Agree to disagree: reaching consensus amongst embryologists on the clinical management of low-quality blastocysts

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Keywords: low-quality blastocysts / embryo fate / embryologists’ consensus / embryo selection / embryo assessment

The October ESHRE Journal Club discussion focused on a study by Chiappetta et al. (2023) on embryologist agreement on the fate of low-quality blastocysts (LQBs), the variability in their assessment by embryologists from different countries, the clinical and legal factors influencing fate decisions, the efforts towards standardization of LQBs assessment, and the importance of a patient-centred approach.

GRAPHICAL ABSTRACT

Factors impacting embryologists decision to discard or use low quality blastocysts (LQBs) as discussed during the October ESHRE journal club

Patient specific factors
- Patient age and medical history
- Number of embryos collected
- Previous cycle prognosis
- Personal cultural, religious and ethical beliefs

Laboratory specific factors
- Laws and regulations of the country regarding embryo use and discard
- Funding status i.e. is the cycle publicly funded or privately funded?
- Laboratory training protocols and embryologist experience
- Availability of resources including Artificial Intelligence (AI) tools and genetic testing, etc.

Conclusions
- Embryo grading is subjective and has inter-observer variability; however, tools like AI could help in standardisation.
- Standardisation of protocols and training for embryologists on available tools is important to improve cycle outcomes.
- Embryologists, clinicians and patients should be involved to take a patient-centred decision.

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Introduction

Blastocyst grading is one of the cornerstones of routine embryology, commonly performed using Gardner’s grading system which entails a qualitative assessment of the morphological features of the inner cell mass (ICM) and the trophectoderm (TE) as well as the level of blastocoel expansion (Gardner and Schoolcraft, 1999). Borderline and low-quality blastocysts (LQB), defined as less than 3BB in the Gardner and Schoolcraft classification system, have received less attention compared to good and high-quality blastocysts. Although these embryos exhibit a worse prognosis compared to their sibling average, good and high-quality blastocysts, their clinical use cannot be disregarded, as they have been shown to result in live births following preimplantation genetic testing for aneuploidy (PGT-A) (Cimadomo et al., 2019). Consensus points for embryo morphology assessment have been developed with the aim of standardizing laboratory practice and leading to more effective comparisons amongst embryologists (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011; Pons et al., 2023). Nonetheless, agreement amongst embryologists regarding the suitability of LQBs for vitrification has been shown to be just fair (Hammond et al., 2020), whilst the uniformity between embryologists when selecting a Day 5 embryo for transfer is not optimal (Storr et al., 2017).

A recent publication in Human Reproduction undertook an anonymous survey across a large network of IVF centres with a total of 117 embryologists from 6 European countries (Italy, Spain, Portugal, Czech Republic, Sweden, and Iceland) and 29 IVF centres participating (Chiappetta et al., 2023). The survey was based on time-lapse videos of LQBs along with key information on patients/cycles for each video. Based on the information, embryologists stated whether they would transfer fresh, cryopreserve, biopsy, or discard each embryo. A total of 2263 (38.7%) ‘discard’ and 3587 (61.3%) ‘use’ decisions were recorded. Embryologists showed a fair agreement on discard rates with Czech, Portuguese, and Italian embryologists expressing lower ‘discard’ inclination towards discarding LQBs with弛缓性Embryologists have shown fair agreement on discard rates compared to intermediate rates from Czech, Portuguese, and Italian embryologists expressing lower discard rates, compared to intermediate rates from Czech, Portuguese, and Italian embryologists expressing lower ‘discard’ inclination towards discarding LQBs with 40 prohibits discarding potentially viable embryos, which could pose a unique constrain not faced by embryologists in other countries (Cecchi et al., 2018; Cimadomo et al., 2019) and lead to a wider range of criteria for determining which embryos to use, biopsy, or discard. An advantage to this restrictive law is that Italian embryologists have unveiled the implantation potential of LQBs and slow-developing (i.e. Day 7) embryos (Cimadomo et al., 2022). Another constraint that could play a role in decision-making is embryologist inter-observer variability (Storr et al., 2017), which can have a significant impact on the blastocyst utilization rate of an IVF centre. Although inter-observer variability among embryologists could be due to a difference in phenotypes of LQBs, it can also be enhanced by the number of embryologists and the number of cycles per year in a clinic. In general, the effects of inter-observer variability between IVF clinics could be alleviated by the adoption of a general standardization in embryo grading. Another important consideration in the discussion of the study by Chiappetta et al. is that the final decision on an embryo’s fate can vary depending on the situation (real or fictitious) and the time when the decision is taken since it has been suggested that embryologists can change their mind on the grading and fate of the same embryo when looking at images at the time of transfer or 3 months later (Sais et al., 2022).

Clinical factors influencing fate decisions: inclination towards discarding LQBs with larger embryo cohorts

Another interesting aspect addressed by Chiappetta et al. was the decision of embryologists to discard LQBs or Day 7 blastocysts. The embryologists’ decisions were recorded on the same set of 50 time-lapse videos and, interestingly, embryologists from Nordic countries were more prone to discard embryos, while embryologists from Italy or Spain were more inclined to biopsy them. It is not an easy decision to choose whether to discard or not, especially when embryologists have been mainly trained to rely on qualitative (and sometimes subjective) embryo morphological features. Previously, it was shown by a Belgian group that the rescue of poor-quality cleavage-stage embryos (Day 3), by prolonging their culture up to the blastocyst stage, could increase pregnancy rates in the IVF lab (Shaw-Jackson et al., 2013). However, an Italian study questioned the use of morphology when evaluating the chances of pregnancy of euploid blastocysts (Minasi et al., 2016). In an assessment of the available literature, Morbeck (2017) questioned the usefulness of grading discarding grade C blastocysts, considered low quality for either ICM or TE grading, in the era of PGT-A and argued that the context in which one operates can also influence the choice to discard embryos based on morphological quality. Another important factor that can influence the discard decision is the number of blastocysts obtained in a specific cycle. The larger the cohort of embryos obtained, the greater the likelihood of choosing to discard an LQB or Day 7 surplus embryo. This seems to be related to the perception an embryologist has of the possibility of completing the parental project with the embryos already available. In terms of LQBs, an Italian study from Cimadomo et al. (2022) showed that utilization of LQBs, when using artificial intelligence (AI) to standardize grading, can result in a 4.4% relative reduction of obtaining a live birth. And the following year, a multicentre study by Zou et al. (2023), using data from Australia, China, and New Zealand, also showed that LQBs can result in a lower live birth rate. In both cases, it was pointed out that miscarriage rates and risk of perinatal adverse outcomes were not increased. An international list of experts recently debated the advantages and disadvantages of using Day 7 blastocysts and LQBs (Cimadomo et al., 2023).
et al., 2023). Thus, the dilemma is not settled yet, and the literature suggests that there is a need to define developmentally incompetent preimplantation embryos, to standardize the parameters when making the decision to discard. Even if some attempts have been made, involving scientific societies of embryologists and geneticists (Cimadomo et al., 2021), many concerns remain as to whether morphology, ploidy, and/or physiology correlate with each other, and if each feature can be used as a separate proxy of the others. For example, the definition of a non-viable embryo has been recently put into discussion, due to the live birth of a healthy baby from a diploid embryo derived from a 4PN zygote (Bredbacka et al., 2023).

**Fate decisions based on clinical and legal settings**

The study by Chiapetta et al. was run in a large network of IVF centres including a total of 117 embryologists from 6 European countries. Interestingly, this large network is composed of only private IVF clinics. In Europe, different countries can have different funding models and the types of expenses covered within an IVF cycle are extremely dissimilar (Calhaz-Jorge et al., 2020). For this reason, it is likely that clinical decisions on embryo fate can vary between private and public institutions. Such divergence and its impact on clinical results can be exemplified by two studies from Spain (Castilla et al., 2009; Alon and Pinilla, 2021). First, Castilla et al. have reported that private clinics in Spain performed more cycles, and more elective embryo transfers and have higher pregnancy rates compared to public clinics. In a follow-up study, Alon and Pinilla confirmed that patients treated in private clinics had on average a higher cumulative pregnancy rate compared to those treated in public clinics and concluded that long waiting periods could be the main reason for the lower incidence of pregnancy in the Spanish public health care system. Adding to the constraint on decision fate between the public and private clinics is maternal age. According to data reported by the European IVF Monitoring Consortium et al., 2023), the pregnancy rate in women ≥40 years ranged between 6.5% and 56.7% for IVF cycles and between 1.5% and 23.8% for ICSI cycles. Most likely, women ≥40 years will have mainly LQBs from an IVF cycle and their chances of pregnancy will decrease dramatically with each year (Klipstein et al., 2005; Cimadomo et al., 2022). Additionally, Spain provides full treatment funding in public institutions for women under 40 years and for up to three treatments (depending on regional legislation). In Italy, the limit of age rises to 46 years for IVF in public institutions. If we consider two women just below the age of 40 starting an IVF treatment cycle in Spain or Italy, the patient in Spain would not be entitled to a second funded cycle (after a first failed attempt) because of the age limit, something that could influence the embryologists’ decision making, leaning towards transfer/vitrification/biopsy of LQBs to ensure at least one transfer before leaving the IVF centre. In contrast, in Italy, the woman will be allowed to do two more attempts and embryologists may be less lenient regarding the decisions to discard LQBs. In some countries such as Belgium, this situation can be even more drastic with coverage for up to 6-cycle attempts up to the age of 45 in public institutions.

Thus, the use/discard dilemma can extend into ethical considerations, since similar LQBs might have a different fate based on how an embryologist perceives the allocation of resources in their public or private IVF centre. Moreover, it is important to recognize cultural and legal constraints related to specific countries and the decision to discard (Simopoulou et al., 2019). For instance, Chiapetta et al. include ‘biopsy’ as one of the choices available for ‘usable’ embryos, but in different countries, PGT might be forbidden, not available, or only allowed within limited justifications, influencing the final outcome.

**Patient-centred approach in decision making**

Regardless of the country, funding scheme or legal framework for IVF practice around the world, embryo fate decisions should always be patient centred. Thus, an embryologist’s decision must adhere to the law and take the patient’s circumstances into consideration as a priority. However, it is still a matter of debate whether variables such as a patient’s fertility history or poor prognosis should be taken into consideration regarding decisions on LQBs and/or extended laboratory cultures since these variables can have an extreme weight/impact on embryo fate. Interestingly, a study by Barnes et al. (2023) showed that an AI approach to predict human blastocyst ploidy improved performance when the classification used both images and clinical variables compared to only images (accuracy 69.3% vs 59.2%, respectively). This suggests that standardization of embryo assessment should consider variables related to the specific patient’s clinical circumstances. On top of clinical variables, patients’ decisions can be influenced by their views on religion, ethics, and mental health. Therefore, patients should be counselled about extended culture and embryo grading with their clinician along with their embryologist. AI tools can help with embryo assessment; however, the role of an embryologist/clinician is imperative in making patient-centred decisions on the fate of IVF embryos and reaching a healthy pregnancy in the shortest time possible, as well as considering the “family planning” desires of the patient (i.e. cumulative pregnancies).

**Conclusion**

To discard or use, an embryo remains a dilemma for embryologists based on variables such as patient age, number of embryos in the cycle, laws and regulations of the country, and personal/cultural views. Embryo grading can be a subjective process that introduces inter-observer variability; nevertheless, tools like AI could help in standardization of assessment. Once a standardized and objective assessment of embryo grading can be reached, embryologists can unveil the actual potential of LQBs and assist in making the difficult decision on whether to discard or use. Regardless of the efficacy of new technologies, it is vital that embryologists understand how to make the best use of the available tools with the aim of increasing the chances of pregnancy for patients. Thus, the role of the embryologist in embryo fate decisions remains pivotal and unreplaceable.

**Data availability**

No datasets were generated or analyzed in the current manuscript.

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**Authors’ roles**

V.P., I.C.-S., and C.S. contributed intellectually to the discussion as experts; Z.E.A. prepared the graphical abstract; all authors provided outlines for the manuscript; K.S., G.L., and J.J.F.-Z. drafted the manuscript. All authors provided critical revisions to the graphical abstract/manuscript and approved the final version.

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