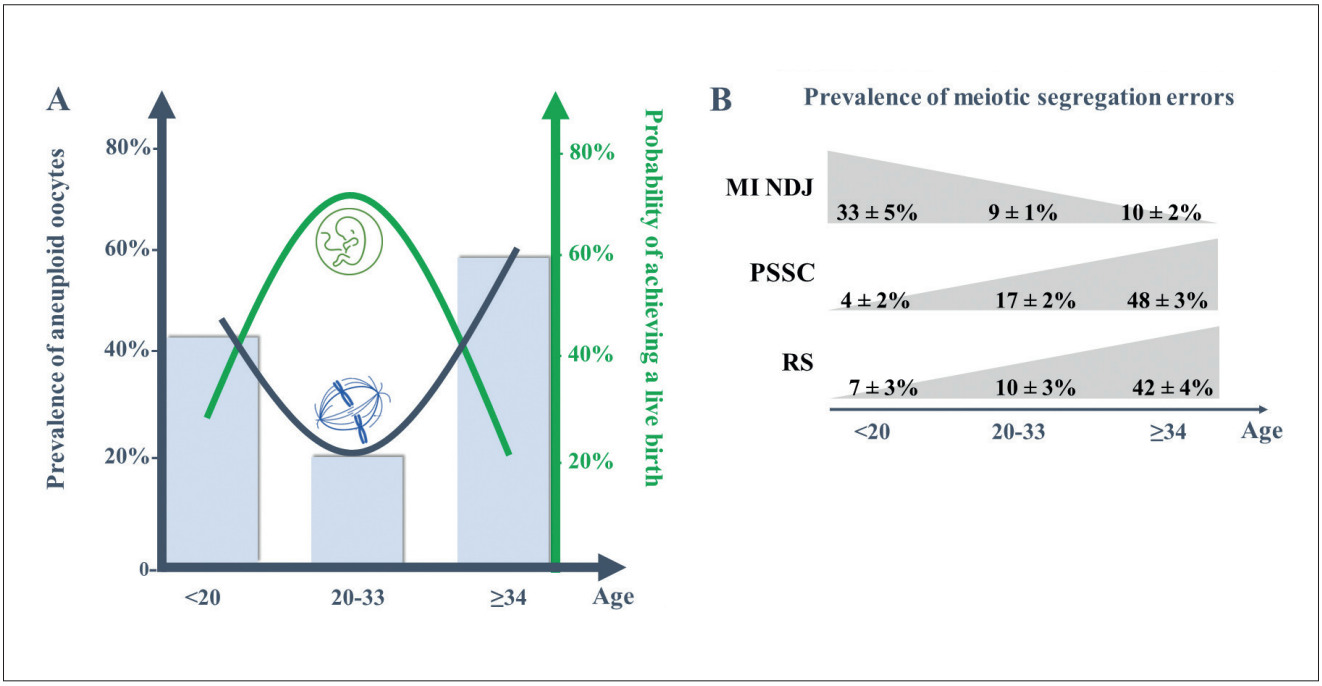
Whilst the mechanism explaining the higher trend of MI NDJ events in adolescents is still unclear, there is emerging evidence of a weakening of centromeric cohesion between two homologous chromosomes as the molecular mechanism determining aneuploidy in AMA women [61]. In the presence of an extensive loss of centromeric cohesion, which determines the loss of a single functional unit of the homologous chromosomes during MI, alterations such as a complete reversal or deterioration of bivalents may correlate with the marked increase in RS in the AMA group. Therefore, weakening centromeric cohesion may play a role as a "molecular clock" that limits the reproductive capacity of women by predisposing certain chromosomes to specific errors. Taken together these data indicate that the U-curve of aneuploidy is the result of specific timing of the incidence of different segregation errors, and that this phenomenon shapes the U-trend of fertility. They also show how the reproductive phase is finely regulated by the appearance of the different types of aneuploidy.

## Clinical and biological implications

The mechanisms underlying the U-shaped fertility curve have important implications for both clinical practice and evolutionary biology. Interestingly, recent clinical studies are focusing attention on the increased risk of aneuploidy in the oocytes of young women. Sills *et al.* [62] reported a high aneuploidy rate (53.2%) in embryos derived from donor eggs (mean ± SD age 24.0 ± 2.7 years), where 88.1% of embryo aneuploidy was of maternal origin. In line with these findings, a large retrospective review of more than 15,000 trophectoderm biopsies found the lowest risk (20–27%) of embryo aneuploidy in women of 26-30 years of age, and a higher incidence (>40%) in women aged 22 and 23 [3]. Moreover, a recent study revealed that egg donors aged 23-29 years were linked to a higher chance of recipient clinical pregnancy and live birth after the first embryo transfer compared with donors aged 18-22 years [63]. The results of these studies, contrary to the common belief that "younger is better", suggest that a younger donor age does not necessarily correlate with a higher chance of pregnancy in egg donation cycles. Considering that most countries set a lower age limit of 18 years for egg donors [64], increasing this age limit might be an option [65].

In relation to the increase in aneuploidy in older women, several evolutionary explanations for the prolonged duration of post-reproductive life in humans have been proposed. Among these, the so-called grandmother hypothesis is attracting increasing interest. First proposed by Peter Medawar in his essay "An Unsolved Problem of Biology" [66], and subsequently elaborated on by others, the hypothesis suggests that older females

**Figure 1** (A) A graphic representation of the "U" trend of female fertility. The distribution of meiotic segregation errors defines the "U-shaped" aneuploidy trend (blue curve). Showing an opposite trend, meiotic error rates throughout the entire reproductive lifespan shape the trend of natural fertility (green curve), reported as the probability of achieving a live birth. (B) Each period of a woman's life is characterized by specific types of aneuploidy: MI NDJ is significantly higher under the age of 20 years, and progressively decreases with increasing maternal age; PSSC increases with increasing age, while RS is significantly higher in the elderly oocytes [59].
(**MI NDJ**, non-disjunction of homologous chromosomes during meiosis I; **PSSC**, premature separation of sister chromatids; **RS**, reverse segregation).



increase their genetic fitness, by helping to raise and support grandchildren, rather than by having other offspring of their own. In this way, natural selection, by favoring features that promote post-reproductive survival, might have driven the evolution of longer post-reproductive lifespans [67]. So far, study of the post-reproductive lifespan phenomenon has been limited to "natural fertility" populations that lack access to modern health care and technology, such as the Hadza hunter gatherers of Tanzania [68], and it has produced convincing evidence that the menopausal phenomenon is not an artefact of modern living or of today's reproductive choices. The grandmother hypothesis has also been debated alongside the "mother hypothesis", which suggests that menopause may have evolved in order to reduce the mortality risk associated with additional pregnancies and deliveries in older mothers with existing children, and thus to increase the latter's chances of survival [69]. Overall, this evidence suggests that further understanding is essential in order to guarantee proper counseling of women who opt for social egg freezing or choose to take part in egg donation programs, so that they can be helped to choose the most appropriate time to freeze their oocytes.

## Conclusions

Infertility is defined as the absence of conception following at least one year of unprotected sexual intercourse [70]. In patients undergoing IVF, it is advisable to investigate the cause of the infertility and define a specific treatment path. The literature reports a significant increase in meiotic errors in human oocytes with female aging [71]. Multiple factors, including cohesin dysfunctions, spindle instability, and alterations in chromosome telomere length, play a role in meiotic chromosomal mis-segregation [12]. On the basis of the emerging "U-shaped" aneuploidy trend it seems possible to predict a high incidence of chromosome alterations not only in women of AMA, but also, for the first time, in young women [59]. In particular, it has been suggested that whole-chromosome MI NDJs are associated with increased rates of aneuploidy in young girls, a phenomenon whose underlying mechanism is still unclear, whereas centromeric and more extensive cohesion weakening drives increases in PSSC and RS and limits fertility in AMA women. This new perspective, which reopens the discussion on the underlying molecular mechanisms, lays the foundations for a new interpretation of the natural curve of fertility. The presence of a biological mechanism that protects women from risky pregnancies, by concentrating meiotic anomalies at a very young age and at AMA, might represent a "safety system", evolutionarily associated with improved reproduction and fitness. In clinical practice, this could be translated into a more targeted approach characterized by treatment personalization, more developed knowledge and technologies, and greater patient safety.

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***Acknowledgments:*** *None*
***Conflict of Interest:*** *The authors declare that there is no conflict of interest.*