RBMO

REVIEW

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

BIOGRAPHY

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KEY MESSAGE

Low-grade blastocysts (LGB) have the potential to provide patients with a chance of pregnancy when other options may not be practically or economically feasible. Furthermore, LGB do not adversely affect pregnancy or perinatal outcomes. The LGB threshold should be quantified and their use reassessed.

ABSTRACT

Embryo quality is a key determinant of the success of IVF. Although the focus has been on selecting the best embryo for transfer, the classification of low-grade blastocysts (LGB) in existing scoring systems has received less attention. This is worrisome; embryo freezing allows optimal use of all created embryos, thus maximizing the cumulative live birth rate, which is arguably the most important outcome for infertile couples. A *PubMed* search was conducted in August 2020, using '((('poor-quality' OR 'poor quality') OR ('low-grade' OR 'low grade')) AND ('embryo' OR 'blastocyst')) AND ('pregnancy' OR 'live birth')'. This scoping review shows that LGB have similar euploidy and pregnancy success rates after implantation and have no adverse effects on pregnancy or perinatal outcomes. Evidence for pregnancy outcomes is lacking for different grades of LGB, with most studies clustering all LQB as one to compare with optimal blastocysts.

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KEYWORDS

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INTRODUCTION

Embryo quality is a key determinant of the success of IVF. As much of the IVF community moves towards solely single embryo transfers (SET), and with the knowledge of advanced maternal age and the higher aneuploidy rates associated therewith, focus has intensified on identifying those embryos destined to produce live births. To maximize the possibility of a successful pregnancy resulting in the birth of a baby, it is important to select the embryo with the highest developmental potential (*Gardner and Balaban, 2016*). This also permits a reduction in the time to achieving a pregnancy and facilitates the selection of embryos for cryopreservation and transfer (*Bergh, 2005*).

Extended culture of embryos to the blastocyst stage has now been widely used as a tool for further selection, by allowing arresting embryos to be naturally deselected. Since 1999, blastocyst quality has been graded by many laboratories using the Gardner and Schoolcraft categorization method (*Gardner and Schoolcraft, 1999*). In turn, new embryo analysis techniques, e.g. preimplantation genetic testing and time-lapse imaging, have had their predictive abilities and outcomes compared with this 'morphological assessment control' (*Armstrong et al., 2018*; *Kemper et al., 2019*).

Low-grade embryos (LGE) and low-grade blastocysts (LGB) have received less attention compared with high-quality, high-transfer order embryos. Low-grade embryos have been widely categorized as the lowest grade of 3/3 described in the Istanbul consensus (*Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology et al., 2011*), whereas LGB have been invariably defined as less than 3BB in the Gardner and Schoolcraft classification system. Traditionally, 'poor-quality' has been used to describe these embryos; this imparts a value statement that may surreptitiously influence patient decisions; we have, therefore, chosen to use 'low-grade' instead. When investigated, two main streams of exploration are observed: the comparison of LGE and LGB (cleavage-stage grade 3 or lower than 3BB, respectively) with good-grade embryos (GGE) and good-grade blastocysts (GGB) (cleavage stage grade 1/2 or 3BB or higher, respectively); and the proof that LGE and LGB can result in live births. Evidence on the outcomes associated with the use of different grades within the LGE and LGB classification is limited. For the purposes of the present review, the focus will be on LGB, as this is the final stage at which embryo grade is assessed.

One main disadvantage conferred by the current research is the inability to help clinicians guide the use of different grades of LGB. Most of the published evidence combines LGB into one group, analysing their outcomes as a homogenous congregation, rather than considering the patient–embryo factors that have the potential to differentially affect clinical outcomes. If many GGB are available for transfer, then these limitations may be of no concern to both patient and clinician, with eventual transfer of LGB increasingly unlikely as the number of GGB increases within the cohort. Consider, however, the case of a patient with four harvested blastocysts, all poor-quality. Current research 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. Should the patient undergo SET of the LGB? Is the transfer of multiple LGB together reasonable? What is the economic analysis of the vitrification of these LGBs? Should further ovarian stimulation and oocyte collection be conducted? All these questions can be further broken down if one considers the quality of the LGB. It is reasonable to assume that, at some grade, the chance of a live birth will be 0%. So far, this threshold has not been defined.

The LGE and LGB are distinct; this review focuses on transfer of LGB, not on transfer of LGE on day 3. When a patient has only one LGE, we advocate a cleavage stage transfer. Although most clinics have moved to vitrifying only at the blastocyst stage, many are also vitrifying LGE. It is yet to be established if this is better than leaving the embryo in culture. For some patients, transferring early (and vitrifying early) is beneficial. Although the number of patients who may benefit from this is small, and the overall efficacy is, therefore, small, changing to day-3 vitrification is inefficient for clinics and is unlikely to be used once an all blastocyst policy is in place.

This scoping review seeks to explore published research on LGB. Although GGB are almost always desired and used preferentially, we discuss the importance of investigating outcomes associated with categories of LGB, and the potential effect this may have on live birth rates. We aim to demonstrate that LGB have been neglected and treated as an identical group, with decisions made on arbitrary thresholds that have not been defined by clinical outcomes presented in published research. We do not seek to present a systematic and exhaustive review of the evidence. This scoping review provides the basis for future investigation using clinical data to further define the subcategories of 'low-grade' and thereby guide clinicians and patients in optimizing the chances of live birth success.

GARDNER AND SCHOOLCRAFT

In 1999, Gardner and Schoolcraft proposed the use of a blastocyst grading method assessing three parameters: the degree of blastocyst expansion or hatching, the quality of the inner cell mass (ICM) and the quality of the trophectoderm (*Gardner and Schoolcraft, 1999*). The former is represented by a number (1–6, 6 being greatest expansion), the latter two by a letter each (A–C, A being highest). Therefore, a 'perfect' embryo is graded as 4AA (by grades 5 and 6 the embryo is hatching). Many studies use the 3BB grade threshold to distinguish between 'good'- and 'low'-grade blastocysts.

In the 2 decades since the publication of this work, limited amendments have been made to the grading system. The Istanbul Consensus on embryo assessment agreed to the continued use of the Gardner and Schoolcraft grading system, using a numerical interpretation rather than the original letters; the core grades remained the same (*Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology et al., 2011*). We acknowledge that alternative grading methods have been proposed, e.g. additional grading tiers, but these will not be explored here.

LOW-GRADE BLASTOCYSTS MATTER

The focus on good-grade blastocysts is understandable; clinicians and patients are primarily interested in knowing

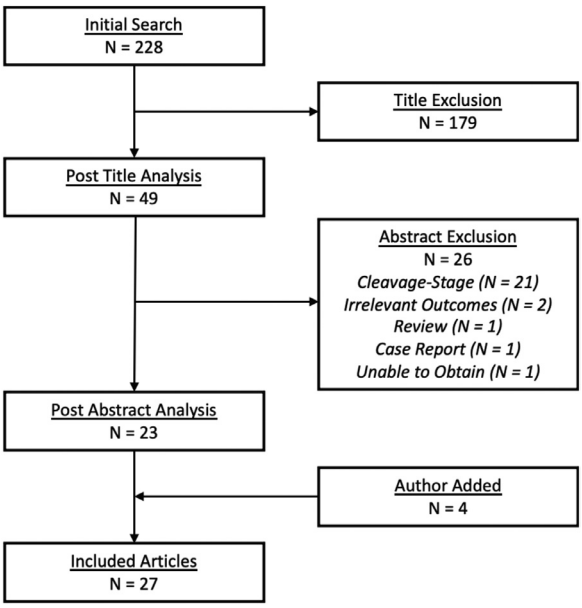

FIGURE 1 Study inclusion and exclusion.

which embryos have the best chance of implanting. This approach has proved beneficial, as embryo culture conditions and embryo selection have improved. Birth rates have continued to improve per embryo transfer, although they have remained stagnant per cycle started (*Human Fertility and Embryology Authority, 2020*). We believe it is timely to consider the optimal use of LGB to realize the maximal benefit (live birth) of all the embryos generated in a treatment cycle, including from LGB.

Uncertainty has always surrounded the decision of what to do with LGB. Studies have shown that many of these LGB are initially discarded, in favour of their good-quality counterparts (*Langley et al., 2001*). This is, in part, due to the difficulty in achieving a live birth, influenced by poor survival of blastocysts frozen with slow freezing methods. As developments in IVF have improved outcomes, focus has shifted to the use of SET, day-3 versus day-5 transfer, embryo vitrification and the use of biopsy and genetic analysis to determine the best embryo. Compared with fresh transfers, rapid vitrification has produced equal or superior pregnancy and live birth rates (*Wang et al., 2017*; *Stormlund et al., 2020*).

LITERATURE SEARCH AND RESULTS

To determine the current state of research on LGB and any previous work on embryonic quality thresholds, we conducted a *PubMed* literature search in August 2020 using 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 after analysing their title, based on lack of relevance to the research question or because of inclusion of non-human embryos. The remaining 49 articles had their abstracts assessed, after which 26 articles were excluded (21 pertaining to only cleavage-stage embryos, one review, one case report, one unable to obtain [Thai] and two with irrelevant outcomes). An additional four articles known to the authors but not contained in the search results were manually included. Twenty-seven articles were included (*Balaban et al., 2001*; *Zhang et al., 2011*; *Tao et al., 2013*; *Capalbo et al., 2014*; *Desai et al., 2014*; *Oron et al., 2014*; *Minasi et al., 2016*; *Wirleitner et al., 2016*; *Yang et al., 2016*; *Bouillon et al., 2017*; *Herbemont et al., 2017*; *Irani et al., 2017*; *2018*; *Wintner et al., 2017*; *Akamine et al., 2018*; *Dobson et al., 2018*; *Haas et al., 2018*; *Park et al., 2018*; *Zhao et al., 2018*; *Abel et al., 2019*; *Cimadomo et al., 2019*; *Tsai et al., 2019*; *Viñals Gonzalez et al., 2019*; *Aldemir et al., 2020*; *Hill et al., 2020*; *Kirillova et al., 2020*; *Li et al., 2020*).

Broadly, the analysed studies show that LGE at day 3 have the opportunity to develop to day 5, and that LGB have similar ongoing rates and perinatal outcomes after implantation. Importantly, no adverse effects on pregnancy or perinatal outcomes have been determined after the use of LGB. As shown in TABLE 1, the percentages reported for live births vary widely. The articles highlight that LGB 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 LGB, as well as by the day age of the blastocyst used (day 5 versus 6 versus 7).

Capalbo et al. (2014) examined the correlation between blastocyst morphology and euploidy and implantation potential. They deemed LGB as those blastocysts graded as 3BB or lower, finding a moderate relationship between blastocyst morphology and euploidy (6.8% versus 27.5%, $P < 0.01$, for excellent- versus low-grade embryos), but no link with euploid implantation potential. These findings were confirmed with untested blastocysts in a retrospective study examining live birth rates for low-grade blastocysts transferred fresh or during a frozen embryo transfer cycle (*Wirleitner et al., 2016*). The investigators concluded that 'our data suggest that too many embryos that might have the capacity for successful implantation after vitrified–warmed embryo transfer are currently discarded instead of being cryopreserved' (*Wirleitner et al., 2016*).

TABLE 1 DETAILS OF INCLUDED STUDIES

Authors	Year	Scoring system	Comparison	Low-grade definition	Justification for definition[a]	Live birth	LGB live birth results, %, *n*[b]
Li *et al.*	2020	G&S	D5/D6/D7 BB versus CC	Not defined	Yes – based on results of previously published research	Yes	16.7 (17/102)
Aldemir *et al.*	2020	G&S	D3/D5 G+G versus G+L versus SET (G)	<3BB	No	Yes	19.2 (10/52)
Hill *et al.*	2020	G&S	D5 G+L versus SET (G)	<CB	No	Yes	50%
Kirillova *et al.*	2020	G&S	D3/D5 LGE/Bs versus D3/D5 GGE/GGB	C for both ICM and TE	No	Yes	8.3 (19/227)
Tsai *et al.*	2019	G&S	Freeze–thawed morulas and D5/D6 blastocyst formation rate	Top-quality: 3AA, 4AA, 5AA, 6AA	No	Yes	22.7 (29/128)
Abel *et al.*	2019	In-house system	Good versus low-grade D5 blastocysts and congenital malformations	<Grade C (poor expansion, few ICM cells, few TE cells)	Yes – to allow comparison with previously published research	No	NA
Cimadomo *et al.*	2019	G&S	D5/D6/D7 GGB versus LGB	<3BC	No	Yes	10.9 (21/193)
Viñals Gonzalez *et al.*	2019	Modified Gardner + Cornell's group scoring system	D5/D6 frozen SET blastocysts after PGT-A: excellent versus good versus average versus poor	B–C, B+C	Yes – to allow comparison with previously published literature	Yes	60.0 (6/10)
Park *et al.*	2018	G&S	D5/D6 vitrified–warmed blastocyst transfer of G+G versus G+L versus SET (G)	<3BB	No	Yes	38.6 (64/166)
Haas *et al.*	2018	G&S Simplified SART (2013)	Outcome of D5 FET blastocysts and blastocyst quality	G&S: not defined SART: ICM C	No	No	NA
Dobson *et al.*	2018	G&S	D5/D6/D7 SET-G versus SET-L versus DET-G+G versus DET-G+L versus DET-L+L	AC/CA/BC/CB	No	Yes	16.3 (8/49)
Irani *et al.*	2018	G&S	D5/D6 blastocyst development rate versus morphologic grading	<2BC	Yes – on the basis of previously published research	Yes	29.5%
Zhao *et al.*	2018	G&S	D5 blastocyst: excellent versus good versus average versus poor	1–2BB	Yes – to allow comparison with previously published resesarch	Yes	25.0 (24/96)
Akamine *et al.*	2018	G&S	Effect of D2/D3 embryo and D5/D6 blastocyst quality on perinatal outcomes	<3BB	No	Yes	7.7 (28/365)
Herbemont *et al.*	2017	G&S	Impact of D2/3 quality on D5 transfer outcomes	Blastocoele <B3, ICM C, TE C.	No	Yes	38.8 (33/85)
Bouillon *et al.*	2017	G&S	Good versus poor-quality D5 blastocysts (4 grades) and obstetric and perinatal outcomes	<3BB	No	Yes	34.1 (119/349)
Wintner *et al.*	2017	G&S	D5: SET-G versus DET-G+G versus DET-G+L	<3BB	No	Yes	27.2 (49/180)
Irani *et al.*	2017	G&S	D5/D6 blastocyst grading and prediction of pregnancy outcomes for FET	<1BC	Yes – to allow comparison with previously published research	No	NA
Minasi *et al.*	2016	G&S	Correlation between D4/D5/D6/D7 blastocyst ploidy status, morphology evaluation and time-lapse kinetics	<3BB	No	Yes	36.6%
Yang *et al.*	2016	G&S	D5/D6 frozen–thawed blastocysts	<3BB	No	No	NA
Wirleitner *et al.*	2016	G&S	D5/D6 fresh versus frozen transfer	<BB	No	Yes	22.5%
Oron *et al.*	2014	G&S	SET D2/D3 GGE versus LGE versus D5 LGB and effect on perinatal outcomes	<3BB	No	Yes	5.2 (23/440)
Desai *et al.*	2014	Desai (1997)	Kinetic markers and association with D5 blastocyst outcomes	Low TE cell number and degenerative TE or ICM cells	No	No	NA
Capalbo *et al.*	2014	G&S	Correlation between D5/D6 blastocyst morphology and euploidy/implantation potential	≤3BB	No	No	NA

(continued on next page)

TABLE 1 *(continued)*

Authors	Year	Scoring system	Comparison	Low-grade definition	Justification for definition[a]	Live birth	LGB live birth results, %, *n*[b]
Tao *et al.*	2013	G&S	Effect of culture medium on D5 blastocyst development	<3BB	No	No	NA
Zhang *et al.*	2011	Balaban (2001)	D5/D6 DET of blastocysts deriving from D3 LGE	Grade III-IV	No	Yes	33.3 (5/15)
Balaban *et al.*	2001	Dokras (1993)	D3 LGE versus D5 LGB	Grade III	No	No	NA

[a] Justification for definition used was searched in the methodology of each paper. If a previously published grading system was used, without justifying why it was used, was insufficient and deemed as 'No'.

[b] Low-grade blastocyst live birth rates; the results for the 'lowest' grade investigated in a particular article were used; percentage live birth rate and number of live births per low-grade embryo; different studies present data as per clinical pregnancy, per cycle, per patient.BB, G&S Grade BB; CC, G&S Grade CC; G, good-grade; GGE/B, good-grade embryo/blastocyst; G&S, Gardner & Schoolcraft; ICM, inner cell mass; L, low-grade; LGE/B, low-grade embryo/blastocyst; NA, not applicable; SART, Society for Assisted Reproductive Technology; SET, single embryo transfer; TE, trophectoderm.

A separate stream of investigation has focused on the potential for poor perinatal outcomes stemming from the use of LGB. *Bouillon et al. (2017)* subsequently examined the obstetric and perinatal outcomes associated with good- versus low-grade blastocysts, finding no difference in results. Furthermore, a retrospective cohort study by *Oron et al. (2014)* used a threshold lower than 3BB to investigate the effect on perinatal outcomes of GGB versus LGB and found that LGB were not associated with poor obstetrical or perinatal outcomes. It can, therefore, be concluded that if an embryo has sufficient quality to develop *ex vivo*, survive vitrification–warming, and then achieve a successful intrauterine pregnancy, it has surpassed the threshold needed to have a live birth with no additional pregnancy or perinatal complications.

After the development of techniques to analyse embryonic genetic material, e.g. preimplantation genetic testing, several studies focused on the outcomes of LGB that were proven to be euploid. *Minasi et al. (2016)* conducted a consecutive case series examining the correlation between blastocyst ploidy status and morphology evaluation. They used lower than 3BB threshold as 'poor', and showed that higher rates of top-quality inner cell mass and trophectoderm, increased expansion rates and decreased time to blastulation, expansion and hatching, were seen in euploid versus aneuploid embryos. A subsequent retrospective cohort analysis by *Irani et al. (2017)* showed that blastocyst morphology was a useful predictor of the ongoing pregnancy rate in euploid embryos, with a definition of lower than 1BC as 'poor' (*Irani et al., 2017*). Despite these findings, some investigators have suggested that embryo morphology has no effect on outcomes after using preimplantation genetic testing (PGT) to select euploid embryos (*Gonzalez et al., 2019*).

Research has subsequently focused on the effect of transferring a GGB in conjunction with a LGB with some debate. *Wintner et al. (2017)* compared blastocyst SET of a GGB versus DET of two GGB versus DET of one GGB and one LGB, and determined that a LGB does not negatively affect a GGB when transferred together. Other investigators have recommended that DET of a LGB and GGB be avoided, as it confers no advantage over the SET of a GGB (*Park et al., 2018*). In comparison, *Dobson et al. (2018)* concluded that SET of a GGB or DET of two LGB were superior to DET of a GGB and a LGB (*Dobson et al., 2018*), suggesting the LGB may have a detrimental effect on its good-quality counterpart.

More recent studies have highlighted what we believe is a key and evolving concept in the use of LGB. A comparison of day-5 GGB and LGB, with a threshold lower than 3BB, showed that, although LGB have a poorer prognosis, their clinical use allows a 2.6% increase in the number of live births achievable (in this case after PGT) (*Cimadomo et al., 2019*). As will be explored further below, although the transfer of a GGB may be optimal, this opportunity will not be available to all women in all IVF cycles.

LIMITATIONS OF CURRENT RESEARCH

Conclusions derived from current research are limited by several factors. Our analysis is not a comprehensive systematic analysis but shows that only a small number of published studies have begun to explore the use of LGB. Furthermore, most studies were retrospective in nature (n = 24), with two prospective studies and one case series. Current research, therefore, has significant room for improvement, considering the hierarchy of evidence types.

The comparison of different embryo scoring systems is also subject to limitations. Although the Gardner and Schoolcraft grading system is the most commonly used, different thresholds are used to determine good- from poor-quality embryos (TABLE 1). The reported live birth rates vary significantly owing to differing denominators: those including all LGB to only the LGB that achieved a clinical pregnancy. Investigators may also use their own nuanced adaptations of existing systems to evaluate embryo quality; however, this makes meta-analyses even harder to conduct.

REDEFINING THE LOW-GRADE BLASTOCYST

We have deliberately chosen not to discuss LGE in depth throughout this scoping review. We acknowledge that these embryos play an important role in certain circumstances. Many clinics, however, will preferentially use blastocysts, and the discussion about LGB, therefore, is perhaps more relevant. We would support further investigation into LGE from clinics with sufficient numbers to power such an examination.

We believe that further focus should be placed on the distinction between different grades of LGB, including factors such as the day the embryo is frozen and female age. Currently, the

threshold of 3BB often eliminates the sub-categorization of LGB, thereby preventing analysis of the outcomes contained within this group. It is envisaged that LGB falling within the lowest grading tier, e.g. CC and day 7, will result in the lowest pregnancy rates, but large datasets are required to determine by what magnitude.

It is useful from a clinical practice perspective, and an ethical imperative, to understand which embryos have no chance of implantation, and which will have a chance of successful implantation, albeit a low one. Equally, it is important to understand the best strategy for using LGB that do have a chance of implantation.

Certain practicalities limit the widespread analysis of LGB. We do not advocate that patients and their precious embryos should be subjected to trials using LGB if this significantly delays the use of GGB and their over-arching goal of achieving a live birth. Furthermore, every IVF clinic will have its own guidelines on how LGB should be used; many will discard these embryos. Lastly, embryo grading is inherently subjective and significant inter- and intra-user variability exists (*Hammond et al., 2020*; *Storr et al., 2016*).

The role of cryopreservation should also be briefly considered. Redefinition of the differing success rates of grades of LGB is particularly important for cycles in which a decision is required about fresh transfer or cryopreservation. Practices vary, however, many clinics do not cryopreserve day-7 blastocysts and some may also exclude day-6 LGB. It must be recognized, however, that the influence of varying individual operator experience and technique will always affect the subjective assessment of embryo quality, thereby complicating study comparison.

Furthermore, when analysing the results of embryos transferred on a non-stimulated cycle, one cannot ignore the effect of the endometrium on the chances of implantation. If the cryopreservation itself does not cause damage, the implantation potential of LGB may be different if transferred on a non-stimulated cycle; research should, therefore, reflect these differences.

The public reporting of success rates by each clinic is becoming mandatory in some countries; however, one obstacle to investigating optimal use of LGB is the preoccupation of presenting the highest pregnancy rate possible. This is achieved by obtaining the best embryo or embryos possible to transfer, i.e. similar to PGT for aneuploidy or blastocyst culture, and presenting the results per embryo transfer. Even a difference of a few percentage points will give clinics a competitive advantage, and likely sway patients to attend one clinic over another. A shift of measurement from live birth rate per transfer to per egg collection could prove helpful but will require regulatory assistance and patient engagement.

We implore clinicians and embryologists to explore the opportunities to use LGB. If, after oocyte harvest, the GGB undergo vitrification before subsequent transfer, an opportunity to transfer one or more fresh LGB exists. Should this result in a viable pregnancy, current research suggests no adverse perinatal outcomes deriving therefrom. If implantation fails, then little is lost. We acknowledge that, for some women, the potential psychological effect of a 'failed' transfer will be too great to justify this transfer. Alternatively, consider a patient with only LGB remaining. Perhaps the transfer of one or more of these could be considered before undertaking further stimulation and oocyte retrieval. By collaborating and collating data from multiple clinics, it is theoretically possible to obtain sufficient numbers of each grade of LGB to begin to identify trends and thresholds among these embryos. It also provides an opportunity to compare and standardize methodologies between services. It must be recognized, however, that individual operator experience and technique will always affect the subjective assessment of embryo quality (*Storr et al., 2016*; *Hammond et al., 2020*). Consensus of the weighting of different morphological parameters of blastocysts is still some way off, although the rapid advancement of artificial intelligence may shed new light on more reproducible assessment of LGB (*Morbeck, 2017*).

With further research, the transfer of several LGB may offer a significant increase in pregnancy rates, with limited additional resources required or physical and mental cost to the patient. If embryos with, theoretically, a 5% chance of success can be identified, transfer of three embryos simultaneously may be a suitable option. This would eliminate the cost of vitrification and storage, provide a greater chance of pregnancy compared with discarding the embryos and be unlikely to result in a multiple pregnancy (given the theoretical statistical chance of three successful pregnancies would be 0.000125% (0.05*0.05*0.05). Clinical experience highlights that such 'throw-away' transfers of multiple poor embryos often results in a higher than expected implantation outcome. These discussions and considerations are not being conducted sufficiently at the present time, and further investigation is required in this area.

FUTURE DIRECTIONS

Given the use of PGT with aneuploidy to remove aneuploid embryos in an attempt to reduce the time to pregnancy, it is important to recognize that a significant proportion (likely more than 20%) of oocyte retrievals will commonly fail to receive any form of embryo transfer after 'deselection' of all initially available embryos.

The addition of four studies to those included in this scoping review may fulfil the requirements for conducting a systematic review, but we believe actual evidence is more imperative. Our group hopes to combine the resources of several IVF clinics to obtain data on the outcomes and use of LGB. Given the potentially limited number of blastocysts in these categories, it is vital to collaborate across clinics to obtain sufficient sample sizes.

In conclusion, reconsideration of those embryos not deemed adequate for biopsy, vitrification, or both, but which may still lead to healthy deliveries, is urged. We advocate that LGB not be universally discarded, but rather be considered for transfer in conjunction with the patient's personalized treatment plan. As this review has shown, LGB have no adverse effects on perinatal outcomes. These LGB 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 threshold of LGB and reassess their use.

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