

Should we look for a low-grade threshold for blastocyst transfer?

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Introduction

Embryo quality is a key determinant of the success of in vitro fertilisation (IVF). Low-grade embryos (LGEs) and low-grade blastocysts (LGBs) have received minimal attention compared to high quality, high transfer order embryos.

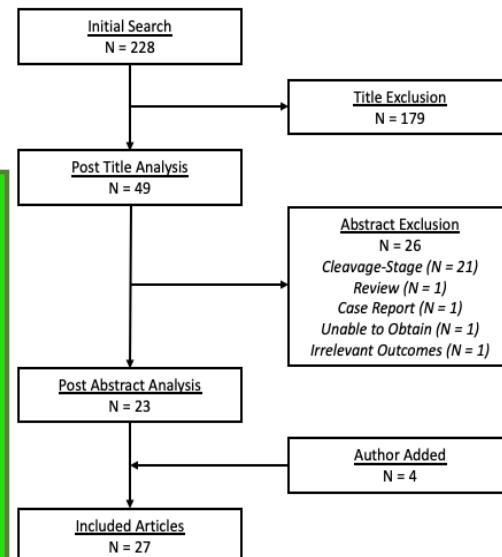
Most of the published evidence combines LGBs into one group, analysing their outcomes as a homogenous congregation, rather than considering the patient/embryo factors that have the potential to differentially impact on clinical outcomes. Current literature is unable to guide the possible options and next steps, as well as provide realistic clinical outcomes according to different grades with the LGB category.

Materials & Methods

To determine the current state of the literature on LGBs and any previous work on embryonic quality thresholds, we conducted a PubMed literature search in August 2020 utilising the search terms “(((“poor-quality” OR “poor quality”) OR (“low-grade” OR “low grade”)) AND (“embryo” OR “blastocyst”)) AND (“pregnancy” OR “live birth”))”. As shown in Figure 1, from the initial 228 results, 179 articles were excluded following analysis of their title, based on lack of relevance to the research question or due to inclusion of non-human embryos. The remaining 49 articles had their abstracts assessed, after which 26 articles were excluded. An additional four articles known to the authors but not contained in the search results were manually included.

Results

Broadly, the analysed articles show LGEs at day three have the opportunity to develop to day five, and that LGBs have similar ongoing rates and perinatal outcomes following implantation. Importantly, no adverse impacts on pregnancy or perinatal outcomes have been determined following the use of LGBs. The percentages reported for live births have a vast range (5.2-60.0%). The articles highlight that LGBs have the ability to provide couples with a chance of pregnancy which should not be ignored. We were unable to delineate the outcomes for different grades of LGBs, as well as by the day age of the blastocyst utilised (day 5 vs. 6 vs. 7).



Redefining the Low-Grade Blastocyst

We believe that further focus should be placed on the distinction between different grades of LGBs, including factors such as day frozen and female age. Currently, the threshold of 3BB often eliminates the subcategorization of LGBs, thereby preventing analysis of the outcomes contained within this group. It is envisaged that LGBs falling within the lowest grading tier, for example CC and day 7, will result in the lowest pregnancy rates, but large datasets are required to determine by what magnitude.

There are practicalities that limit the widespread analysis of LGBs. We do not advocate that patients and their precious embryos should be subjected to trials utilising LGBs if this significantly delays the use of GGBs and their over-arching goal of achieving a live birth. Furthermore, every IVF clinic will have its own guidelines regarding how LGBs should be utilised; many will discard these embryos. Lastly, embryo grading is inherently subjective and significant inter- and intra-user variability exists.

The role of cryopreservation should also be briefly considered. Practices vary, however many clinics do not cryopreserve day 7 blastocysts, and some may also exclude day 6 LGBs.

Furthermore, when analysing the results of embryos transferred on a non-stimulated cycle, one cannot ignore the impact of the endometrium on the chances of implantation. Assuming the cryopreservation itself does not cause damage, the implantation potential of LGBs may be different if transferred on a non-stimulated cycle, and thus literature should reflect these differences.

We implore clinicians and embryologists to explore the opportunities to utilise LGBs. If, following oocyte harvest, the GGBs will undergo vitrification prior to subsequent transfer, there exists an opportunity to transfer one or more fresh LGBs. Should this result in a viable pregnancy, the current literature suggests no adverse perinatal outcomes deriving therefrom. Were implantation to fail, then little is lost; we acknowledge of course that for some women the potential psychological impact of a ‘failed’ transfer will be too great to justify this transfer.

By collaborating and collating data from multiple clinics, it is theoretically possible to obtain sufficient numbers of each grade of LGBs to begin to identify trends and thresholds amongst these embryos. It also provides an opportunity to compare and standardise methodologies between services.

Future Directions

This review is a call to reconsider those embryos not deemed adequate for biopsy and/or vitrification, but that may still lead to healthy deliveries. We advocate that LGBs not be universally discarded, but rather be considered for transfer in conjunction with the patient’s personalized treatment plan. LGBs have no adverse impacts on perinatal outcomes. These LGBs have the potential to provide patients with a chance of pregnancy when other options may not be practically or economically feasible; it is time to further quantify the LGBs threshold and reassess their use.