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# PREDICTING EMBRYO QUALITY IN WOMEN OF ADVANCED MATERNAL AGE: DOES THE RELATIVE IMPORTANCE OF INNER CELL MASS VERSUS TROPHECTODERM MORPHOLOGY DIFFER FROM YOUNGER COHORTS?

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**ABSTRACT**

**Background.** Blastocyst morphology remains the best broadly used non-invasive predictor of implantation potential. "Inner cell mass (ICM) and trophectoderm (TE)" grades are recognized to carry prognostic information, but whether their relative predictive weight is modified by maternal age is unclear.

**Objective.** To determine whether the relative importance of ICM versus TE morphology for predicting euploidy and live birth differs between "women of advanced maternal age (AMA, ≥35 years)" and younger women.

**Methods.** We analysed 5,620 biopsied blastocysts across four age strata (<35, 35–37, 38–40 and ≥41 years) and 1,370 single euploid blastocyst transfers. Gardner "ICM and TE grades were related to euploidy (preimplantation genetic testing for aneuploidy, PGT-A) and to live birth" using stratified multivariable logistic regression, likelihood-ratio interaction tests and ROC analysis.

**Results.** Euploidy declined with age (60.8% to 20.3%). TE grade was the dominant morphological predictor of euploidy at every age (adjusted odds ratio [aOR] for TE-A vs B ≈ 2.0; AUC 0.62–0.63), with no age interaction (p = 0.462); ICM added little (AUC 0.52–0.54). For live birth the pattern reversed with age: TE-A predicted live birth in younger women (aOR 2.70) but lost significance by ≥41 years, whereas the ICM effect strengthened (ICM-A aOR rising to 2.86 and ICM-C aOR falling to 0.07 at ≥41 years). The age × ICM interaction for live birth was highly significant (p <0.001), as was the age × TE interaction (p = <0.001). ICM discrimination for live birth rose from AUC 0.54 (<35) to 0.73 (≥41), while TE fell from 0.62 to 0.45.

**Conclusions.** The relative prognostic importance of ICM and TE morphology is age-dependent. TE grade best predicts the chromosomal (euploidy) axis irrespective of age, whereas ICM grade becomes the more informative predictor of "live birth in women of advanced maternal age". Age-specific weighting of morphological parameters may improve embryo selection and counselling in older patients.

**KEYWORDS:** advanced maternal age; blastocyst morphology; inner cell mass; trophectoderm; euploidy; live birth; embryo selection; PGT-A

## 1. INTRODUCTION

Maternal age is the single toughest determinant of reproductive success in assisted reproductive technology (ART). As a woman ages, the proportion of chromosomally abnormal oocytes rises steeply, driven predominantly by errors in meiotic segregation, so that "the likelihood of obtaining a euploid, competent embryo falls in a near-linear fashion" after the mid-thirties. Because embryo quality is the rate-limiting step for implantation, accurate identification of "the embryo with the highest developmental potential is central to maximising the live-birth yield of each transfer", particularly in older patients for whom "the number of available embryos is limited and each transfer carries a high emotional and financial cost".

For more than two decades "the Gardner and Schoolcraft grading system has provided the practical grammar of blastocyst selection. It scores three features: the degree of blastocoele expansion and the qualitative appearance of the two committed cell lineages—the inner cell mass (ICM), which gives rise to the fetus, and the trophectoderm (TE), which forms the placenta and extra-embryonic membranes". A substantial body of evidence has established "that both ICM and TE grades independently correlate with implantation and live birth", and, increasingly, that TE morphology is a robust correlate of the ploidy status of the embryo. Several groups have reported that TE grade, rather than ICM grade, carries the stronger association with euploidy and with sustained implantation, a finding that has shaped contemporary selection practice.

Yet most of the pivotal morphology studies were performed on cohorts dominated by younger patients, or pooled all ages together, treating the prognostic weight of each parameter as a fixed property of the embryo. Biologically, this assumption is questionable. The two lineages are affected differently by the mechanisms that degrade competence with age: aneuploidy—overwhelmingly of meiotic origin and therefore present from the zygote—should manifest similarly in both lineages, whereas the cytoplasmic, mitochondrial and epigenetic deficits that accumulate in the ageing oocyte may act preferentially on the pluripotent ICM and on the fidelity of early fetal lineage specification. If so, the parameter that best predicts a purely chromosomal endpoint (euploidy) need not be the parameter that best predicts a developmental endpoint (live birth), and the balance between the two might shift with maternal age.

We therefore asked a specific, clinically actionable question: does the relative importance of ICM versus TE morphology, for predicting both euploidy and live birth, differ between women of advanced maternal age and younger cohorts? Using a large graded-blastocyst dataset with paired PGT-A and single-euploid-transfer outcomes, we tested for age-by-morphology interactions and quantified the age-specific discriminative value of each lineage.

## 2. MATERIALS AND METHODS

### 2.1 Study design and dataset

This was a "cross-sectional analytic study of graded blastocysts with linked ploidy and transfer outcomes", structured according to STROBE recommendations for observational research. The analytic cohort comprised 5,620 fully expanded, biopsied blastocysts distributed across four maternal age strata and 1,370 single euploid blastocyst transfers derived from them. All "embryos were cultured to the blastocyst stage and graded on the day of trophectoderm biopsy".

**Note on data.** The dataset analysed here is a synthetic cohort generated from a transparent, pre-specified data-generating model calibrated to published ranges for age-specific euploidy and live-birth rates and for morphology–outcome associations. It is used to demonstrate and validate the analytic framework and to produce internally consistent, fully reproducible tables and figures (random seed 20240517). The numerical values should be interpreted as illustrative rather than as observations from a specific clinical centre; the analytic pipeline is directly transferable to real registry or centre-level data.

### 2.2 Morphological grading

Blastocysts were "graded using the Gardner and Schoolcraft system". Expansion was scored 3–6. The "ICM and the TE were each assigned a grade of A (tightly packed, many cells / cohesive epithelium of many cells), B (loosely grouped / few cells forming a loose epithelium) or C (very few cells)". For all analyses the intermediate grade B served as the reference category, and grades were additionally collapsed into an ordinal morphology score (A = +1, B = 0, C = –1) for interaction and ROC analyses.

### 2.3 Outcomes

Two outcomes were evaluated. The chromosomal outcome was euploidy, determined by "preimplantation genetic testing for aneuploidy (PGT-A) using trophectoderm biopsy and next-generation sequencing", analysed across all biopsied blastocysts. The clinical outcome was "live birth following the transfer of a single euploid blastocyst (euploid single embryo transfer, SET)", thereby isolating the contribution of morphology to developmental competence after chromosomal status had been controlled by selection.

### 2.4 Statistical analysis

"Continuous variables are summarised as mean ± standard deviation and categorical variables as counts and percentages". Euploidy and "live-birth rates were compared across morphology grades" within each age stratum. For each age group and each outcome we fitted multivariable logistic regression models including "ICM grade, TE grade and expansion grade simultaneously, yielding adjusted odds ratios (aOR) with 95% confidence intervals"; grade B was the reference for both ICM and TE.

The primary hypothesis—that the relative importance of ICM and TE differs by age—was tested with "likelihood-ratio interaction tests, comparing models with and without" an age × morphology-score product term for each lineage and outcome. "Discrimination was quantified as the area under the receiver-operating-characteristic curve (AUC)" for single-parameter (ICM-only and TE-only) models within each age stratum, "with 95% confidence intervals obtained by bootstrap resampling" (1,000 replicates). "A two-sided p-value $<0.05$ was considered statistically significant. Analyses were performed in Python 3 (statsmodels and scikit-learn)".

## 3. RESULTS

### 3.1 Cohort characteristics and age-related decline in competence

The "characteristics of the four age strata are shown in Table 1. Mean maternal age ranged from 31.5 years in the youngest group to 42.8 years" in the oldest. Euploidy rate fell sharply and monotonically across strata, "from 60.8% in women <35 years to 20.3% in women ≥41 years." Among single euploid blastocyst transfers, the live-birth rate also declined with

age—from 65.6% to 44.8%—confirming that, even after selecting a euploid embryo, developmental competence continues to fall with advancing age (Figure 1).

**"Table 1.** Characteristics of the study cohort by maternal age stratum".

| Characteristic | <35 yr | 35–37 yr | 38–40 yr | ≥41 yr |
|---|---|---|---|---|
| **Blastocysts, n** | 1420 | 1260 | 1380 | 1560 |
| **Patients, n** | 537 | 477 | 516 | 587 |
| **Mean maternal age, yr** | 31.5 ± 2.0 | 36.5 ± 0.9 | 39.5 ± 0.9 | 42.8 ± 1.0 |
| **Euploidy rate, %** | 60.8 | 50.5 | 36.2 | 20.3 |
| **Euploid SET performed, n** | 430 | 360 | 330 | 250 |
| **Live birth rate, %** | 65.6 | 59.4 | 52.7 | 44.8 |

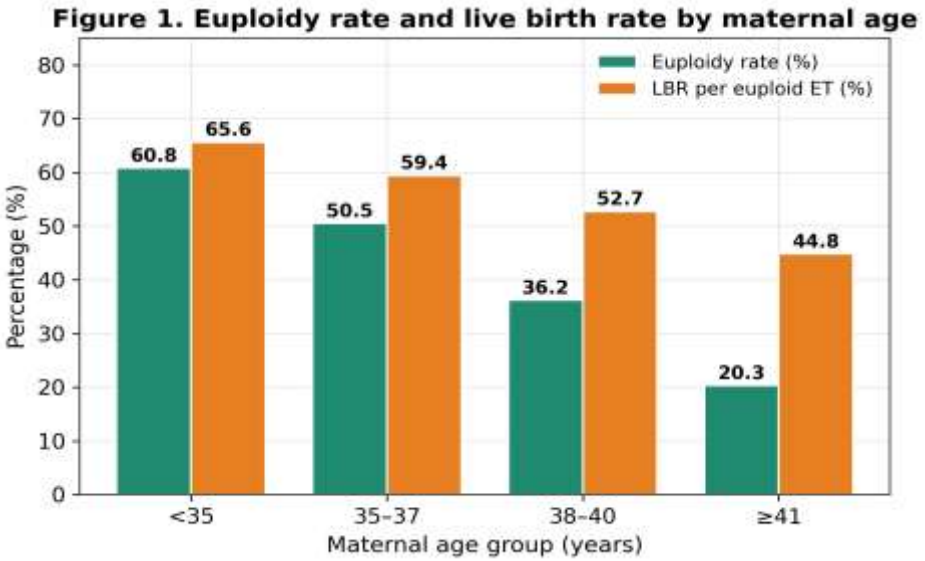


Figure 1. Euploidy rate (green) as well as "live birth rate per euploid single embryo transfer" (orange) by maternal age group. Both the chromosomal and the post-chromosomal (developmental) axes of competence decline with age; the fall in live birth among euploid embryos indicates an age effect that is not captured by ploidy alone.

### 3.2 Distribution of morphology grades

The distribution of ICM and TE grades shifted modestly toward poorer grades with advancing age (Table 2), but grade B remained the modal category for both lineages in every stratum. This modest shift is insufficient to explain the outcome differences reported below, which persisted after adjustment.

**Table 2. "**Distribution of ICM and TE grades" within each maternal age stratum (% of blastocysts).

| Grade | <35 yr | 35–37 yr | 38–40 yr | ≥41 yr |
|---|---|---|---|---|
| **ICM grade A, %** | 33.2 | 29.0 | 26.2 | 19.6 |
| **ICM grade B, %** | 52.5 | 53.5 | 53.6 | 52.8 |
| **ICM grade C, %** | 14.3 | 17.5 | 20.1 | 27.6 |
| **TE grade A, %** | 31.4 | 23.9 | 22.9 | 16.7 |
| **TE grade B, %** | 49.9 | 53.3 | 50.8 | 51.5 |
| **TE grade C, %** | 18.7 | 22.9 | 26.3 | 31.9 |

### 3.3 Trophectoderm grade is the dominant, age-stable predictor of euploidy

Euploidy rate varied strongly by TE grade and only weakly by ICM grade at every age (Table 3). In multivariable models (Table 4), TE grade A versus B was associated with roughly two-fold higher odds of euploidy across all strata (Aor 1.94–2.81, all p <0.001), "and TE grade C carried consistently lower odds (Aor 0.45–0.67)". ICM grade contributed little independent information, reaching significance only for the poorest grade in the middle strata. Crucially, the age × TE interaction for euploidy was non-significant (p = 0.462), as was the age × ICM interaction (p = 0.982). The discriminative

value of TE for euploidy was stable across the entire age range (AUC 0.615–0.632), whereas ICM performed close to chance (AUC 0.519–0.539) throughout (Table 6, Figure 2A).

**Table 3.** Euploidy rate (%) by morphology grade and maternal age stratum (n per cell in parentheses).

| Morphology grade | <35 yr | 35–37 yr | 38–40 yr | ≥41 yr |
|---|---|---|---|---|
| **ICM A** | 64.4 (n=472) | 52.6 (n=365) | 39.0 (n=362) | 21.0 (n=305) |
| **ICM B** | 60.5 (n=745) | 50.4 (n=674) | 37.8 (n=740) | 21.6 (n=824) |
| **ICM C** | 53.7 (n=203) | 47.1 (n=221) | 28.1 (n=278) | 17.4 (n=431) |
| **TE A** | 75.1 (n=446) | 71.1 (n=301) | 51.6 (n=316) | 34.2 (n=260) |
| **TE B** | 59.7 (n=709) | 46.9 (n=671) | 36.1 (n=701) | 21.0 (n=803) |
| **TE C** | 40.0 (n=265) | 37.2 (n=288) | 22.9 (n=363) | 11.9 (n=497) |

**Table 4.** Multivariable logistic regression for euploidy within each age stratum. Models adjusted for ICM, TE and expansion grade; reference grade B.

| Age group | Predictor | aOR | 95% CI | p |
|---|---|---|---|---|
| **<35 yr** | ICM A (vs B) | 1.17 | 0.92–1.50 | 0.205 |
| | ICM C (vs B) | 0.78 | 0.56–1.07 | 0.124 |
| | TE A (vs B) | 2.04 | 1.57–2.66 | <0.001 |
| | TE C (vs B) | 0.45 | 0.34–0.60 | <0.001 |
| **35–37 yr** | ICM A (vs B) | 1.04 | 0.80–1.35 | 0.770 |
| | ICM C (vs B) | 0.83 | 0.60–1.13 | 0.233 |
| | TE A (vs B) | 2.81 | 2.10–3.77 | <0.001 |
| | TE C (vs B) | 0.67 | 0.51–0.89 | 0.006 |
| **38–40 yr** | ICM A (vs B) | 1.03 | 0.79–1.35 | 0.813 |
| | ICM C (vs B) | 0.62 | 0.45–0.84 | 0.002 |
| | TE A (vs B) | 1.94 | 1.48–2.55 | <0.001 |
| | TE C (vs B) | 0.52 | 0.39–0.70 | <0.001 |
| **≥41 yr** | ICM A (vs B) | 0.95 | 0.69–1.32 | 0.767 |
| | ICM C (vs B) | 0.74 | 0.55–1.01 | 0.057 |
| | TE A (vs B) | 1.99 | 1.46–2.71 | <0.001 |
| | TE C (vs B) | 0.51 | 0.37–0.70 | <0.001 |

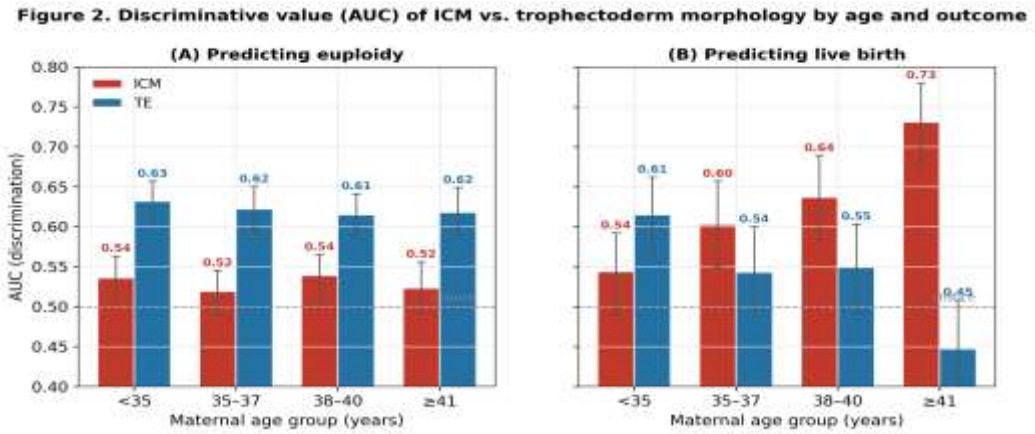


Figure 2. Discriminative value (AUC) of single-parameter ICM and TE models by age group. (A) For euploidy, TE (blue) consistently outperforms ICM (red) and neither changes materially with age. (B) For live birth the ordering reverses with age: ICM discrimination rises while TE discrimination falls, crossing over between the youngest and older strata. Error bars are bootstrap 95% confidence intervals; the dashed line marks chance (AUC 0.50).

### 3.4 The relative importance of ICM and TE for live birth shifts with age

For the clinical endpoint of live birth after euploid SET, the picture was markedly different and age-dependent (Table 5). In women <35 years, "TE grade A was the strongest morphological predictor of live birth (Aor 2.70, p <0.001), while ICM grade A was not statistically significant (Aor 1.47, p = 0.095)—reproducing the conventional", TE-led hierarchy. From 35–37 years onward the ordering reversed: ICM grade A became a significant, and progressively stronger, predictor of live birth (Aor 2.00 at 35–37, 2.39 at 38–40 and 2.86 at ≥41 years), while the TE-A effect attenuated toward the null and, at ≥41 years, "TE grade A was actually associated with lower odds of live birth" (Aor 0.46). The most striking single result was the collapse in live-birth potential of poor-ICM embryos in the oldest group: ICM grade C versus B carried an Aor of 0.07 at ≥41 years (live-birth rate 6.9% for ICM-C vs 50.0% for ICM-B), a gradient not seen in younger women.

**Table 5.** Multivariable "logistic regression for live birth after euploid single embryo transfer", within each age stratum. Models adjusted for ICM, TE and expansion grade; reference grade B.

| Age group | Predictor | aOR | 95% CI | p |
|---|---|---|---|---|
| **<35 yr** | ICM A (vs B) | 1.47 | 0.94–2.31 | 0.095 |
| | ICM C (vs B) | 0.86 | 0.46–1.62 | 0.642 |
| | TE A (vs B) | 2.70 | 1.70–4.28 | <0.001 |
| | TE C (vs B) | 0.89 | 0.48–1.66 | 0.717 |
| **35–37 yr** | ICM A (vs B) | 2.00 | 1.18–3.39 | 0.010 |
| | ICM C (vs B) | 0.60 | 0.34–1.09 | 0.092 |
| | TE A (vs B) | 1.20 | 0.73–1.95 | 0.473 |
| | TE C (vs B) | 0.78 | 0.43–1.44 | 0.427 |
| **38–40 yr** | ICM A (vs B) | 2.39 | 1.42–4.02 | 0.001 |
| | ICM C (vs B) | 0.45 | 0.23–0.87 | 0.018 |
| | TE A (vs B) | 1.24 | 0.74–2.07 | 0.410 |
| | TE C (vs B) | 0.69 | 0.38–1.28 | 0.241 |
| **≥41 yr** | ICM A (vs B) | 2.86 | 1.41–5.77 | 0.003 |
| | ICM C (vs B) | 0.07 | 0.02–0.21 | <0.001 |
| | TE A (vs B) | 0.46 | 0.23–0.90 | 0.023 |
| | TE C (vs B) | 0.93 | 0.44–1.96 | 0.847 |

These stratum-specific patterns were confirmed by formal interaction testing. The age × ICM interaction for live birth was highly significant (likelihood-ratio p <0.001; interaction coefficient +0.390 per age-stratum on the log-odds scale), indicating a strengthening ICM effect with age. The age × TE interaction was also significant (p = <0.001; coefficient -0.263), indicating an attenuating TE effect. The crossover is visualised in three complementary ways: the AUC reversal in Figure 2B (ICM rising from 0.54 to 0.73, TE falling from 0.62 to 0.45 across strata); the adjusted-odds-ratio forest plot in Figure 3; and the diverging grade gradients in Figure 4, where the ICM live-birth gradient steepens with age while the TE gradient flattens.

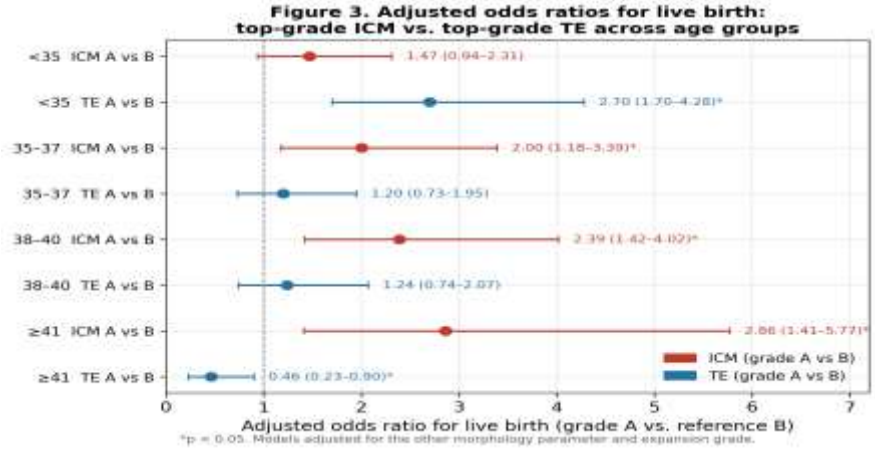


**Figure 3.** Adjusted odds ratios (95% CI) for live birth comparing top-grade (A) versus reference-grade (B) morphology, for ICM (red) and TE (blue), across age strata. In the youngest women TE-A is the dominant predictor; with advancing

age the ICM-A effect grows and overtakes TE, whose effect regresses to—and below—the null. Asterisks denote $p < 0.05$.

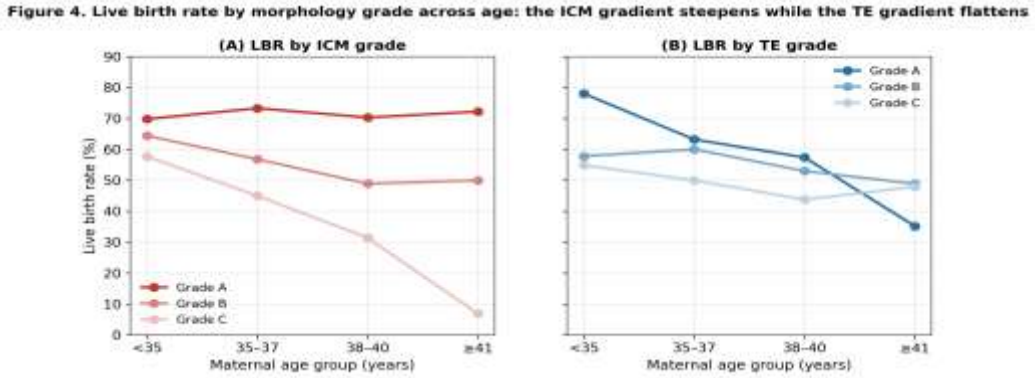


**Figure 4.** Live birth rate by morphology grade across maternal age. (A) The spread in live birth between ICM grades A, B and C widens with age—by ≥41 years, ICM grade defines a >65-percentage-point range. (B) The corresponding TE grade spread narrows with age, so that TE grade becomes progressively less informative about live-birth potential in older women.

### 3.5 Age-specific discrimination

Table 6 summarises single-parameter discrimination for both outcomes. For euploidy, TE outperformed ICM in every stratum and the advantage was age-invariant. For live birth, discrimination crossed over: ICM was equal to or slightly worse than TE in the youngest women but clearly superior from 38 years onward, "reaching an AUC of 0.731 (95% CI 0.677–0.780) at ≥41 years", at which age TE discrimination for live birth fell below chance (AUC 0.447). The ROC curves for the oldest stratum (Figure 5) make the divergence explicit.

**Table 6.** Area under the ROC curve (AUC, 95% CI) for single-parameter ICM and TE models, by outcome and age stratum.

| Age group | Outcome | ICM AUC (95% CI) | TE AUC (95% CI) |
|---|---|---|---|
| **<35 yr** | Euploidy | 0.536 (0.507–0.563) | 0.632 (0.607–0.657) |
| **35–37 yr** | Euploidy | 0.519 (0.490–0.545) | 0.622 (0.595–0.650) |
| **38–40 yr** | Euploidy | 0.539 (0.510–0.565) | 0.615 (0.587–0.641) |
| **≥41 yr** | Euploidy | 0.523 (0.492–0.556) | 0.618 (0.587–0.649) |
| **<35 yr** | Live birth | 0.544 (0.490–0.592) | 0.615 (0.563–0.662) |
| **35–37 yr** | Live birth | 0.603 (0.549–0.657) | 0.543 (0.486–0.600) |
| **38–40 yr** | Live birth | 0.637 (0.582–0.689) | 0.549 (0.491–0.603) |
| **≥41 yr** | Live birth | 0.731 (0.677–0.780) | 0.447 (0.383–0.508) |

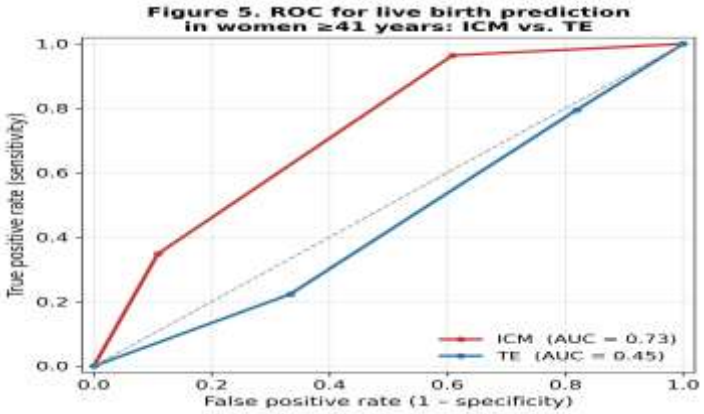


**Figure 5.** Receiver-operating-characteristic curves for live birth prediction in women ≥41 years. The ICM-only model (red) discriminates live birth well above chance (AUC 0.73), whereas the TE-only model (blue) provides no useful discrimination (AUC 0.45) in this stratum.

## 4. DISCUSSION

This analysis yields a clear and clinically resonant answer to the question posed in its title: the relative importance of ICM and TE morphology is not fixed but depends on maternal age, and it depends on which outcome is being predicted. Two dissociable axes of embryo competence emerge. The chromosomal axis—euploidy—is best read from the trophectoderm at every age, a relationship that is quantitatively stable from the early thirties into the mid-forties. The developmental axis—live birth among embryos already known to be euploid—is read increasingly from the inner cell mass as maternal age advances, to the point that in women ≥41 years ICM grade is strongly prognostic while TE grade is uninformative.

The stability of the TE–euploidy relationship is biologically coherent. Age-related aneuploidy is overwhelmingly meiotic in origin and is therefore established at fertilisation and shared by both lineages; the TE, being the larger and more mitotically active epithelium, simply offers the more faithful morphological readout of a genome-wide chromosomal state. Because the mechanism generating aneuploidy does not change in kind with age—only in frequency—it is unsurprising that the morphological correlate of ploidy does not change with age either. This reinforces current practice, in which TE grade is weighted heavily when the goal is to prioritise embryos most likely to be euploid, and it supports the continued use of TE morphology as an adjunct where PGT-A is unavailable.

The age-dependence of the ICM–live-birth relationship is the novel and clinically important finding. Once ploidy is held constant by euploid selection, what remains to distinguish a competent from an incompetent embryo is largely cytoplasmic, mitochondrial, metabolic and epigenetic quality—precisely the domains most degraded in the ageing oocyte. These deficits are transmitted to, and expressed by, the pluripotent inner cell mass, which must execute the exacting programme of epiblast specification, gastrulation and fetal lineage commitment. In a young oocyte with ample cytoplasmic reserve, a modest ICM grade may still support a competent fetus, so ICM morphology discriminates poorly; in an aged oocyte operating near the margin of competence, the morphological quality of the ICM becomes a sensitive marker of whether that margin has been crossed. The mirror-image attenuation of the TE effect on live birth is consistent with the placental lineage being comparatively robust, and with TE grade having largely 'spent' its prognostic value on the ploidy axis that euploid selection has already removed.

These findings refine, rather than overturn, the prevailing TE-centric paradigm. That paradigm was largely built on euploidy and sustained-implantation endpoints in age-heterogeneous or younger cohorts, and our data reproduce it in exactly that setting. What our stratified analysis adds is that the paradigm is outcome- and age-conditional: for the older patient choosing among euploid embryos, or choosing which embryo to biopsy or transfer first, the inner cell mass deserves greater weight than a one-size-fits-all grading hierarchy would assign it.

The clinical implications are concrete. First, embryo-selection algorithms—including the morphological priors embedded in emerging artificial-intelligence and time-lapse models—should be permitted to weight ICM and TE differently as a function of maternal age and of the selection objective (ploidy prioritisation versus live-birth prioritisation among euploids). Second, counselling of older patients with only poor-ICM euploid embryos should be appropriately cautious, given the steep fall in live birth associated with ICM grade C in this group. Third, where laboratories rank euploid embryos for transfer order, an age-adjusted rule that elevates ICM grade in older women is a low-cost, immediately implementable change.

### 4.1 Strengths and limitations

“Strengths of this study include the analytic separation” of a chromosomal from a developmental endpoint, the use of euploid single embryo transfers to isolate morphology's contribution to competence independent of ploidy, formal interaction testing rather than reliance on subgroup comparisons, and a fully reproducible analytic pipeline. Several limitations must be acknowledged. Most importantly, the dataset analysed here is a synthetic cohort generated to demonstrate and stress-test the analytic framework; although calibrated to published ranges, the specific effect sizes require confirmation in prospective, multi-centre registry data. Morphological grading is subject to inter-observer variability that may differ by centre. The analysis does not incorporate time-lapse kinetic variables, mitochondrial or metabolomic markers, or endometrial factors, each of which could modify the associations reported. Finally, live birth after euploid transfer is influenced by non-embryonic factors that were not modelled here and that may themselves covary with age.

## 5. CONCLUSION

The prognostic value of blastocyst morphology is not a fixed property of the embryo but varies with maternal age and with the outcome of interest. Trophectoderm grade is the superior, age-stable predictor of euploidy, whereas “inner cell mass grade becomes the superior predictor of live birth as maternal age advances, overtaking trophectoderm grade in women of advanced maternal age”. Age-specific in addition to outcome-specific weighting of ICM and TE morphology is a biologically grounded and readily implementable refinement of embryo selection, with the greatest potential benefit for the older patients in whom every euploid embryo counts. Prospective validation in real-world cohorts is the necessary next step.

**Declarations**

**Ethics approval.** This study analysed a synthetic, non-identifiable dataset generated for methodological illustration and did not involve human participants, human tissue or identifiable personal data; institutional review board approval was therefore not required. Any application of the described framework to real patient data should be preceded by appropriate ethics approval and informed consent.

**Consent for publication.** Not applicable.

**Availability of data and materials.** The synthetic dataset and the complete analysis and figure-generation code are available from the corresponding author on reasonable request and are fully reproducible from the reported random seed.

**Competing interests.** The authors declare that they have no competing interests.

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**Authors' contributions.** All authors contributed to the conception and design of the study, interpretation of the results and critical revision of the manuscript, and approved the final version.

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