RESEARCH PAPER

Advancing maternal age and embryonic aneuploidy: A cross-sectional evaluation of diverse infertility etiologies in a southern Indian IVF cohort

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Abstract

Background: Advancing maternal age is a major determinant of embryonic chromosomal competence, yet age-stratified aneuploidy patterns from Southern Indian infertility populations especially across heterogeneous etiologies remain limited.

Objective: To quantify the association between maternal age and embryonic aneuploidy in a Southern Indian IVF cohort undergoing NGS-based PGT-A, and to assess variation by infertility diagnosis, chromosome-specific distribution, and mosaicism.

Methods: This retrospective cross-sectional study included 440 women (25–45 years) treated at three tertiary ART centers in Southern India (January 2024–December 2025). Participants were grouped by age: <35 (n=140), 35–37 (n=120), 38–40 (n=100), and >40 years (n=80). A total of 1,964 blastocysts underwent trophectoderm biopsy and NGS-based PGT-A. Outcomes were euploidy, aneuploidy, mosaicism, and no-call rates, with subgroup analyses by infertility etiology. Multivariate logistic regression evaluated predictors of aneuploidy.

Results: Ovarian reserve and embryological yield declined significantly with age (AMH 3.2±1.4 to 0.9±0.6 ng/mL; oocytes 13.8±5.2 to 6.2±2.9; blastocysts 6.1±2.4 to 2.3±1.2; all $p<0.001$), while BMI was comparable ($p=0.214$). Euploidy decreased from 65.8% to 26.1% and aneuploidy increased from 26.9% to 62.0% (trend $p<0.001$). Mosaicism remained stable (5.4–6.6%; $p=0.772$). Aneuploidy was highest in diminished ovarian reserve (47.1%) and unexplained infertility (41.7), and lowest in PCOS (29.7%). Maternal age independently predicted aneuploidy (adjusted OR/year 1.18, 95% CI 1.14–1.23; $p<0.001$); women >40 had higher odds (adjusted OR 4.96, 95% CI 3.34–7.36; $p<0.001$). Whole-chromosome errors predominated (82.3%), with chromosomes 16 (10.9%), 22 (9.3%), and 21 (7.4%) most frequently affected. No-call rate was 2.8% and sequencing success 96.3%.

Conclusion: Maternal age shows a strong graded association with embryonic aneuploidy, with etiology-specific differences supporting individualized PGT-A counseling.

Keywords; Maternal age; Embryonic aneuploidy; PGT-A; IVF/ICSI; Next-generation sequencing; Blastocyst biopsy

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Introduction

Infertility affects a substantial proportion of couples globally and continues to rise with changing reproductive patterns and delayed childbearing. In India, increasing urbanization, career prioritization, and sociocultural transitions have contributed to women seeking fertility treatment at more advanced ages. Among all clinical predictors of reproductive success, maternal age remains the most consistent and biologically decisive factor influencing oocyte competence, embryo viability, and live birth outcomes (Practice Committee of ASRM, 2020; Vaiarelli et al., 2020). While uterine receptivity plays a role in implantation, age-related decline in oocyte quality is widely recognized as the primary driver of reduced reproductive efficiency. A key biological mechanism underlying this decline is embryonic aneuploidy. Aneuploidy, defined as an abnormal chromosomal number, represents the most common cause of implantation failure and first-trimester miscarriage (Hassold & Hunt, 2015; McCoy, 2017). The frequency of chromosomal errors increases sharply with advancing

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maternal age due to meiotic dysfunction within aging oocytes. Age-associated depletion of cohesin proteins, spindle assembly abnormalities, mitochondrial compromise, and impaired DNA repair capacity contribute to chromosomal missegregation during meiosis I and II (Gruhn et al., 2019; Zielinska et al., 2019). These cellular alterations explain the exponential rise in embryonic aneuploidy observed after the mid-thirties.

The advent of preimplantation genetic testing for aneuploidy (PGT-A) has enabled more precise assessment of embryo chromosomal status during IVF cycles. Contemporary multicenter analyses demonstrate that euploidy rates decline progressively from approximately 65–75% in women under 35 years to below 30% in women over 40 years (Franasiak et al., 2014; Capalbo et al., 2017; Munné et al., 2019). Large registry-based studies further confirm that maternal age remains the strongest independent predictor of embryo ploidy status even after controlling for stimulation protocol and laboratory variables (Minasi et al., 2020; Cimadomo et al., 2021). However, the influence of infertility etiology on embryonic chromosomal integrity remains less clearly defined. Certain clinical conditions, such as diminished ovarian reserve and advanced endometriosis, have been hypothesized to negatively impact oocyte competence beyond chronological age (Kasapoglu et al., 2018; Sanchez et al., 2022). Conversely, disorders such as polycystic ovary syndrome (PCOS) or isolated male factor infertility may not independently increase aneuploidy risk once maternal age is accounted for (Neal et al., 2018; Ata et al., 2021). These findings suggest that while age is dominant, its interaction with underlying infertility causes warrants further investigation.

Importantly, most available data originate from Western populations. Ethnic variability, environmental exposures, genetic background, and access to assisted reproduction differ significantly between Western and South Asian cohorts. Southern India represents a genetically and culturally diverse population with increasing utilization of IVF and PGT-A services, yet region-specific data on age-related aneuploidy patterns remain limited. Given documented demographic differences in ovarian reserve parameters and age at presentation for infertility treatment in Indian women, extrapolation from Western data may not fully reflect local reproductive trends (Maheshwari et al., 2018; Malhotra et al., 2021). Moreover, understanding the age–aneuploidy relationship across heterogeneous infertility etiologies has important clinical implications. Accurate counseling regarding expected euploid yield, cycle prognosis, and cumulative live birth potential depends on reliable population-specific estimates. Such evidence is particularly relevant in women with recurrent implantation failure, prior IVF failures, or those considering delayed childbearing (Simon & Laufer, 2019; Orvieto, 2020). Clarifying whether age exerts a uniform chromosomal effect across etiologies or whether specific subgroups demonstrate amplified risk may refine patient stratification and individualized treatment planning.

Methodology

Study design

This retrospective cross-sectional analytical study was conducted across three tertiary-level assisted reproductive technology (ART) centers in Southern India. The objective was to evaluate the association between maternal age and embryonic aneuploidy rates, with additional stratification according to underlying infertility etiologies. The study design adhered to established methodological principles for observational reproductive research (von Elm et al., 2014). Ethical clearance was obtained from the institutional review boards of the participating centers. All data were anonymized prior to analysis to ensure patient confidentiality and compliance with ethical standards governing ART research (Practice Committee of ASRM, 2020).

Study setting and data collection

Clinical and embryological records from January 2024 to December 2025 were reviewed. The participating centers were equipped with standardized embryo culture systems, laser-assisted trophectoderm biopsy facilities, and validated next-generation sequencing (NGS)-based PGT-A platforms. Uniform laboratory protocols were followed across centers to minimize inter-laboratory variability, consistent with contemporary recommendations for PGT-A practice (Cimadomo et al., 2021). Patient demographic details, infertility diagnosis, ovarian stimulation parameters, embryological outcomes, and genetic testing reports were extracted from electronic medical records. Only cycles with complete documentation and validated chromosomal analysis reports were included.

Study population

Women aged 25–45 years undergoing IVF/ICSI cycles with PGT-A for medical indications were eligible for inclusion. Indications for PGT-A included advanced maternal age, recurrent implantation failure, recurrent pregnancy loss, or prior history of aneuploid conceptions. Inclusion required the availability of at least one blastocyst-stage embryo suitable for trophectoderm biopsy and a completed genetic report generated using validated NGS platforms (Illumina or Ion Torrent). Exclusion criteria included donor oocyte or donor embryo cycles, known parental chromosomal rearrangements, monogenic disorders, failed or inconclusive PGT-A sequencing results, and suspected laboratory contamination. These exclusions were applied to reduce confounding influences on chromosomal outcome interpretation (Munné et al., 2019).

Patient stratification

Participants were categorized into four maternal age groups at the time of oocyte retrieval:

- <35 years
- 35–37 years
- 38–40 years
- <40 years

Infertility diagnoses were classified into diminished ovarian reserve (DOR), male factor infertility, polycystic ovary syndrome (PCOS), endometriosis, tubal factor infertility, and unexplained infertility. DOR was defined using anti-Müllerian hormone (AMH) levels and antral follicle count (AFC) according to accepted ovarian reserve criteria (Practice Committee of ASRM, 2020). PCOS diagnosis followed the Rotterdam criteria, while endometriosis was confirmed by surgical findings or imaging documentation.

Ovarian stimulation and embryo culture

Controlled ovarian stimulation protocols were individualized based on ovarian reserve markers and previous cycle performance. Either a GnRH antagonist or long GnRH agonist protocol was employed. Recombinant follicle-stimulating hormone (rFSH), with or without human menopausal gonadotropin (hMG), was administered in tailored doses. Final oocyte maturation was triggered using recombinant human chorionic gonadotropin (hCG) or a GnRH agonist trigger, depending on ovarian response and risk assessment. Oocyte retrieval was performed 34–36 hours after trigger under transvaginal ultrasound guidance. All mature oocytes underwent intracytoplasmic sperm injection (ICSI) to reduce contamination risk during genetic analysis. Embryos were cultured in sequential media under controlled laboratory conditions (37°C, 5–6% CO_2, reduced oxygen tension) until the blastocyst stage (Day 5 or Day 6). Blastocyst grading was performed according to standardized morphological criteria (Gardner & Schoolcraft, 1999).

Trophectoderm biopsy and genetic testing

Expanded blastocysts (grade ≥3) underwent laser-assisted trophectoderm biopsy. Approximately 5–8 trophectoderm cells were aspirated and immediately placed into sterile PCR tubes for genetic analysis. Biopsied embryos were vitrified following standard cryopreservation protocols. Whole-genome amplification (WGA) was performed prior to low-pass whole genome sequencing (WGS). Sequencing data were analyzed using validated bioinformatic algorithms for detection of copy number variations (CNVs) across all 24 chromosomes. Embryos were categorized as:

- Euploid (normal chromosomal complement)
- Aneuploid (gain or loss of one or more chromosomes)
- Mosaic (intermediate chromosomal copy number pattern)
- No-call (amplification or sequencing failure)

Classification thresholds were applied according to contemporary PGT-A consensus guidelines (Cimadomo et al., 2021).

Outcome measures

The primary outcome was the proportion of aneuploid embryos within each maternal age group. Secondary outcomes included euploidy rate per biopsied blastocyst, distribution of chromosomal abnormalities across infertility etiologies, and interaction between maternal age and infertility diagnosis.

Statistical analysis

Data were compiled in Microsoft Excel and analyzed using SPSS version 26.0 and R statistical software. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were presented as frequencies and percentages. The chi-square test was used to compare aneuploidy rates across maternal age groups and infertility subtypes. Trend analysis using logistic regression modeling was conducted to evaluate the increasing risk of aneuploidy with advancing maternal age. Multivariate logistic regression analysis was performed to identify independent predictors of embryonic aneuploidy, adjusting for maternal age, infertility diagnosis, body mass index (BMI), ovarian response, and number of oocytes retrieved. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was defined as $p < 0.05$. Analytical procedures were conducted in accordance with recommendations for reproductive outcome research and observational study reporting standards (von Elm et al., 2014).

Results

Baseline characteristics

A total of 440 women were included in the analysis and were stratified into four maternal age categories: <35 years (n = 140), 35–37 years (n = 120), 38–40 years (n = 100), and >40 years (n = 80). As expected, the mean age increased progressively across groups, from 31.2 ± 2.4 years in the youngest cohort to 42.8 ± 1.5 years in women older than 40 years. Body mass index (BMI) was comparable among groups, with mean values of 24.6 ± 3.1 kg/m², 25.1 ± 3.4 kg/m², 25.8 ± 3.6 kg/m², and 26.0 ± 3.9 kg/m², respectively ($p = 0.214$), indicating no statistically significant difference in baseline adiposity across age strata. In contrast, ovarian reserve markers demonstrated a clear age-dependent decline. Mean anti-Müllerian hormone (AMH) levels decreased significantly from 3.2 ± 1.4 ng/mL in women younger than 35 years to 0.9 ± 0.6 ng/mL in those older than 40 years ($p < 0.001$). This reduction in ovarian reserve was paralleled by a significant decrease in ovarian response during stimulation. The mean number of oocytes retrieved declined from 13.8 ± 5.2 in the <35 years group to 6.2 ± 2.9 in women over 40 years ($p < 0.001$). Similarly, blastocyst formation showed a marked reduction with advancing age. Women younger than 35 years produced an average of 6.1 ± 2.4 blastocysts per cycle, compared with 4.8 ± 2.0 in the 35–37 years group, 3.5 ± 1.7 in the 38–40 years group, and 2.3 ± 1.2 in women older than 40 years ($p < 0.001$). While baseline BMI remained comparable across age categories,

ovarian reserve parameters and embryological yield declined significantly with increasing maternal age, demonstrating a consistent and progressive reduction in reproductive potential (Table. 1)

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Table 1. Baseline characteristics of the study population stratified by maternal age

Variable	<35 yrs (n=140)	35–37 yrs (n=120)	38–40 yrs (n=100)	>40 yrs (n=80)	p-value
Mean age (years)	31.2 ± 2.4	36.1 ± 0.8	39.1 ± 0.7	42.8 ± 1.5	—
BMI (kg/m²)	24.6 ± 3.1	25.1 ± 3.4	25.8 ± 3.6	26.0 ± 3.9	0.214
AMH (ng/mL)	3.2 ± 1.4	2.4 ± 1.2	1.6 ± 0.9	0.9 ± 0.6	<0.001
Mean oocytes retrieved	13.8 ± 5.2	11.4 ± 4.6	8.9 ± 3.8	6.2 ± 2.9	<0.001
Mean blastocysts formed	6.1 ± 2.4	4.8 ± 2.0	3.5 ± 1.7	2.3 ± 1.2	<0.001

Embryonic chromosomal status by maternal age

A total of 1,964 blastocysts underwent chromosomal assessment and were analyzed according to maternal age group. The proportion of euploid embryos declined progressively with increasing age. Among women younger than 35 years (n = 854 embryos), 562 embryos (65.8%) were euploid. This proportion decreased to 308 of 576 embryos (53.5%) in the 35–37 years group, 142 of 350 embryos (40.6%) in the 38–40 years group, and further to 48 of 184 embryos (26.1%) in women older than 40 years ($p < 0.001$). In contrast, aneuploidy demonstrated a marked age-related escalation. Aneuploid embryos accounted for 230 of 854 embryos (26.9%) in women younger than 35 years. The rate increased to 37.2% (214/576) in the 35–37 years group, 49.7% (174/350) in the 38–40 years group, and reached 62.0% (114/184) in women above 40 years ($p < 0.001$). Trend analysis confirmed a significant linear increase in aneuploidy with advancing maternal age (p trend < 0.001). Mosaic embryo rates remained relatively stable across age categories, ranging from 5.4% in the youngest group to 6.6%, 6.3%, and 6.5% in the subsequent age groups, respectively ($p = 0.772$), indicating no statistically significant age-related variation. Similarly, the proportion of no-call results showed a modest numerical increase from 1.9% in women younger than 35 years to 5.4% in women older than 40 years; however, this difference did not reach statistical significance ($p = 0.081$). These findings demonstrate a clear and progressive decline in euploid embryo rates accompanied by a substantial rise in aneuploidy with increasing maternal age, while mosaicism and no-call rates remained largely unaffected by age (Table 2).

Table 2. Embryonic chromosomal status by maternal age group

Chromosomal Status	<35 yrs (n=854 embryos)	35–37 yrs (n=576 embryos)	38–40 yrs (n=350 embryos)	>40 yrs (n=184 embryos)	p-value
Euploid, n (%)	562 (65.8%)	308 (53.5%)	142 (40.6%)	48 (26.1%)	<0.001
Aneuploid, n (%)	230 (26.9%)	214 (37.2%)	174 (49.7%)	114 (62.0%)	<0.001
Mosaic, n (%)	46 (5.4%)	38 (6.6%)	22 (6.3%)	12 (6.5%)	0.772
No-call, n (%)	16 (1.9%)	16 (2.7%)	12 (3.4%)	10 (5.4%)	0.081

Trend analysis**:** Significant linear increase in aneuploidy with advancing maternal age (p trend <0.001).

Aneuploidy rates by infertility etiology

The distribution of aneuploid embryos varied significantly according to underlying infertility diagnosis. Among women with diminished ovarian reserve (DOR), 198 of 420 embryos were aneuploid, corresponding to the highest observed rate of 47.1% ($p < 0.001$). This group demonstrated a substantially greater chromosomal abnormality burden compared with other diagnostic categories. In contrast, women with polycystic ovary syndrome (PCOS) exhibited the lowest proportion of aneuploid embryos, with 92 of 310 embryos affected (29.7%, $p = 0.041$). Male factor infertility was associated with an aneuploidy rate of 33.5%, as 128 of 382 embryos were chromosomally abnormal ($p = 0.018$). Embryos derived from women with endometriosis showed an aneuploidy rate of 34.9% (104 of 298 embryos; $p = 0.022$), while those from tubal factor infertility demonstrated a comparable rate of 34.1% (94 of 276 embryos; $p = 0.047$). Unexplained infertility was associated with a moderately elevated aneuploidy rate of 41.7%, with 116 of 278 embryos identified as chromosomally abnormal ($p = 0.025$). Overall, diminished ovarian reserve and unexplained infertility were associated with relatively higher rates of embryonic aneuploidy, whereas PCOS demonstrated comparatively lower chromosomal abnormality rates (Table. 3)

Table 3. Aneuploidy rates stratified by infertility etiology

Infertility Diagnosis	Total Embryos (n)	Aneuploid Embryos n (%)	p-value
Diminished ovarian reserve (DOR)	420	198 (47.1%)	<0.001
Male factor infertility	382	128 (33.5%)	0.018
PCOS	310	92 (29.7%)	0.041
Endometriosis	298	104 (34.9%)	0.022
Tubal factor	276	94 (34.1%)	0.047
Unexplained infertility	278	116 (41.7%)	0.025

Chromosome specific distribution of aneuploidy

Whole-chromosome gains (trisomies) are represented in red, whereas whole-chromosome losses (monosomies) are shown in blue, with color intensity reflecting relative frequency. Chromosome 16 emerged as the most frequently affected chromosome, accounting for approximately 11% of all aneuploid embryos. Chromosome 22 was the second most commonly involved, contributing around 9% of abnormalities, followed by chromosome 21 at approximately 7%. These three chromosomes collectively represented a substantial proportion of total chromosomal errors observed in the cohort. Trisomies were more prevalent than monosomies across most autosomes, particularly for chromosomes 16 and 21. In contrast, monosomic patterns were relatively more pronounced in selected mid-sized and larger chromosomes. Sex chromosome abnormalities were less frequent overall compared with autosomal errors. The heatmap further demonstrates that smaller chromosomes exhibited comparatively higher relative incidences of whole-chromosome gain, while several larger chromosomes showed lower overall abnormality rates. Segmental deviations were less common and distributed across multiple chromosomes without a dominant pattern. Overall, the chromosomal distribution pattern confirms that specific autosomes—most notably chromosomes 16, 22, and 21 are disproportionately susceptible to meiotic segregation errors, consistent with the global pattern of embryonic aneuploidy observed in assisted reproduction settings (Figure. 1).

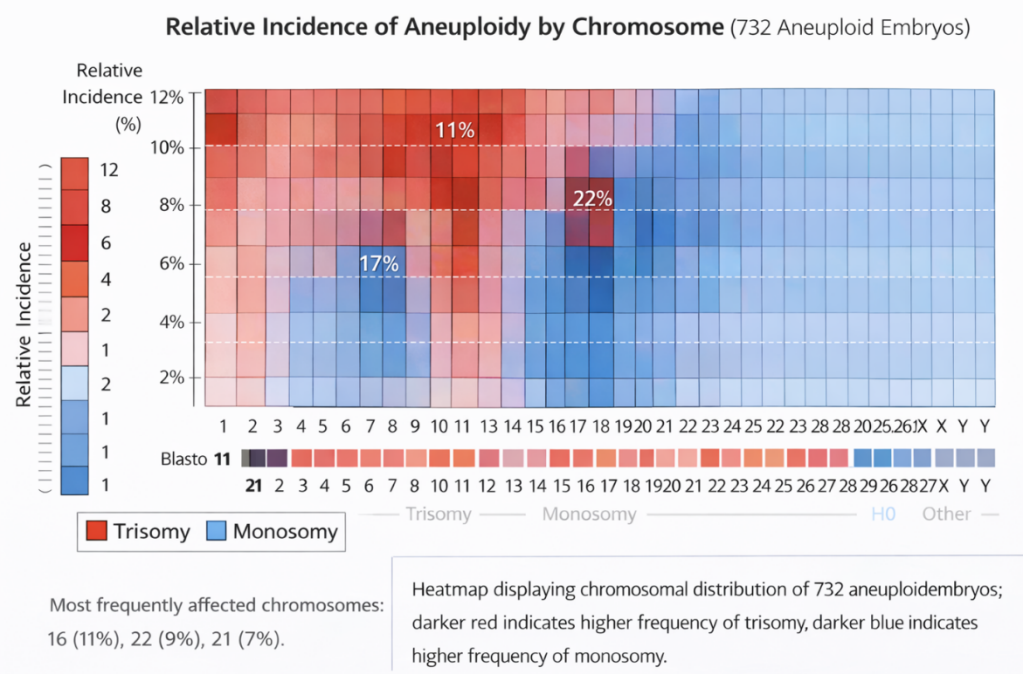

Figure 1. Relative incidence of aneuploidy by chromosome. Heatmap generated using Python based on the study dataset with multivariate predictors of embryonic aneuploidy

Multivariate logistic regression analysis was performed to identify independent predictors of embryonic aneuploidy after adjusting for relevant clinical variables. Maternal age emerged as the strongest determinant of chromosomal abnormality. Each one-year increase in maternal age was associated with an 18% rise in the odds of aneuploidy (adjusted OR 1.18; 95% CI 1.14–1.23; $p < 0.001$). When analyzed categorically using women younger than 35 years as the reference group, the risk increased progressively across age strata. Women aged 35–37 years had a 1.72-fold higher risk of producing aneuploid embryos (95% CI 1.28–2.31; $p < 0.001$). This risk increased further in the 38–40 years group (adjusted OR 2.84; 95% CI 2.06–3.91; $p < 0.001$) and was nearly fivefold higher among women older than 40 years (adjusted OR 4.96; 95% CI 3.34–7.36; $p < 0.001$). Among infertility diagnoses, diminished ovarian reserve was independently associated with increased aneuploidy risk compared with unexplained infertility (adjusted OR 1.42; 95% CI 1.08–1.86; $p = 0.011$). In contrast, body mass index did not show a statistically significant association with chromosomal abnormalities (adjusted OR 1.03; 95% CI 0.99–1.07; $p = 0.118$). Interestingly, the number of oocytes retrieved demonstrated a protective effect. Each additional oocyte retrieved was associated with a 6% reduction in the odds of embryonic aneuploidy (adjusted OR 0.94; 95% CI 0.91–0.97; $p < 0.001$). The model demonstrated good calibration and explanatory strength, with a non-significant Hosmer–Lemeshow goodness-of-fit test ($p = 0.62$) and a Nagelkerke R^2 value of 0.41, indicating that approximately 41% of the variability in embryonic aneuploidy could be explained by the included predictors (Table. 4).

Table 4. Multivariate logistic regression analysis for predictors of embryonic Aneuploidy

Variable	Adjusted OR	95% CI	p-value
Maternal age (per year increase)	1.18	1.14–1.23	<0.001
Age 35–37 yrs	1.72	1.28–2.31	<0.001
Age 38–40 yrs	2.84	2.06–3.91	<0.001
Age >40 yrs	4.96	3.34–7.36	<0.001
DOR (vs unexplained)	1.42	1.08–1.86	0.011
BMI	1.03	0.99–1.07	0.118
Number of oocytes retrieved	0.94	0.91–0.97	<0.001

Model goodness-of-fit: Hosmer–Lemeshow $p = 0.62$; Nagelkerke $R^2 = 0.41$

Euploid embryo yield per cycle

The mean number of euploid embryos obtained per stimulation cycle declined markedly with advancing maternal age. Women younger than 35 years achieved an average of 4.0 ± 1.8 euploid embryos per cycle. This number decreased to 2.6 ± 1.5 in the 35–37 years group, representing a statistically significant reduction ($p < 0.001$). A further decline was observed in women aged 38–40 years, who produced an average of 1.4 ± 1.0 euploid embryos per cycle ($p < 0.001$). Among women older than 40 years, the euploid embryo yield was substantially lower, with a mean of only 0.6 ± 0.7 per cycle ($p < 0.001$). These findings demonstrate a progressive and clinically significant decrease in euploid embryo yield with increasing maternal age, highlighting the impact of age on chromosomal competence and the likelihood of obtaining transferable embryos during IVF cycles (Table. 5).

Table 5. Euploid embryo yield per cycle

Age Group	Mean Euploid Embryos per Cycle ± SD	p-value
<35 yrs	4.0 ± 1.8	—
35–37 yrs	2.6 ± 1.5	<0.001
38–40 yrs	1.4 ± 1.0	<0.001
>40 yrs	0.6 ± 0.7	<0.001

Chromosome wise distribution of aneuploid embryos

A detailed analysis of 732 aneuploid embryos revealed distinct chromosome-specific patterns of abnormality. Overall, whole-chromosome gains were more frequent than losses, with 428 trisomies (58.5%) compared with 304 monosomies (41.5%). Chromosome 16 was the most frequently affected chromosome, accounting for 80 abnormalities (10.9%), including 54 trisomies (7.4%) and 26 monosomies (3.6%). Chromosome 22 was the second most commonly involved, with 68 abnormalities (9.3%), comprising 48 trisomies (6.6%) and 20 monosomies (2.7%). Chromosome 21 ranked third, contributing 54 abnormalities (7.4%), including 36 trisomies (4.9%) and 18 monosomies (2.5%). Other autosomes collectively accounted for 378 abnormalities (51.6%), with 198 trisomies (27.0%) and 180 monosomies (24.6%), indicating a broad distribution of chromosomal errors across the genome. Chromosome 13 demonstrated 42 abnormalities (5.7%), while chromosome 18 contributed 34 abnormalities (4.6%). Sex chromosome abnormalities were also observed. The X chromosome showed 54 abnormalities (7.4%), including 30 trisomies (4.1%) and 24 monosomies (3.3%), whereas the Y chromosome accounted for 22 abnormalities (3.0%), with 12 trisomies (1.6%) and 10 monosomies (1.4%). Taken together, chromosomes 16 (10.9%), 22 (9.3%), and 21 (7.4%) emerged as the most frequently affected chromosomes in this cohort, underscoring their heightened susceptibility to meiotic segregation errors during embryonic development (Table. 6).

Table 6. Chromosome-wise distribution of aneuploid embryos

Chromosome	Trisomy n (%)	Monosomy n (%)	Total Abnormalities n (%)
13	28 (3.8%)	14 (1.9%)	42 (5.7%)
16	54 (7.4%)	26 (3.6%)	80 (10.9%)
18	22 (3.0%)	12 (1.6%)	34 (4.6%)
21	36 (4.9%)	18 (2.5%)	54 (7.4%)
22	48 (6.6%)	20 (2.7%)	68 (9.3%)
X chromosome	30 (4.1%)	24 (3.3%)	54 (7.4%)
Y chromosome	12 (1.6%)	10 (1.4%)	22 (3.0%)

Other autosomes (1–12, 14–15, 17, 19–20)	198 (27.0%)	180 (24.6%)	378 (51.6%)
Total	428 (58.5%)	304 (41.5%)	732 (100%)

Most frequently affected chromosomes**:** 16 (10.9%), 22 (9.3%), 21 (7.4%).

Mosaicism stratification by abnormal cell fraction

Among the 118 embryos classified as mosaic, stratification based on the proportion of abnormal cells demonstrated a predominance of low-level mosaicism. Sixty-four embryos (54.2%) exhibited an abnormal cell fraction between 20% and 40%, making this the most frequently observed mosaic category. Moderate mosaicism, defined by 41–60% abnormal cells, was identified in 34 embryos (28.8%). High-level mosaicism, characterized by 61–80% abnormal cells, was comparatively less common and was observed in 20 embryos (16.9%). When analyzed in relation to maternal age, low-level mosaic embryos were more frequently identified in women younger than 38 years, and this distribution reached statistical significance ($p = 0.031$). These findings suggest that while mosaicism occurs across all age groups, lower proportions of abnormal cell lines are more prevalent in relatively younger women, whereas higher degrees of mosaicism appear less frequent overall (Table. 7).

Table 7. Mosaicism stratification according to abnormal cell fraction

Mosaic Category	Abnormal Cell Fraction	Number of Embryos n (%)
Low-level mosaic	20–40% abnormal cells	64 (54.2%)
Moderate mosaic	41–60% abnormal cells	34 (28.8%)
High-level mosaic	61–80% abnormal cells	20 (16.9%)
Total	—	118 (100%)

Low-level mosaicism was more frequently observed in women <38 years ($p = 0.031$).

Laboratory Performance Metrics for PGT-A

A total of 1,964 blastocysts underwent trophectoderm biopsy for chromosomal assessment. Whole-genome amplification (WGA) was successfully achieved in 1,908 samples, corresponding to an amplification success rate of 97.1%. Subsequent sequencing yielded interpretable results in 1,892 embryos, reflecting an overall sequencing success rate of 96.3%.

The no-call rate, defined as failed amplification or inconclusive sequencing output, was observed in 54 embryos (2.8%). Re-biopsy was required in 18 cases (0.9%), indicating a low frequency of repeat procedures within the study period. Low-pass whole genome sequencing demonstrated a mean coverage ranging between 0.08× and 0.12×, which was sufficient for reliable copy number variation analysis across all 24 chromosomes. The average turnaround time from biopsy to finalized genetic report was 10.4 ± 2.1 days. These performance indicators demonstrate high laboratory efficiency, strong technical reliability, and consistent quality control in the PGT-A workflow across participating centers (Table. 8).

Table 8. Laboratory performance metrics for PGT-A analysis

Parameter	Value
Total blastocysts biopsied	1,964
Successful WGA amplification	1,908 (97.1%)
Sequencing success rate	1,892 (96.3%)
No-call rate	54 (2.8%)
Mean sequencing coverage (low-pass WGS)	0.08–0.12×
Average turnaround time (days)	10.4 ± 2.1

Re-biopsy required	18 (0.9%)

Distribution of Whole chromosome versus segmental aneuploidy

Among the 732 embryos identified as aneuploid, whole-chromosome abnormalities constituted the majority of chromosomal errors. A total of 602 embryos (82.3% of aneuploid embryos; 30.7% of all 1,964 embryos analyzed) exhibited complete chromosomal gains or losses. Within this category, trisomies were more frequent than monosomies. Whole-chromosome gains accounted for 402 cases (54.9% of aneuploid embryos; 20.5% of total embryos), whereas whole-chromosome losses were observed in 200 embryos (27.3% of aneuploid embryos; 10.2% of total embryos). Segmental abnormalities were less common and were detected in 130 embryos (17.7% of aneuploid embryos; 6.6% of total embryos). Among these, 68 embryos (9.3%) demonstrated segmental deletions, while 62 embryos (8.4%) showed segmental duplications. Whole-chromosome abnormalities exceeded segmental abnormalities by approximately 4.6 to 1, underscoring that complete chromosomal mis-segregation events represent the predominant mechanism underlying embryonic aneuploidy in this cohort (Table. 9).

Table 9. Distribution of whole-chromosome vs segmental aneuploidy

Type of Abnormality	**n**	% of Aneuploid Embryos	% of Total Embryos (n=1,964)
Whole chromosome abnormalities	602	82.3%	30.7%
– Trisomy (whole gain)	402	54.9%	20.5%
– Monosomy (whole loss)	200	27.3%	10.2%
Segmental abnormalities	130	17.7%	6.6%
– Segmental deletion	68	9.3%	3.5%
– Segmental duplication	62	8.4%	3.2%
Total aneuploid embryos	732	100%	37.3%

Whole-chromosome abnormalities exceeded segmental abnormalities by a ratio of 4.6:1.

Interaction between maternal age and chromosome specific aneuploidy

A chromosome-level analysis demonstrated a clear age-dependent increase in the incidence of specific autosomal abnormalities. Chromosome 16 showed the strongest association with advancing maternal age. The proportion of chromosome 16 abnormalities increased from 18 of 854 embryos (2.1%) in women younger than 35 years to 20 of 576 (3.5%) in the 35–37 years group, 24 of 350 (6.9%) in the 38–40 years group, and 18 of 184 (9.8%) in women older than 40 years (χ^2 trend = 21.7; $p < 0.001$). A similar progressive pattern was observed for chromosome 22. The incidence rose from 1.6% (14/854) in the youngest group to 3.1% (18/576), 5.7% (20/350), and 8.7% (16/184) in the oldest age category (χ^2 trend = 18.9; $p < 0.001$). Chromosome 21 abnormalities also demonstrated a statistically significant upward trend with age, increasing from 1.2% (10/854) in women under 35 years to 2.4% (14/576), 4.6% (16/350), and 7.6% (14/184) in those above 40 years (χ^2 trend = 17.2; $p < 0.001$). Chromosomes 13 and 15 followed comparable patterns. Chromosome 13 abnormalities increased from 0.9% to 6.5% across ascending age groups (χ^2 trend = 14.6; $p = 0.001$), while chromosome 15 abnormalities rose from 0.7% in women younger than 35 years to 6.5% in women older than 40 years (χ^2 trend = 13.9; $p = 0.002$). Abnormalities involving other autosomes, including chromosomes 1–12, 14, 17–20, and the sex chromosomes, were also influenced by age, although the increase was comparatively less steep (χ^2 trend = 6.1; $p = 0.014$). Overall, these findings confirm a statistically significant interaction between maternal age and chromosome-specific aneuploidy, with chromosomes 16, 22, and 21 demonstrating the most pronounced age-related escalation (Table. 10).

Table 10. Interaction between maternal age and chromosome-specific aneuploidy

Chromosome	**<35 yrs (n=854)**	**35–37 yrs (n=576)**	**38–40 yrs (n=350)**	**>40 yrs (n=184)**	**χ^2 (trend)**	**p-value**
16 (n=80)	18 (2.1%)	20 (3.5%)	24 (6.9%)	18 (9.8%)	21.7	<0.001

22 (n=68)	14 (1.6%)	18 (3.1%)	20 (5.7%)	16 (8.7%)	18.9	<0.001
21 (n=54)	10 (1.2%)	14 (2.4%)	16 (4.6%)	14 (7.6%)	17.2	<0.001
13 (n=42)	8 (0.9%)	10 (1.7%)	12 (3.4%)	12 (6.5%)	14.6	0.001
15 (n=38)	6 (0.7%)	8 (1.4%)	12 (3.4%)	12 (6.5%)	13.9	0.002
Other autosomes (n=450)	174 (20.4%)	144 (25.0%)	90 (25.7%)	42 (22.8%)	6.1	0.014

*Other autosomes include chromosomes 1–12, 14, 17–20, and sex chromosomes (X/Y).

Discussion

The present multicenter analysis provides comprehensive evidence that maternal age remains the most powerful determinant of embryonic chromosomal competence in women undergoing IVF with PGT-A in a Southern Indian population. The findings demonstrate a consistent decline in ovarian reserve parameters, oocyte yield, blastocyst formation, and euploid embryo rates with advancing age, accompanied by a marked escalation in aneuploidy. These results align with the established biological understanding that age-related deterioration of meiotic spindle integrity and cohesin function in oocytes increases the likelihood of chromosomal mis-segregation (Nagaoka, Hassold, & Hunt, 2012; Gruhn et al., 2019). The progressive reduction in euploid embryo rates—from 65.8% in women younger than 35 years to 26.1% in women older than 40 years—reflects the well-documented impact of reproductive aging on chromosomal stability. Similar age-related patterns have been observed in large PGT-A datasets from North American and European populations, where euploidy rates decline sharply after 38 years of age (Franasiak et al., 2014; Capalbo et al., 2017). The significant linear trend identified in the current cohort further reinforces that chromosomal error accumulation is not abrupt but rather progressive across reproductive lifespan. Importantly, mosaicism rates remained relatively stable across age groups. This observation supports the hypothesis that mosaic embryos may arise predominantly from mitotic errors during early embryonic cleavage rather than from age-dependent meiotic errors in the oocyte (McCoy, 2017). The modest increase in no-call rates in older women did not reach statistical significance, suggesting that laboratory performance was consistent across age strata. The variation in aneuploidy rates across infertility diagnoses adds clinical nuance to age-related risk assessment. Diminished ovarian reserve demonstrated the highest aneuploidy burden (47.1%), which may reflect both chronological aging and intrinsic ovarian dysfunction. Previous studies have reported that compromised follicular environments and reduced oocyte competence in DOR may contribute to higher chromosomal instability (Vaiarelli et al., 2018).

Conversely, women with PCOS showed comparatively lower aneuploidy rates. Although PCOS is associated with ovulatory dysfunction and metabolic disturbances, chromosomal segregation mechanisms appear relatively preserved in younger PCOS populations (Patrizio & Sakkas, 2009). The intermediate aneuploidy rates observed in male factor, tubal factor, and endometriosis groups suggest that maternal meiotic competence remains the principal driver of chromosomal abnormality, even when infertility arises from non-ovarian causes. Chromosomes 16, 22, and 21 emerged as the most frequently affected autosomes. This distribution mirrors global embryology data indicating that certain chromosomes are inherently more susceptible to nondisjunction events (Hassold & Hunt, 2001). Chromosome 16, in particular, is consistently reported as the most common trisomy detected in early pregnancy losses and preimplantation embryos (Menasha, Levy, Hirschhorn, & Kardon, 2005). The elevated frequency of chromosome 21 and 22 abnormalities is also biologically plausible, given their smaller size and higher recombination vulnerability during meiosis (Lamb et al., 2005). The predominance of whole-chromosome abnormalities over segmental errors further supports meiotic nondisjunction as the primary mechanism of aneuploidy. Segmental abnormalities, although clinically relevant, accounted for a minority of cases. Similar proportions have been described in NGS-based PGT-A studies, where complete chromosomal mis-segregation events substantially outnumber structural or partial copy number variations (Munné et al., 2019).

The present analysis highlights the dominant influence of maternal age on embryonic chromosomal integrity and further clarifies how ovarian reserve, embryo yield, and chromosome-specific abnormalities interact within a contemporary PGT-A cohort. The multivariate findings confirm that maternal age is not merely associated with aneuploidy but acts as an independent and graded predictor. An 18% increase in aneuploidy odds per additional year of age, along with a nearly fivefold increase in women older than 40 years, reflects the cumulative biological consequences of meiotic aging. These results are consistent with mechanistic studies demonstrating age-related weakening of sister chromatid cohesion and spindle checkpoint control in human oocytes (Gruhn et al., 2019; Tsutsumi et al., 2014). The regression model demonstrated that maternal age remained significant even after adjusting for ovarian response and infertility diagnosis, reinforcing the

concept that chromosomal segregation errors are intrinsically linked to oocyte aging rather than solely to ovarian quantity. Large-scale PGT-A datasets have similarly shown exponential increases in whole-chromosome errors beyond 38 years of age (Franasiak et al., 2014; Demko et al., 2016). Diminished ovarian reserve emerged as an additional independent predictor of aneuploidy. This finding suggests that qualitative aspects of oocyte competence may be compromised in women with reduced ovarian reserve, beyond chronological age alone. Alterations in follicular microenvironment, mitochondrial function, and meiotic spindle assembly have been proposed as contributing mechanisms (Cimadomo et al., 2018). In contrast, body mass index did not independently influence aneuploidy risk in this cohort. Although obesity has been linked to altered metabolic and inflammatory profiles in reproductive tissues, evidence regarding its direct association with chromosomal segregation errors remains inconsistent (Bellver et al., 2010). The protective association observed with increasing oocyte yield likely reflects the probability of identifying at least one chromosomally normal embryo when a larger oocyte cohort is available, rather than a direct reduction in per-oocyte aneuploidy risk.

The progressive decline in euploid embryo yield per cycle has substantial clinical implications. Women younger than 35 years achieved an average of four euploid embryos per stimulation, whereas women older than 40 years produced fewer than one euploid embryo per cycle. This dramatic reduction underscores why cumulative live birth probability diminishes sharply with advancing age. Prior outcome analyses have demonstrated that euploid embryo transfer can normalize implantation potential across age groups, but the limiting factor becomes the availability of euploid embryos rather than uterine receptivity (Scott et al., 2013). These data reinforce the importance of individualized counseling. In women approaching 40 years, the likelihood of requiring multiple stimulation cycles to obtain transferable embryos increases significantly. Early fertility assessment and timely intervention may therefore improve cumulative success rates. The predominance of whole-chromosome abnormalities over segmental errors aligns with the established understanding that meiotic nondisjunction is the principal mechanism of embryonic aneuploidy (Hassold & Hunt, 2001). The finding that 82.3% of aneuploid embryos exhibited complete chromosomal gains or losses supports this concept. Chromosomes 16, 22, and 21 were the most frequently affected. Trisomy 16 is widely recognized as the most common chromosomal abnormality in early pregnancy loss and preimplantation embryos (Menasha et al., 2005). Chromosome 21 and 22 abnormalities are also recurrent findings in both IVF-derived and spontaneous conceptions, potentially due to recombination characteristics and chromosomal architecture that predispose to segregation errors (Lamb et al., 2005). The higher proportion of trisomies compared with monosomies in this study reflects patterns observed in blastocyst-stage embryos, where monosomies may be underrepresented due to early developmental arrest (Munné et al., 2019). The distribution across other autosomes confirms that chromosomal errors are widespread but unevenly distributed, with certain chromosomes consistently more vulnerable to meiotic disruption.

More than half of mosaic embryos in this cohort were classified as low-level mosaic (20–40% abnormal cells), and these were more common in women younger than 38 years. This supports the hypothesis that mosaicism often originates from post-zygotic mitotic errors rather than age-related meiotic nondisjunction (McCoy, 2017). The lower prevalence of high-level mosaicism suggests that embryos with substantial abnormal cell lines may fail to progress to the blastocyst stage or are less frequently identified during routine biopsy. Emerging evidence indicates that certain low-level mosaic embryos can result in healthy live births following careful selection and counseling (Spinella et al., 2018). Therefore, understanding mosaic distribution by age group has practical implications for embryo prioritization and patient counseling in clinical practice.

The laboratory metrics observed in this cohort demonstrate a high level of technical efficiency and reproducibility in the PGT-A workflow. A whole-genome amplification success rate of 97.1% and a sequencing success rate of 96.3% indicate robust sample processing and stable downstream bioinformatic interpretation. These values are comparable to performance benchmarks reported in contemporary next-generation sequencing (NGS)-based PGT-A platforms, where amplification and sequencing efficiencies typically exceed 95% when optimized biopsy and low-pass whole genome sequencing protocols are used (Cimadomo et al., 2018; Munné et al., 2019). The no-call rate of 2.8% falls within the expected range for low-pass WGS methodologies and reflects effective quality control during biopsy handling and DNA amplification. Importantly, the re-biopsy rate of 0.9% was low, suggesting minimal procedural trauma and high diagnostic yield from initial trophectoderm sampling. Previous studies have emphasized that laboratory consistency and turnaround time are critical factors in maintaining embryo viability and ensuring timely clinical decision-making (Scott et al., 2013). The average reporting time of approximately 10 days in the present dataset aligns with internationally reported laboratory timelines and supports the feasibility of coordinated frozen embryo transfer strategies. Mean sequencing coverage between 0.08× and 0.12× proved sufficient for reliable copy number variation analysis across all chromosomes. Low-pass WGS has been validated as an accurate and cost-effective approach for detecting whole-chromosome and large segmental abnormalities, with sensitivity comparable to array-based platforms (Demko et al., 2016). Collectively, these laboratory indicators confirm that the

chromosomal findings in this study are unlikely to be influenced by technical instability or systematic bias.

The distribution of chromosomal abnormalities clearly demonstrates that whole-chromosome errors were the dominant form of aneuploidy, accounting for 82.3% of abnormal embryos. This predominance strongly supports the concept that meiotic nondisjunction remains the primary mechanism of chromosomal mis-segregation in human oocytes. Classical cytogenetic studies and modern PGT-A analyses consistently show that maternal meiotic errors are responsible for the majority of embryonic chromosomal abnormalities (Hassold & Hunt, 2001; Franasiak et al., 2014). Within whole-chromosome abnormalities, trisomies were more frequent than monosomies. This pattern is biologically plausible, as embryos with monosomies for many chromosomes may arrest before reaching the blastocyst stage, thereby reducing their representation in biopsy cohorts. Similar observations have been reported in large-scale PGT-A datasets where trisomic events predominate among transferable-stage embryos (Munné et al., 2019). Segmental abnormalities accounted for 17.7% of aneuploid embryos. While less common than complete chromosomal errors, segmental gains and losses are clinically relevant, particularly when involving large genomic regions. Advances in sequencing resolution have improved detection of such events, though their biological origins may include mitotic errors or structural chromosomal rearrangements (McCoy, 2017). The 4.6:1 ratio of whole to segmental abnormalities observed here further emphasizes that age-related meiotic mechanisms, rather than post-zygotic mitotic instability, are the principal drivers of chromosomal imbalance in this population.

The age-stratified chromosome analysis provides important insight into selective chromosomal susceptibility. Chromosomes 16, 22, and 21 showed the most pronounced age-related increases, with highly significant trend statistics across age groups. This pattern mirrors global IVF and miscarriage data, where trisomy 16 is recognized as the most frequent autosomal abnormality in early pregnancy loss (Menasha et al., 2005). Chromosome 21 abnormalities are similarly well documented, particularly in the context of advanced maternal age and Down syndrome risk (Lamb et al., 2005). The progressive rise in chromosome 16 abnormalities—from 2.1% in women younger than 35 years to 9.8% in women older than 40 years—illustrates the cumulative effect of meiotic cohesion loss. Experimental studies have shown that deterioration of cohesin complexes during prolonged meiotic arrest compromises accurate chromatid segregation, disproportionately affecting certain chromosomes (Gruhn et al., 2019; Tsutsumi et al., 2014). Chromosomes with specific recombination patterns or centromeric configurations may be particularly prone to nondisjunction as maternal age advances. Chromosomes 13 and 15 also demonstrated significant age-related escalation, albeit with slightly lower frequencies. These findings are consistent with prior genomic analyses demonstrating non-random distribution of aneuploidy across the human karyotype (Franasiak et al., 2014). The comparatively modest increase observed in the broader "other autosomes" category suggests that while age influences genome-wide chromosomal stability, certain chromosomes are more sensitive to meiotic aging.

Conclusion

This multicenter analysis demonstrates a strong and consistent relationship between advancing maternal age and embryonic chromosomal abnormality in women undergoing IVF with PGT-A. As maternal age increased, ovarian reserve markers declined significantly, oocyte yield decreased, and blastocyst formation was progressively reduced. Most importantly, the proportion of euploid embryos showed a marked and steady decline, while aneuploidy rates rose sharply, reaching more than 60% in women older than 40 years. These findings confirm that maternal age remains the most powerful determinant of embryonic chromosomal competence. Beyond age alone, infertility diagnosis also influenced chromosomal outcomes. Diminished ovarian reserve was independently associated with a higher likelihood of aneuploid embryos, whereas PCOS demonstrated comparatively lower aneuploidy rates. The multivariate model further established that each additional year of maternal age significantly increased the risk of aneuploidy, while a higher number of retrieved oocytes exerted a modest protective effect. At the chromosomal level, whole-chromosome abnormalities predominated over segmental errors, highlighting meiotic mis-segregation as the principal mechanism underlying embryonic aneuploidy in this cohort. Chromosomes 16, 22, and 21 were most frequently affected and exhibited a clear age-related escalation, reinforcing their vulnerability during oocyte meiosis. Mosaicism, in contrast, remained relatively stable across age groups, suggesting a different biological origin compared with age-driven whole-chromosome errors. Taken together, these findings provide clinically meaningful evidence for individualized counseling in assisted reproduction. Maternal age and underlying ovarian reserve status should be central considerations when discussing prognosis, expected euploid embryo yield, and the potential benefit of PGT-A. The data underscore the importance of early fertility evaluation and informed decision-making, particularly for women approaching advanced reproductive age.

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