

WHY HUMAN PRE-IMPLANTATION DEVELOPMENT IS INEFFICIENT

And a note

Until now, estimates of pregnancy loss have relied heavily on daily urine hCG monitoring in volunteer women, a method that can only "see" one specific window of development: the one that begins at implantation, when the trophoblast starts producing the hormone. Everything that happens before that (from fertilization through the blastocyst stage) is invisible to this approach, simply because there's no hormonal signal yet to detect. The new Cell paper from Li et al. (1) captures exactly this hidden phase: by filming living human and monkey embryos continuously for 5 full days, they show that roughly half of fertilized eggs arrest before ever reaching the blastocyst stage — well before the point where urine-based studies could ever pick them up.

Roughly 50% of fertilized human eggs never make it to the blastocyst stage — a major bottleneck in IVF. By imaging ~150 living human and monkey embryos continuously for up to 5 days (a first), researchers at NIBS Beijing and collaborators identified two distinct, stage-specific causes of failure:

Early arrest (before day 3): The second cell division — not the first, as long assumed — is the error-prone one. Random over-duplication of centrioles causes 2-cell embryos to build multipolar spindles, which missegregate chromosomes. Those errors trigger the arrested daughter cells to self-destruct within a few divisions. Treating embryos briefly with a PLK4 inhibitor (centrinone) prevented the defect entirely.

Late arrest (day 4, morula stage): A completely separate mechanism — activation of endoplasmic reticulum stress — blocks expression of proteins needed for cell junctions and polarity, preventing the morula from transitioning into a blastocyst.

The upshot: embryo loss isn't one problem but two, occurring at different times for different reasons, opening distinct therapeutic angles (e.g., PLK4 inhibition for early arrest) to potentially improve IVF success rates.

Comment 1.

Li et al. report that ~50% of fertilized eggs arrest before reaching the blastocyst stage. Classic urine-based hCG studies [e.g., Wilcox et al., 1988 (2)] found that roughly 25-31% of pregnancies that do establish (i.e., successfully implant) are subsequently lost, mostly before clinical recognition.

Putting the two together: of 100 fertilized eggs, about 50 reach the blastocyst stage; of those, roughly 70-75% go on to a pregnancy that isn't lost post-implantation. That's only about 35-38 out of the original 100 fertilized eggs resulting in an ongoing, clinically recognized pregnancy, meaning total loss could be as high as 62-65%, once pre- and post-implantation failures are combined. This is likely still an underestimate, since it doesn't account for eggs that fail to fertilize at all, or for blastocysts that form but never successfully attach to the endometrium (implantation failure proper), a stage neither study directly measures.

Comment 2.

The mouse exhibited a significantly (and well known) higher rate of blastocyst formation than either humans (>90% compared to approximately 50% for human). The comparison with the macaque, on the contrary, challenges the long-held assumption that low pre-implantation success is a uniquely human trait, suggesting instead that it may be a broader phenomenon across primates.

Caveat: these figures come from IVF/ICSI-derived embryos from patients undergoing fertility treatment, combined with a separate cohort of naturally-conceiving volunteers (Wilcox et al.) — an extrapolation useful as a rough order of magnitude, not a precise estimate for natural conception.

1. [https://www.cell.com/cell/fulltext/S0092-8674\(26\)00637-9?returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867426006379%3Fshowall%3Dtrue](https://www.cell.com/cell/fulltext/S0092-8674(26)00637-9?returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867426006379%3Fshowall%3Dtrue)
2. https://www.nejm.org/doi/10.1056/NEJM198807283190401?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20pubmed