When embryology meets genetics: the definition of Developmentally Incompetent Preimplantation Embryos (DIPE). The consensus of two Italian scientific societies.

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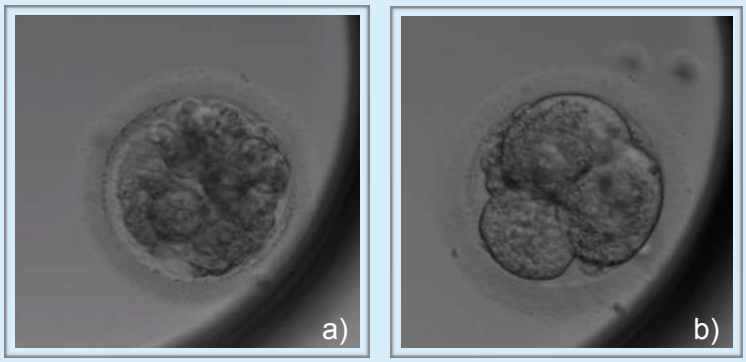
Abstract

A clear definition of developmentally incompetent preimplantation embryo (DIPE) is missing in the world health organization (WHO)- International Committee for Monitoring Assisted Reproductive Technologies (ICMART) glossary of infertility [1, 2] and some authors in the literature used DIPE in their studies but did not define them clearly. Therefore, the only official document to date which might be used to this end is the Istanbul consensus of the European Society of Human Reproduction and Embryology (ESHRE) and Alpha - Scientists in Reproductive Medicine [3, 4]. In this document an international panel of experts in clinical embryology stated that “a non-viable embryo is an embryo in which development has been arrested for at least 24 h, or in which all the cells have degenerated or lysed” (examples are shown in Fig. 1).

Figure 1:
a) Day+3 embryo (72 h.p.i.) with the majority of the cells degenerated or lysed
b) Embryo showing only three blastomeres, 48hrs after the first cleavage division.



In 2018, the American Society for Reproductive Medicine (ASRM) also released its experts’ opinion on “blastocyst culture and transfer” [5] where they stated that “reliable criteria to identify embryos destined to develop to viable blastocysts in vitro remain to be established”, although there is an “intense investigation to find markers”.

Apparently, extended culture to the blastocyst stage, possibly up to day7 [6, 7] is per se the only practice to outline DIPE. Any embryo that develops to the blastocyst stage, regardless of its morphological quality might be euploid-diploid and result in a healthy live birth if transferred [8, 9]. Nonetheless, meiotic aneuploidies, which (except for sex chromosome ones and vital trisomies) are most certainly not compatible with a live birth [10], are known to just mildly affect embryo development and blastocyst quality [9, 11].

Some countries like Italy have a specific Law (for Italy: Benagiano 2004) which protects the status of the embryos. Italian law establishes that embryos can be discarded only if not viable and cannot be used for research purposes either. Therefore, thousands of embryos diagnosed affected and/or aneuploid by preimplantation genetic testing (PGT) and clinically not utilizable, are actually cryopreserved and stored indefinitely in Italian IVF centres, with important psychological and economic implications. With the aim of updating the definition of DIPE by complementing it with a genetic perspective, the Italian Society of Embryology, Reproduction and Research (SIERR) and the Italian Society of Human Genetic (SIGU) reviewed the literature on this topic, found a Consensus and produced a list of criteria.

Materials and methods

Study design, size, duration: Five SIERR embryologists and two SIGU geneticists (a clinician and a biologist), representative of their respective scientific societies, worked as a committee in 6 board meetings through 2018 and 2019, in order to draft the document. The consensus was then approved by the steering committee of the two scientific societies and made open through publication on their websites.

Participants/materials, setting, methods: Over a hundred between scientific articles and guidelines have been selected through systematic search on the topic of DIPE. The most recent studies on embryo morphology and morphokinetics and the most recent studies reporting data produced with advanced PGT technologies, allowed the committee to develop standard criteria to define DIPE.

Glossary: Current definitions and terms of use are derived from the revised glossary on Assisted Reproductive Terminology by the WHO-ICMART [1, 2] and the Istanbul consensus [3, 4].

SIERR AND SIGU CONSENSUS

SIERR in collaboration with SIGU drafted a consensus document to define DIPE. The two societies agreed on which embryos should be considered not useful for reproduction purpose since unable to result in a live birth. These include developmentally-arrested and degenerated embryos, zygotes with a number of pronuclei (PN) equal or higher than 3, and embryos affected from lethal genetic and/or chromosomal conditions. The destiny of these embryos is strictly related to the specific Laws in force in each different country. Yet, a Consensus on their definition was pivotal to build evidence-based directives or Laws and promote Research and progress in this important area of medicine and healthcare.

Definitions

The definitions we agreed on in this Consensus paper are summarized in Figure 2. Based on the chance that embryos would result in a healthy live birth and on the risk that they might instead cause serious adverse events if transferred, we have classified them into three categories: developmentally competent preimplantation embryos (from here onwards defined **DeCE**), developmentally competent preimplantation embryos of undefined reproductive competence (from here onwards defined **DeCURC**), and **DIPE**.

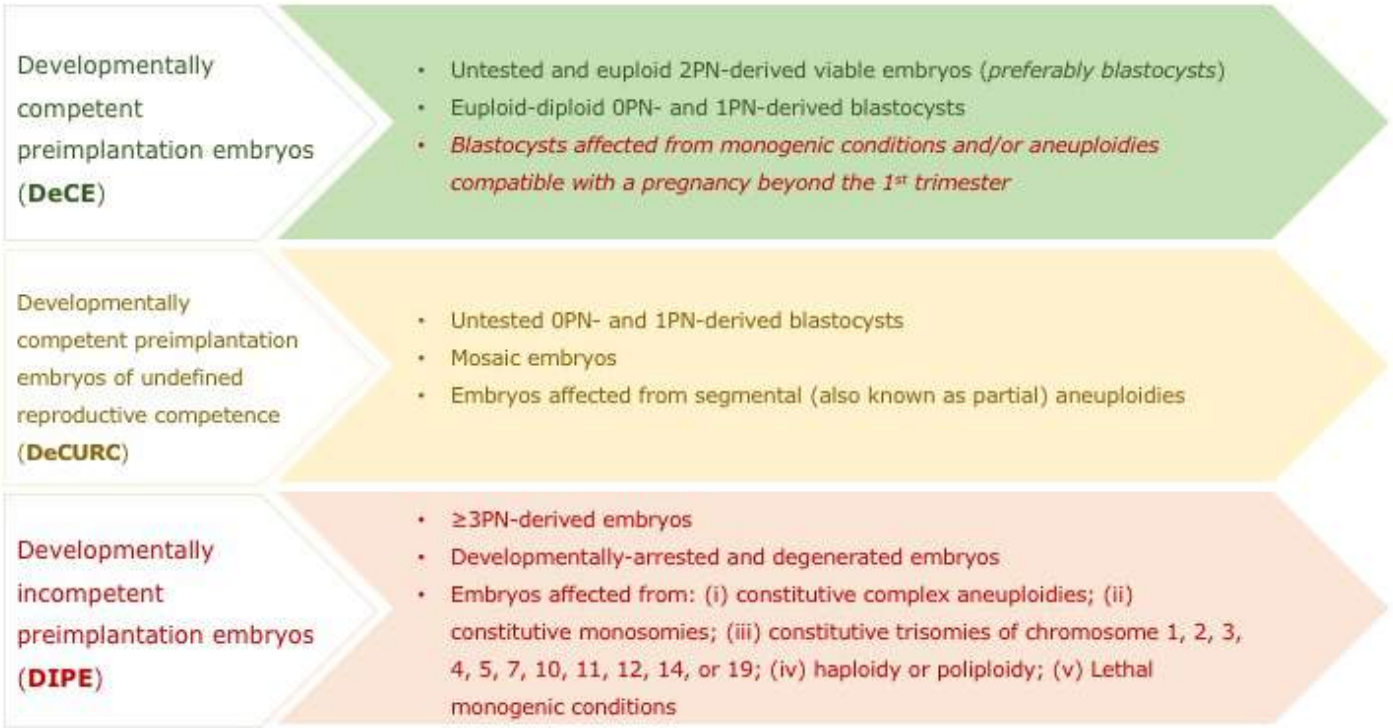


Figure 2: Summary of the definitions outlined in this Consensus paper by SIERR and SIGU

Conclusions

The definition of degenerated and developmentally arrested embryos as not viable does not have any ethical and/or scientific implication. Instead, the inclusion of both aneuploid embryos and embryos affected from severe monogenic conditions in such a definition opens to novel perspectives for those Countries, like Italy, that currently must keep them cryopreserved indefinitely with all the inherent psychological and economic implications for the couples and for the centers. DIPE might be instead used for Research (under couples' informed consent and the approval of an ethic committee) and contribute to technical improvement and scientific progress, as well as to produce embryonic stem cells (ESCs).

An official definition of DIPE that complements the embryological with the genetic evidences is critical (i) for the clinicians, who will be able to provide a more complete counseling to the couple with respect to the non-viability of their embryos, (ii) for the Legislator and the related institutional Ethic Committees, who are called to draw up Laws that define which embryos are not intended for reproduction and which ones instead are, and (iii) for the couples, who may more serenely decide the fate of their DIPE based on the current knowledge and the Consensus of two scientific societies.

While for DIPE, the event of a false positive classification is remote, DeCURC category includes embryos more subject to false positive assessments in both the embryology and molecular biology laboratories. After a comprehensive and evidence-based genetic and gynecologic counseling on the realistic short- and long-term prognosis of these embryos ("quoad vitam et quoad valetudinem"), the parents shall always be given the possibility to make an independent embryo disposition decision on their destiny. In an experimental setting DeCURC might even be transferred, but recognizing their negligible chance to result in a healthy live birth and/or the considerable risk they might involve serious adverse events. Lastly, among DeCE we included also blastocysts affected from monogenic conditions and/or aneuploidies compatible with a pregnancy beyond the 1st trimester since they might be compatible with a live birth although syndromic, and some couples might even decide to transfer them after careful genetic and gynecologic counseling [12].

The definitions included in this manuscript are clearly subject to future updates based on the scientific and clinical evidence that might be produced in the coming years in this field.

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