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Review Article

The Risk of Advanced Maternal Age: Causes and Overview

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Abstract

As an important factor of chromosome abnormality in offspring, elderly pregnant women have attracted more and more attention. Studies have confirmed that the offspring of older pregnant women, whether conceived naturally or through assisted reproductive technology, are more likely to develop chromosome abnormalities than younger pregnant women, and the reasons have not been fully explained. The spindle assembly checkpoint monitors the correct connection between all mobile axes and the spindle. The bipolar spindle is the key to cell division to guide the correct separation of chromosomes and is the main gatekeeper to prevent the development of oocytes carrying DNA damage. Older pregnant women lead to the error of sister chromatid separation and the decrease of chromosome cohesion. The integrity of telomeres also affects the folding of DNA and the ability of cells to replicate. In addition, more oxidative stress makes the ovaries of older pregnant women unable to support fertilization and embryonic development. With the oxygen free radicals increase, the pathway of ovarian cell apoptosis and mitochondrial repair were changed. Therefore, the analysis of the causes of fetal chromosome abnormalities in elderly pregnant women is helpful to improve the understanding of the particularity of pregnancy in elderly pregnant women, so as to reduce the birth of defective babies and improve the birth quality.

Background

Since 1980, the progress of modern society has greatly affected the fertility of women. In recent years, there has been an increase in the number of (AMA) among non-pregnant and older mothers-that is, women with childbearing age greater than or equal to 35 years of age, especially at the senior level in both developed and developing countries. Over the past few decades, the age structure of the world's reproductive population has changed dramatically. In China, the age structure of childbearing population keeps changing. The fertility rate of women aged 35 to 39 was 8.65% in 2004 and 17.04% ten years later. By 2016, the rate of late pregnancy was about 31% [1-3]. In Europe, the probability of chromosomal abnormalities increases with the age of the mother. In 2016, the Chinese government liberalized the "two-child policy" and gradually replaced the "one-child policy". The new policy encourages couples to have two or more children, which may lead to more pregnant woman [4]. AMA has gradually become an important social and clinical issue. At present, the proportion of women who have delayed their childbearing age to 35 years old has increased significantly, especially in Western countries. At present, the delay in childbearing age may be related to a variety of factors, such as female education level and career goals, effective contraceptive strategies, lack of support for parental social incentives, and a widely disseminated misconception that assisted reproductive technology can compensate for infertility that naturally decreases with age [3]. The older the parents are pregnant, the higher the risk of illness in their offspring [5]. There is a large body of research and data confirming a negative correlation between maternal age and child health at birth. The live birth rate of AMA is lower than that of young women conceived through natural or assisted reproductive technology. To some extent, the decrease of fertility is due to the increase of ovary aneuploidy, which leads to the decrease of embryo quality and abortion [6,7]. However, the biochemical mechanism of aging affecting ovary and embryo quality remains to be clarified. The reasons for the decline of ovarian reserve in AMA are considered to be energy production disorders, cell cycle checkpoints, and meiotic

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errors. The error may occurs in the number of divisions I, and meiosis II can be partially corrected. It is estimated that 20% of woman's egg are aneuploidy, and the number increases exponentially over 30 years old, reaching 80% at 42 years old [8]. More than 40% of those women have experienced abortion and infertility [9]. Evidence suggests that female aging and mitochondrial decline are associated with abnormal meiosis and embryonic aneuploidy [10]. This article aims to summarize the mechanisms of chromosomal abnormalities in AMA.

advanced maternal age and chromosomal abnormalities

Spindle assembly checkpoint: In mitosis and meiosis, the transition from metaphase to anaphase requires the activity of an ligase called anaphase-promoting complex/cycle (APC/C). The activation of APC/C in the medium term is controlled by a checkpoint mechanism called Spindle Assembly Checkpoint (SAC) [11], which monitors the correct connection of all moving shafts to the spindle, bipolar spindle is the key to cell division in order to guide the correct separation of chromosomes [12]. It was found that the oocytes damaged by DNA stopped in the metaphase of the first meiosis (MI). MI arrest is induced by SAC, because inhibition of SAC overrides MI arrest induced by DNA damage. In addition, this situation also occurred in the oocytes of older mice. These data led Petros et al to propose that SAC is the main gatekeeper to prevent the development of oocytes carrying DNA damage. SAC protects aneuploidy and DNA damage comprehensively by preventing the production of abnormally mature oocytes and subsequent embryos [13]. The SAC adjusts the late start time in response to the incorrect arrangement of chromosomes on the metaphase plate. If a defect is detected, a signal is transmitted to stop further progress in the cell cycle until the correct bipolar connection to the spindle is achieved. Current eukaryotic cell cycle regulation models show that it is driven by an oscillating biochemical clock, which is regulated by a monitoring system called checkpoints in order to prevent failures, such as DNA damage, monitor the integrity of spindles, and determine whether chromosomes are evenly separated. The failure of the surveillance system may lead to genomic instability, which may be the reason for the increase in the incidence of aneuploidy in gametes in older women. To explore this possibility, Nury et al detected the concentration of transcripts in human oocytes at different stages of maturation. The results showed that the transcriptional information degenerated with the increase of ovary age. This may impair the checkpoint function of aged oocytes and may be a contributing factor to age-related aneuploidy [14]. Budding Uninhibited by Benzimidazole-related 1 (BubR1) is the core component of the SAC system. BubR1 participates in appropriate chromosome segregation during mitosis through SAC signal activation. BubR1 is necessary in several key steps of oocyte meiosis. More specifically, it is necessary for SAC activity, the time of the first meiosis and the stable attachment of chromosomes to spindles. A significant decrease in BubR1 levels was detected in aging human and mouse oocytes. Qiu confirmed that SIRT2 gene knockout in mouse oocytes led to spindle defects and chromosome disintegration, accompanied by damage to kinetochore-microtubule (K-MT) junctions. The two-way interaction between the chromosome and the spindle ensures the correct separation of the chromosome through the terminal connection between the microtubule and the centromere [15].

Chromosome separation disorder: Elderly pregnant women are prone to misseparation of chromosomes during meiosis, resulting in an increase in the incidence of abnormal chromosomal embryos, early abortion and birth defects [16]. Before the birth of a female infant, the eggs in her body are already in the stage I of meiosis. Before puberty, the gonad is still, undeveloped and not ovulated. With the increase of stimulation of hypothalamic GnRH generator, ovulation begins to appear after the development of dominant follicles in adolescence. Ovulation has a periodic menstrual cycle, which can be divided into follicular phase, luteal phase and menstrual phase. Mammals complete the first meiotic division before and after ovulation. After ovary excretion, it meets with sperm in the ampulla of fallopian tube to form fertilized eggs and complete the second meiotic division. Chromosomal separation disorders caused by AMA are common in meiotic disorders, common separation disorders include non-segregation of sister chromatids, premature separation (Figure 1), and recently discovered reverse separation [2]. Chromosomal error separation of ovary may be caused by different mechanisms, the first mechanism is that it cannot be reorganized and correctly crossed, thus failing to maintain the correct connection of chromosomes, the second mechanism involves premature loss of cohesion between sister chromatin centromeres (Figure 1) [17]. Most mammalian ovary develop long and discontinuous. Until the menarche, the ovary enters the stagnation phase in the early stage of meiosis I. After the stagnation period, the ovary acquires the ability to divide. After chromosome separation, the ovary extrudes the first polar body (Pb1) and waiting for fertilization in Phase II (MII). Many factors affect the maturation of ovary. The quality of ovary in most mammals is negatively correlated with age. Homologous chromosomes recombine in primary ovary, forming a bivalent configuration in the pre-meiotic phase, maintaining a bivalent structure is the key to maternal meiosis, and the divalent structure may be impaired during prolonged stagnation. Importantly, when the metaphase lasts too long, for example, when the cell cannot solve the chromosome dislocation, apoptosis is usually triggered, which is more likely to lead to cell death than the possible chromosome abnormality in the screwdriver cell [18,19]. There are two hypotheses that AMA leads to this phenomenon: (1) bivalent degeneration throughout the process, (2) defective reconstituted ovary are expelled from the ovary [2]. Sister chromatids cohesion decreases with age. The loss of sister chromatids cohesion destroys the structure of centromere and weakens unipolar binding. The cohesion defect of the distal arm of the crossing point leads to premature separation of bivalent structure, leading to the existence of univalent chromosomes at the crossing site (Figure 1) [17]. Based on the whole genome amplification and comparative gene hybridization of a single or a small number of cells in living embryo tissues before implantation, the sequence analysis of three meiotic products pb1, pb2 and their corresponding fertilized eggs showed that the high incidence of ovary aneuploidy and chromosome separation errors in AMA were mainly due to the premature separation of sister chromatids, a few of them showed complete chromosome disjunction [20].

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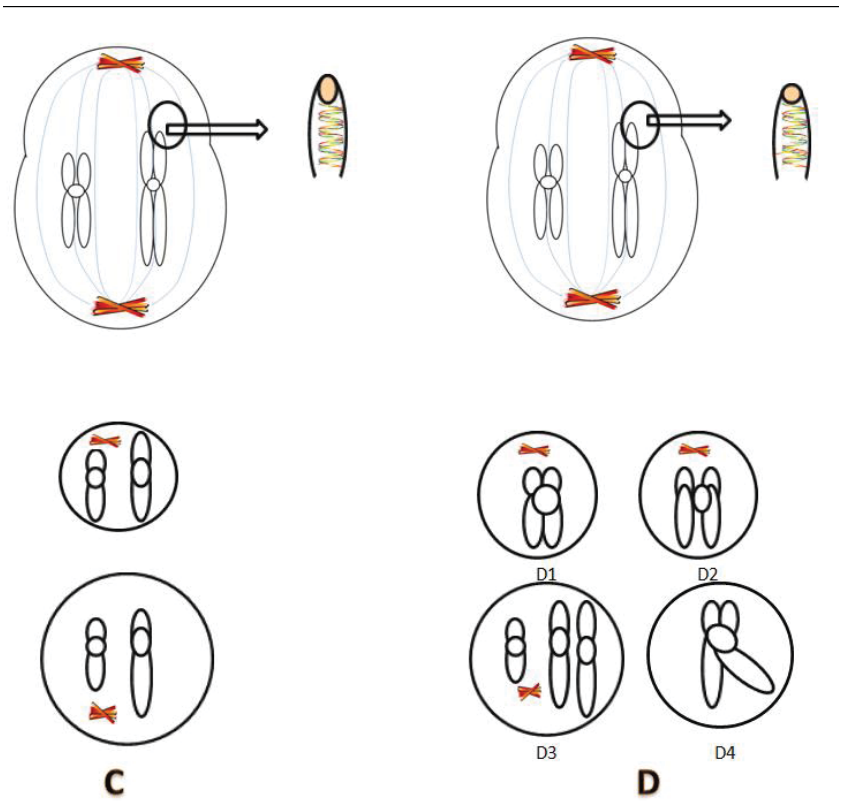

Figure 1: Chromatids separation pattern in young pregnant women and abnormal sister chromatids separation in the AMA and comparison of pattern and telomere length. The sister chromatids in the young pregnant women arranged on the equatorial plate in the middle of the second meiosis and moved to the opposite bipolar with the division of the centromere at the later stage of the second meiosis (C). Sister chromatids mistakenly separated in the AMA (D). D1 indicates that sister chromatids are not separated, D2 indicates that the decrease of centromeric cohesion between sister chromatids leads to the destruction of centromere structure and premature separation. D3 indicates the production of triploid cells due to sister chromatids misseparation, while D4 indicates decreased distalchromatids cohesion and unstable attachment between centromeres. In addition, the telomere length in the AMA was shorter than that in young women.

Telomere shortening: Telomere is a nuclear protein structure at the end of eukaryotic chromosomes, which has the function of protecting chromosomal DNA. Telomere is a marker of metabolic activity of embryonic stem cells (Figure 1) [21]. In humans, telomere length is thought to be a sign of aging as cells shorten with each division, reflecting cell turnover [22]. Telomere length is closely related to biological age, and is affected by oxidative stress and inflammation. The main participants in oxidative stress are mitochondria and telomeres [23]. With the increase of age, senile cells will produce inflammatory mediators leading to further damage of tissues and organs. Telomere shortening interacts with the age of pregnant women. Telomere shortening leads to reduced protein absorption and consequently to the formation of protective nucleotide rings leading to cell senescence or apoptosis. Senile cells will undergo genetic and morphological changes such as chromosome genome instability, leading to loss of function. Telomere integrity affects not only cell replication but also DNA folding [24]. Telomeric theory suggests that it may be due to mitotic end replication problems and exposure to oxidative stress before egg production, resulting in telomere shortening, making ovary unable to support fertilization and embryonic development. Previous studies have suggested that the length of telomeres is related to the stability of chromosomes. According to a previous study by Mania, et al., on the 5th day after fertilization, the length of telomeres in embryos bred by older pregnant women was shortened. Another study have shown that older women who have had children with Down syndrome have shorter telomeres than women in the control group. In order to verify the hypothesis that the telomere length of aneuploidy is shorter than that of normal embryo telomeres, Kara, et al. compared the embryo telomeres in the same fertilization cycle of parents of the same age: the telomere length of aneuploid embryos did differ from the control group, but it was also found that there was no significant difference in telomere length between older women and women younger than 35 years old, which was consistent with previous results of embryo analysis using quantitative fluorescence in situ hybridization [25]. Down's syndrome is the most common chromosome abnormality. Chromosome 21 disjunction is the most common cause. At least 90% of them occur in ovary. There is a strong correlation between age and chromosome 21 disjunction. I. Albizua, et al. 's study confirmed the hypothesis that due to chromosome wrong separation, the telomeres of mothers pregnant with down's children were shorter than those of women of the same age who were not pregnant with down's children. They also found that young women who gave birth to a child with down syndrome appeared to have a older physiological age than their actual age [26].

Other causes: In addition to the above factors, chromosome abnormalities in the offspring of the AMA are also considered to

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be related to a variety of factors. Life begins with the combination of sperm and egg. The appearance of human sperm and egg is formed by diploid cells through a series of events, including protein replication, the first meiosis and the second meiosis. Premature sister chromatid separation can lead to widespread genome randomization. When adhesion is lost prematurely, a single chromatid lacks the opposite force to ensure the proper tension between the moving points, resulting in an unstable microtubule-moving point interaction. Lack of cohesion of mitosis can lead to random chromosome segregation, which is very likely to produce aneuploidy. Most mitotic defects can be corrected over time, but premature adhesion loss is an irreversible mistake, and prolonged mitosis further enhances the randomness of the genome [27]. Overall, a decrease in follicular glucose levels and an increase in lactic acid levels in patients with AMA may indicate an up-regulation of follicular glycol sis. The decrease of glucose level in follicular fluid had a negative effect on the nuclear and cytoplasm maturation of oocytes. Increased glycol sis and mitochondrial respiratory system defects in patients lead to increased oxidative stress, which may be the main reasons for the destruction of oocytes quality and follicle formation [28]. Staessen demonstrated that blast cyst transfer can reduce the rate of abortion caused by chromosome abnormalities in patients over the age of 36, and studies have confirmed that 59% of D3 embryos in older women are genetically abnormal, while only 35% of D5 high-quality blast cysts are aneuploid. However, whether there is a relationship between age and blast cyst formation is still controversial. Chen, et al. found that female age and the number of transferable D3 embryos were significantly correlated with the results of blast cyst culture [29]. AMA is related to the degeneration of mitochondria, especially the slow renewal of mitochondria [30]. The mitochondria in the ovary provide energy through oxidative phosphorylation and support fertilization, embryo division and blast cyst formation. Mitochondrial DNA copy number is a marker reflecting mitochondrial energy reserve, depletion and oxidative stress. Older pregnant women lead to the decline of ovarian quality, which is not only related to the ability of mtDNA to regulate the follicular cistern, but also lead to the accumulation of mutations and embryo aneuploidy [31]. The loss of key proteins in AMA may also lead to spindle defects. The chromosomes are arranged on the equatorial plate. In order to ensure an even distribution between ovaries and polar bodies, age-related incorrect movement and particle-microtubule interactions may lead to chromosomal abnormalities [32-34].

Conclusion

Life begins with the fusion of two haploid gametes. Gametes (mammalian eggs and sperm) are produced by diploid precursor cells through a series of carefully arranged chromosome events, including one round of DNA replication, followed by two rounds of cell division, called meiosis I and meiosis II (Figure 1). In the process of cell division, the SAC is the guardian of chromosome segregation. The impairment of SAC function during meiosis may lead to the formation of aneuploid gametes. In most cases, these gametes are incompatible with subsequent embryonic development, which may be due to a large number of genetic imbalances caused by chromosome missupplements. The chance of AMA producing blast cysts with normal chromosomes may even be less than 5%. On the one hand, this can be attributed to the gradual depletion of ovarian reserves, and on the other hand, it can be attributed to the gradual decline of oocytes / embryo capacity, decreased SAC, dysfunctional adhesion, telomere shortening and impaired mitochondrial metabolic activity. All these processes are directly or indirectly involved in appropriate chromosome segregation, thereby regulating the ability of the embryo [33]. Most of trisomy embryos were found to originate from female meiosis, while the risk of chromosomal abnormalities in older mothers increased [34]. The integrity of telomeres also affects the folding of DNA and the ability of cells to replicate. In most countries in the world, the proportion of AMA is increasing, and the possibility of chromosome abnormalities is also increasing. A more comprehensive understanding of the causes of chromosome abnormalities in AMA offspring will help to improve the detection rate of chromosome abnormalities, thus improve the detection rate of chromosome problems in offspring, improve fertility quality and reduce family burden. At present, the chromosomal abnormalities of offspring are mainly concentrated in the mother, and the age of the father should also be concerned.In addition, how to formulate the corresponding screening strategies and treatment techniques for the causes of chromosome abnormalities in the offspring of elderly women are still being explored.

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