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Aneuploidy in oocytes: understanding causes and exploring therapeutic options

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Abstract

Ploidy in the preimplantation embryo refers to a normal chromosomal complement within each cell. It indicates properly coordinated cytoplasmic mechanisms that govern cytoskeletal organization and dynamics, which are essential for accurate chromosomal segregation during meiotic and mitotic divisions. Interruptions in upstream cytoplasmic signaling or metabolic pathways can compromise cytoskeletal function, thereby increasing the risk of aneuploidy. Thus, chromosomal abnormalities are a phenotypic manifestation of underlying cellular dysfunction, rather than the primary cause.

Aneuploidy, therefore, should be viewed not merely as a genetic anomaly but as a downstream consequence of disrupted intracellular regulation, particularly during oogenesis, where the complexity of chromosomal segregation mechanisms renders the process especially vulnerable to errors. These errors, arising from compromised cytoskeletal or metabolic integrity, can manifest at multiple stages of oocyte maturation, ultimately affecting embryo viability and developmental competence.

This review explores the incidence of aneuploidy across different developmental stages of oogenesis. We aim to address key questions regarding the timing of aneuploidy onset, the potential for error correction, and the prospects for therapeutic intervention. Additionally, we will explore the circumstances under which corrective strategies may offer hope to patients and when it is necessary to acknowledge the limitations of current approaches.

Keywords: Aneuploidy; Meiosis; Meiotic maturation; Co Q10; Oocyte quality.

First Question: At what points during the journey from oogenesis to embryo development does aneuploidy typically arise?

1. Pre-Pubertal Born Errors

Aneuploidy can originate as early as fetal development. Beginning around the 8th week of gestation, primordial germ cells (PGCs) undergo extensive mitotic proliferation, expanding to approximately 6–8 million cells per ovary by the 12th week.

Narrative Review

These PGCs then initiate meiosis I to form primordial follicles, each containing a primary oocyte. During this stage, homologous maternal and paternal chromosomes pair and undergo meiotic recombination, with sister kinetochores of each chromosome fused via a cohesin complex (1,2). This complex acts as a molecular “glue,” enabling the formation of bivalent chromosomes, which function as a single unit for proper segregation (3).

By approximately 16 weeks of gestation, primordial follicles are established, and primary oocytes arrest at the dictyate stage of prophase I, maintaining the bivalent chromosome configuration within the germinal vesicle (GV). This arrested state persists until ovulation resumes at puberty (4).

During the second trimester, the number of primordial follicles continues to rise and plateaus in the third trimester, with an estimated 350,000–400,000 follicles per ovary at birth (5). Errors in chromosomal segregation during these early developmental events can lead to chromosomal abnormalities, contributing to aneuploidy. Such errors likely drive the process of follicular atresia, as oocytes harboring aneuploidy are preferentially eliminated via programmed cell death (6). However, in rare cases, aneuploid oocytes may evade this control mechanism and progress through development. These oocytes can result in pregnancy loss or lead to chromosomal disorders. Nonetheless, such escape events are relatively infrequent, accounting for an estimated 10% of total aneuploidy cases (7).

2. Pubertal Born Errors

Following puberty, a limited cohort of primordial follicles is recruited daily into the growth phase, progressing through distinct stages of development: the primary (preantral), secondary (antral or Graafian), and ultimately the preovulatory phase. These follicles contain oocytes that are initially arrested at prophase I of meiosis. Upon recruitment, a surge in luteinizing hormone (LH) initiates the first meiotic resumption and induces a shift in follicular steroidogenesis from estrogen to progesterone production. This hormonal signal promotes germinal vesicle breakdown (GVBD), marking the re-entry of the oocyte into meiosis (8).

In a typical menstrual cycle, approximately 10–20 oocytes resume meiosis, though only one usually progresses to full maturation and is ovulated. During this maturation process, asymmetric cytokinesis gives rise to a polar body with minimal cytoplasmic content, while the oocyte arrests again at metaphase II of meiosis. Importantly, oocyte meiosis is particularly prone to errors in chromosomal segregation, making this phase a key contributor to aneuploidy. This susceptibility highlights a critical window during which targeted interventions could potentially improve oocyte quality and enhance chromosomal stability (9).

3. Fertilization Born Errors

This stage can be referred to as the “release from the final block,” representing the last phase of oocyte activation and maturation. It involves the resumption and completion of meiosis, culminating in the extrusion of the second polar body and the initiation of zygotic cleavage. Once meiosis is completed, the risk of aneuploidy becomes prominent, as chromosomal segregation errors at this stage may be propagated through subsequent mitotic divisions during early embryonic cleavage (10).

4. Post-Fertilization Born Errors

It is well established that a significant proportion of human preimplantation embryos exhibit chromosomal mosaicism, characterized by the presence of both euploid and aneuploid cells within the same embryo. During early cleavage stages prior to trophectoderm (TE) differentiation, binucleate blastomeres have been observed. These binucleated cells may result from aberrant cytokinesis, where one daughter cell retains two nuclei while the other is anucleate. Additionally, aneuploidy can trigger activation of the spindle assembly checkpoint, potentially leading to multinucleation as a cellular response to mitotic errors (11).

This multinucleation may represent a cell cycle control mechanism, analogous to a checkpoint response, with the potential to facilitate self-correction of chromosomal abnormalities. In this context, early mitotic errors during the first cleavage divisions are considered a primary driver of

embryonic mosaicism. Although embryos displaying irregular cleavage patterns are generally at higher risk for developmental arrest, a subset can progress to the blastocyst stage and give rise to chromosomally normal embryos (12).

Interestingly, some of these embryos demonstrate incomplete compaction at the morula stage, accompanied by the exclusion of specific cells. This phenomenon is hypothesized to be a potential corrective mechanism, in which aneuploid cells are selectively eliminated to preserve the genomic integrity of the embryo. However, the efficiency of such self-correction processes appears to decline with maternal age, with embryos from women over 39 years showing reduced capacity for this form of chromosomal rescue (13).

Second Question: What are the causes of this high rate of aneuploidy?!

1. **Role of Reactive Oxygen Species (ROS):**

   ROS are integral to physiological processes, influencing cell growth, differentiation, and migration via redox-sensitive transcription factors. Their impact on kinase enzymes causes mitochondrial dysfunction, leading to errors during meiosis and contributing to aneuploidy (14).

2. **Meiotic Spindle Assembly in Human Oocytes:**

   Human oocytes lack centrosomes and detectable microtubule organizing centers (MTOCs), leading to inefficient spindle assembly (15), characterized by:

   a. Slow Assembly: Meiotic spindle assembly takes approximately 16 hours (15).

   b. Kinetochore Behavior: Many sister kinetochores behave independently, with over 20% having abnormal attachments during anaphase, increasing the likelihood of lagging chromosomes and aneuploidy (16).

   c. Age-Related Effects: Sister kinetochore separation increases with maternal age, affecting chromosome alignment and segregation (16).

   d. Freeze-Thaw Sensitivity: Human oocytes are vulnerable to freeze-thaw damage, causing cytoskeletal disruption and meiotic spindle issues, leading to aneuploidy (17).

   e. Temperature Sensitivity: Transient cooling can irreversibly disrupt meiotic spindles and chromosome integrity, necessitating strict temperature control during IVF manipulations (18).

   f. Low Oxygen Tension: Poor blood flow to follicles can decrease pH and impair chromosomal organization and microtubule assembly, leading to segregation errors (15).

   g. Follicular Vascularity: Reduced vascularity correlates with increased incidence of triploid zygotes, potentially affecting cortisol levels in follicular fluid (1).

   h. Energy Production Issues: Inadequate energy during early cleavage stages due to mitochondrial dysfunction may disrupt chromosome alignment and segregation (19).

3. **Homeostasis and Signaling Pathways:**

   Oocyte homeostasis relies on the interaction of signaling and metabolic pathways. Defective signaling can lead to cytoskeletal deficiencies, contributing to aneuploidy (20).

4. **Sperm Factors:**

   a. Sperm Quality: Fertilization by diploid sperm with poor chromatin packaging may induce aneuploidy and affect embryo viability (21).

   b. Centrosome Integrity: Anomalies in sperm centrosome may disrupt microtubule organization, impacting chromosome segregation and early embryonic development (22).

Examples of Chromosomal Aneuploidies:

Aneuploidy encompasses deviations from the normal diploid chromosome number, most notably trisomies, monosomies, as well as structural rearrangements such as translocations and inversions, that can produce an unbalanced chromosomal complement in the developing embryo. Age-related aneuploidy arises spontaneously (non-hereditary) and predominantly affects chromosomes 13, 16, 18, 21, X, and Y. Its incidence increases with advancing maternal age (23), such as:

1. Trisomy 21 (Down syndrome) is the most frequent autosomal trisomy, comprising approximately 50–60 % of all trisomic conceptions (24).

2. Trisomy 18 (Edwards syndrome) accounts for 10–20 % of trisomies, with a maternal-age–related risk increase that is less pronounced than in Trisomy 21 (25).

3. Trisomy 13 (Patau syndrome) represents 5–10 % of trisomies, with a weaker maternal-age correlation than Trisomy 21 (26).

4. Sex chromosome aneuploidy can give rise to disorders of sexual development. Errors in meiotic recombination (e.g., failure of homologues to rejoin at diplotene) may result in chromosome loss or abnormal attachment, producing partial trisomies or balanced translocations (27), such as:

    a. Monosomy X (Turner syndrome): the most common monosomy, its prevalence is largely independent of maternal age (28).

    b. Additional sex-chromosome aneuploidies (e.g., 47, XXY [Klinefelter syndrome], 47, XYY, 47, XXX) also occur at rates that are relatively constant across maternal ages (29).

Third Question: Is there any Hope of improving oocyte quality and ploidy state?

During folliculogenesis, a human primordial follicle harbours a primary oocyte of approximately 35 µm in diameter, which undergoes a protracted growth phase of ~85 days to reach a final diameter of ~120 µm. Throughout this period, the oocyte must acquire full developmental competence, the capacity for successful fertilization, and support of early embryogenesis (1,8). Oocyte maturation is orchestrated by the mid-cycle luteinizing hormone (LH) surge and involves two semi-independent but integrated processes, nuclear maturation and cytoplasmic maturation (Table 1), Figure 1 (1,30). Therefore, it is important to note that any intervention aimed at optimizing and improving oocyte quality and euploidy should be implemented during this critical window of folliculogenesis, beginning at the time of the LH surge (30).

Nuclear maturation encompasses (1):

1. Germinal vesicle breakdown (GVBD): disintegration of the nuclear envelope,
2. Resumption of meiosis: progression from prophase I arrest,
3. Completion of the first meiotic division: extrusion of the first polar body, thereby establishing the haploid chromosome complement.

Cytoplasmic maturation requires extensive organellar reorganisation and molecular redistribution, including (1):

1. A marked increase in mitochondrial biogenesis and ribosome content.
2. Remodelling of plasma-membrane transporters and channels.
3. Expansion and peripheral translocation of the Golgi apparatus.
4. Accumulation of storage and secretory inclusions, membrane-bound vesicles, multivesicular bodies, crystalline inclusions, lipid droplets, and glycogen granules.

Collectively, these nuclear and cytoplasmic events culminate in an oocyte capable of fertilization and supporting subsequent pre-implantation development.

Table 1: Timing of Nuclear events during oocyte maturation (1):

Timing of events:	
LH surge (GV with nucleolus)	0 hours
GVBD	+15 hours
first meiotic metaphase	+20 hours
second meiotic metaphase	+35 hours
ovulation	+38 hours

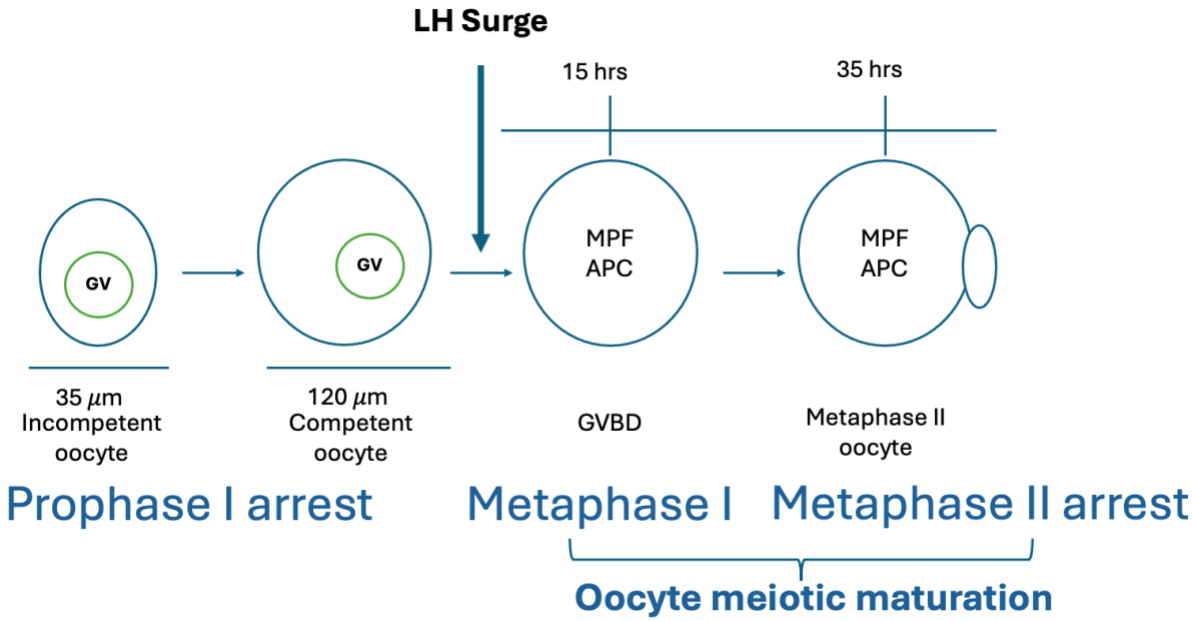

Figure 1. Stages of oocyte maturation after the LH surge.

MPF: Maturation-promoting factor
APC: Anaphase-promoting complex

At this stage, the initiation of targeted treatment modalities to optimize oocyte competence is warranted. Such strategies may include the administration of specific pharmacological adjuvants alongside evidence-based lifestyle interventions, each designed to enhance both nuclear and cytoplasmic maturation and thereby promote the generation of euploid oocytes. Crucially, the timely application of these approaches can mitigate developmental abnormalities and prevent oocyte damage before it occurs.

Potential Complementary Approaches to Improve Oocyte Quality

1. Coenzyme Q10 (CoQ10) Supplementation:

Bentov et al. have demonstrated that CoQ10 supplementation can significantly reduce aneuploidy rates in women over 35 years of age. Ann it was found that by extension, in women aged over 40, a 14-day CoQ10 supplementation regimen initiated prior to ovulation or at the commencement of ovarian stimulation during IVF cycles may result in a 10–20% reduction in the incidence of aneuploid oocytes (31).

2. DHEA Supplementation:

Emerging evidence suggests that dehydroepiandrosterone (DHEA) supplementation may enhance oocyte quality and decrease aneuploidy rates. Implementing a 14-day DHEA supplementation protocol starting before ovulation or at the onset of controlled ovarian stimulation may yield a reduction in aneuploidy rates (32).

3. Antioxidant Supplementation:

Supplementation with antioxidants such as vitamins C and E, as well as beta-carotene, has been associated with reduced oxidative stress and improved oocyte quality. A 14-day antioxidant regimen initiated before ovulation or at the start of stimulation may contribute to a reduction in aneuploidy rates (33).

4. Omega-3 Fatty Acid Supplementation:

The administration of omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may exert anti-inflammatory effects that support oocyte development and enhance overall oocyte quality (34).

5. Myo-Inositol Supplementation:

Myo-inositol, a naturally occurring isomer of inositol, has been shown to improve oocyte maturation and reduce aneuploidy rates, likely through its effects on intracellular signaling and metabolic regulation (35).

Potential Synergistic Treatment Strategies

The concurrent administration of certain therapeutic agents may have synergistic effects on oocyte quality, acting through complementary mechanisms:

1. CoQ10 and DHEA Combination Therapy:

This combination may exert additive effects through multiple biological pathways:

- Mitochondrial Enhancement: CoQ10 serves a critical role in mitochondrial electron transport and ATP production, while DHEA has been shown to improve mitochondrial efficiency and reduce oxidative stress. Together, these agents may enhance mitochondrial bioenergetics, thus improving oocyte competence (36).

- Antioxidant Protection: Both CoQ10 and DHEA possess antioxidative properties, which may synergistically reduce oxidative damage within the ovarian environment, fostering an optimal milieu for oocyte development (31,32,36).

- Hormonal Modulation: DHEA supplementation has been associated with improved androgen levels and hormonal balance, while CoQ10 may indirectly contribute to hormonal homeostasis via reduction of oxidative stress, supporting improved follicular dynamics (37).

2. CoQ10 and N-Acetylcysteine (NAC) Co-Supplementation:

- NAC, a precursor to glutathione and a potent antioxidant, may enhance the antioxidative capacity provided by CoQ10 (38). Their combined use could offer superior protection against oxidative stress, thus preserving oocyte integrity and competence.

3. DHEA and Myo-Inositol Co-Supplementation:

The combination of DHEA and myo-inositol may synergistically improve oocyte quality by concurrently enhancing mitochondrial function, optimizing hormonal balance, improving insulin sensitivity, and promoting cytoplasmic and nuclear maturation, thereby contributing to reduced rates of oocyte aneuploidy (31,32,36,37).

Lifestyle Modifications to Support Oocyte Quality

In conjunction with pharmacological interventions, lifestyle factors play an important role in optimizing oocyte health. These modifications address factors such as oxidative stress, hormonal balance, and overall reproductive health.

- **Weight Management:**

  Maintaining a healthy body weight is essential, as excess adiposity is linked to increased oxidative stress, systemic inflammation, and impaired oocyte quality (39).

- **Regular Physical Activity:**

  Moderate-intensity exercise has been shown to reduce oxidative stress, improve metabolic health, and support better oocyte maturation, thereby enhancing reproductive outcomes (39).

- **Stress Management:**

  Chronic stress has a detrimental impact on reproductive health by disrupting hormonal homeostasis and increasing oxidative stress (40). Stress-reducing activities, such as yoga, meditation, and mindfulness, may contribute to improved oocyte quality.

- **Sleep Optimization:**

  Adequate and quality sleep is critical for hormonal regulation (41). Disrupted sleep patterns can interfere with endocrine function and negatively affect oocyte quality, making proper sleep hygiene essential for reproductive health.

- **Minimizing Exposure to Environmental Toxins:**

  Reducing exposure to harmful environmental substances such as pesticides, heavy metals, and endocrine-disrupting chemicals is crucial for protecting oocyte development and overall reproductive function (41).

Key Considerations for the Implementation of Complementary Treatment Approaches

When incorporating supplementary therapies, several important factors must be considered to ensure optimal outcomes:

- **Dosage and Duration:**

  The correct dosage and treatment duration must be carefully determined when combining supplements. Excessive or prolonged supplementation may lead to side effects, making individualized dosing protocols essential for efficacy and safety.

- **Individual Variability:**

  Patient response to combined treatments may vary due to genetic differences, baseline health status, and lifestyle factors. Personalization of supplementation regimens is necessary to achieve optimal results.

- **Monitoring and Treatment Adjustment:**

  Continuous monitoring of treatment progress is essential. Adjustments to the treatment protocol should be made based on patient response and ongoing assessment of oocyte quality and IVF outcomes.

- **Potential Adverse Effects:**

  Longer supplementation periods can increase the risk of adverse effects, such as gastrointestinal disturbances and hormonal imbalances. Regular evaluations of the risk-benefit profile of the regimen are critical for ensuring patient safety.

Conclusion:

Most aneuploidy events occur during oocyte maturation at the time of the LH surge, highlighting the importance of this critical phase in determining oocyte quality. Targeted interventions, such as supplements and lifestyle modifications, offer promising strategies for mitigating aneuploidy and enhancing oocyte quality. To maximize their effectiveness, these interventions should be implemented during the critical window of folliculogenesis, starting at the time of the LH surge, ensuring optimal conditions for oocyte maturation and improving the chances of achieving euploidy and successful pregnancy outcomes.

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