As practiced today, embryo selection marginally benefits few, - while potentially harming many.

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Since early IVF days, the concept of embryo selection (ES) has been at the core of clinical practice. In recent years, as, first European colleagues, and later colleagues all over the world, started to increasingly embrace the idea that delivery of a single healthy child should be the ultimate goal of every IVF cycle, the search for the "best" embryo gained further momentum.

In this presentation we, however, argue that the concept of ES requires reconsideration. Such reconsideration is due (i) because of the realities of reproductive biology; but (ii) also because clinical practices involved in embryo selection often cause more harm than benefits.

Biologically, it appears important to consider that that embryo quality is overwhelmingly determined by oocyte quality; yet, oocyte quality is the end product of weeks to months of follicular maturation, greatly influenced by the quality of the ovarian micro-environment during folliculogenesis. It would appear naïve to assume that, once an oocyte has reached maturity, is retrieved and fertilized, the resultant embryo's quality can still to significant degrees be influenced and/or that a single oocyte cohort in a single stimulation cycle will to significant degrees differ (of course, considering obvious differences in maturation, etc.), considering that the follicles of the cohort matured within the same ovarian micro-environment.

This, of course, does not mean that there may not be minor variations in quality of mature oocytes that can translate into minor quality differences in embryos; but to expect major differences and/or to expect that interventions at those late stages can still significantly affect oocyte/embryo quality, appears unlikely. Only therapeutic interventions into earlier stages of folliculogenesis can be expected to improve oocyte and, therefore, embryo quality.

The concept of ES gathered steam in clinical practice with the suggestion that extended embryo culture to blastocyst stage improves IVF outcomes. Proponents of this concept, however, misrepresented outcome data, not recognizing that their outcomes, reported with reference embryo transfer, were based on selecting out good-prognosis patients. It, therefore, is not surprising that subsequent studies were unable to confirm outcome benefits from blastocyst stage embryo transfers. Indeed, limited data that exist on this subject in the literature suggest that blastocyst-stage embryos transfer does marginally improve implantation rates but does so only in good-prognosis patients. In all other patients, blastocyst-stage embryo transfer does not improve outcomes and, indeed, likely negatively affects outcomes in poor-prognosis patients.

The explanation for these findings lies in the observation that cumulative pregnancy chances from a single cycle cohort of oocytes is greater if all embryos are transferred at cleavage stage (day-3) rather than at blastocyst stage (days-5/6). The only explanation for this is that some embryos, which do not survive *in vitro* to days 5/6, if transferred on day-3, can still result in perfectly normal pregnancies and

deliveries. Poor-prognosis patients, of course, much more frequently fail to reach blastocyst stage than good-prognosis patients. They, therefore, significantly more frequently fail to reach embryo transfer.

Considering above made arguments about ES in general, it should not surprise that other methods of ES, like closed incubation systems with time lapse imaging (discussed elsewhere) also have failed to improve IVF outcomes

Translational relevance: Since ES, at best, only marginally affects IVF outcomes beneficially, and only in good-prognosis patients who, even without ES, produce excellent IVF outcomes, IVF centers should carefully evaluate the cost effectiveness of ES methods they plan on integrating into their practice. Moreover, it is important to consider that ES in poor-prognosis patients can have significantly negative effects on IVF outcomes.