

DEVELOPMENT OF AN EXTERNAL QUALITY ASSESSMENT (EQA) SCHEME FOR EMBRYO MORPHOLOGY USING THE UK STANDARD EMBRYO GRADING SCHEME

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Introduction

The lack of standardised embryo morphology grading systems in clinics worldwide has made the definition of embryo 'quality' and comparison of studies very difficult. Recently, there has been a move towards consensus of embryo grading internationally (Cutting et al, 2008; Alpha/ESHRE Istanbul Consensus, 2011) and the development of EQA schemes to assess inter-laboratory performance and reduce operator subjectivity.

Development of an EQA Scheme for embryo morphology assessment: Pilot study

In 2009, 27 ACE members (UK Association of Clinical Embryologists) from 16 labs were asked to assess still and video images for embryos from 2-8 cell stage. Marked differences were found between assessments for still images compared with video images, particularly for embryos with uneven blastomere size or a high degree of fragmentation. The consensus of results decreased with increasing cell stage and increasing fragmentation i.e. large fragments could be counted as blastomeres.

Launch of the Embryology Scheme (as part of the UK National External Quality Assessment Service : UK NEQAS Reproductive Science)

UK NEQAS Reproductive Science launched the Embryology Scheme in 2011 with all participants using the UK Embryo Grading Scheme (2008, Cutting et al; Table 1): 62 UK and 29 overseas labs currently participate. Reproductive Science also includes EQA for Andrology (1994; 205 UK and 97 overseas participants). UK NEQAS has education as a primary aim with 390 (non-profit) pathology schemes operating from 26 centres. Scheme participants receive independent, objective and impartial reports on their performance, enabling them to identify weakness and take appropriate action.

EQA Scheme Format: Participating labs assess embryo video images four times per year on line (Gamete Expert website). A single set of results (from one 'assigned' embryologist per lab) are submitted for each distribution; including four each of day 2, 3 and 5 stage embryos (1 minute 'rolling' embryo videos); plus 2 time lapse videos from 1 cell to blastocyst stage. Target values are derived from an all laboratory consensus (>50%) and an EQA performance report is produced for each laboratory.

Results and monitoring performance: The measurement of performance takes the form of cumulative penalty points when results do not match consensus values. Histograms and 'rolling' penalty graphs are given for each embryo parameter and overall performance each distribution.

Between April 2011 - December 2015, a total of 264 embryo images (152 day 2/3 videos and 112 day 5 videos) were distributed on 19 occasions. Least agreement between laboratories was found for blastocyst inner cell mass grading with a consensus value reached for only 70% (78/112) of embryos; 80% of blastocysts reached consensus for expansion and 96% for trophoctoderm grading. Consensus was reached for 99% of day 2/3 embryos assessed for degree of fragmentation, 95% for cell number and 90% for evenness/cell size.

Review of UK embryo grading scheme and UK NEQAS Scheme

A questionnaire was sent to the ACE membership in January 2016: 78 embryologists responded (20%); 87% (68/78) participated in the EQA scheme; 59% of respondents routinely used the UK grading scheme for cleavage stage embryos and 65% for blastocysts; the remainder mainly used 'in-house' grading schemes. The majority of respondents (88%) wanted to see a review of the UK grading scheme. Only 41% (32/78) of respondents routinely used time-lapse imaging, but 78% (61/78) were interested in EQA for time-lapse annotation.

References:

- Cutting et al, 2008** Elective single embryo transfer: guidelines for practice British Fertility Society and Association of Clinical Embryologists. Hum Fert. Sep;11(3):131-46.
Alpha and ESHRE, 2011 The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting Hum Reprod, Vol.26, No.6 pp. 1270-1283, 2011

A recent review of the UK Grading Scheme by an ACE working group resulted in the following recommendations (to be implemented during 2016, see Table 1 in red):

- Use of stage specific cell evenness at early cleavage stage, rather than assessment 'as seen'
- Reduction of ICM grades (from 5 to 4) and an additional TE grade (from 3 to 4), giving 4 grades for all embryo parameters (from 2 cell to unhatched blastocysts).

Early cleavage embryo and blastocyst stage assessment (hosted by Gamete Expert website)

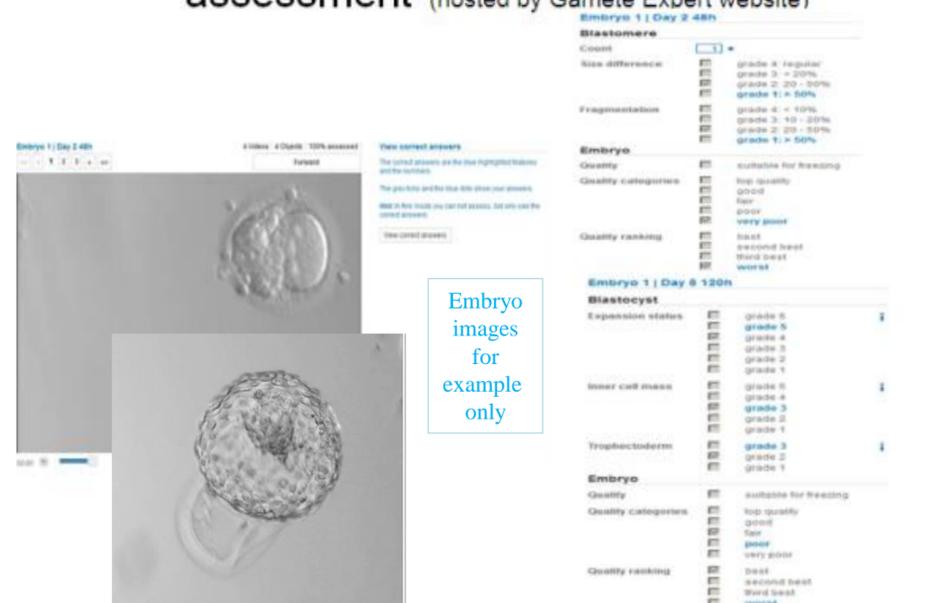


Table 1 UK Embryo Grading Scheme 2008 Proposed changes (2016) to grading scheme shown in red

Scores	UK National Grading Scheme for cleavage stages (2008)		Proposed updates/changes (2016)	
	Count blastomere/cell number	Fragmentation	Count blastomere/cell number	Fragmentation
4	Regular even division	<10% fragmentation by volume	Same as ideal stage specific embryo	<10%
3	<20% difference (cell diameter)	10-20%	Stage specific size for majority of blasts (i.e. slightly uneven sizes)	Up to 25%
2	20-50% difference	>20-50%	Majority of blasts different sizes	25-50%
1	>50% difference	>50%	Not stage specific	>50%

Scores	National Grading Scheme 2008 Blastocyst stage		
	Expansion status* (propose for hatching/hatched blastocysts: 5 H= hatching; 6 H= hatched)	Inner cell mass (ICM)	Trophoctoderm (TE)
6	Hatched blastocyst; the blastocyst has evacuated the ZP	N/A	N/A
5	Hatching blastocyst; trophoctoderm has started to herniate through ZP	ICM prominent, easily discernible, tightly adhered compacted cells (Propose Score 5 becomes score 4; i.e. no score 5)	N/A
4	Expanded (blastocoel volume larger than the embryo, with thinning of zona pellucida)	ICM cells less prominent (cells appear compacted and larger in size, loosely adhered)	N/A Propose score 3 becomes score 4
3	Full blastocyst (blastocoel completely fills embryo)	Very few cells visible (cells similar to TE)	Continuous layer small identical cells (Propose: fewer cells with gaps, not continuous)
2	Blastocyst (blastocoel >50% volume of embryo)	Cells of ICM appear degenerate or necrotic (Propose score 2 combines with score 1)	Fewer small cells with large cells, not continuous (Propose: fewer small cells with large cells, not continuous)
1	Early blastocyst (blastocoel <50% volume of embryo)	No visible ICM cells visible in any focal plane	Sparse cells, large/flat/degenerate

Future scheme developments

- Pilot for time lapse annotation EQA (August 2016) with target values set by expert 'assessors' rather than by consensus (possible roll out of 'assessor' derived values for all scheme targets by 2017)
- Implementation of updated UK Embryo Grading Scheme by 2017 following ACE recommendations.