A Review of The Society for Assisted Reproductive Technology Embryo Grading System and Proposed Modification

Amjad Hossain, Ph.D.¹[,], John Phelps, M.D., J.D., LL.M.¹, Ashok Agarwal, Ph.D.², Eduardo Sanz, M.Sc.³, Maha Mahadevan, Ph.D.⁴

 Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, The University of Texas Medical Branch at Galveston, Galveston, Texas, USA
 Department of Urology, Cleveland Clinic Foundation, Cleveland, OH, USA
 Center for Reproductive Health, Crest Hill, IL, USA
 Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Abstract-

The Society for Assisted Reproductive Technology (SART) method of embryo grading is unique, simple, and widely practiced, and its use has been mandatory for SART membership programs since 2010. Developed by SART in 2006, the current embryo grading system categories, "good, fair, and poor," are limited because they do not describe the best 1-2 embryos in the interest of keeping pace with the shift in clinical practice to be more selective and to transfer fewer embryos. This inspired us to conduct a review on the SART embryo grading system.

In this retrospective study, the literature on evaluation of human embryo quality in general, and the SART method of evaluation in particular, were reviewed for the period of 2000 to 2014. A multifaceted search pertaining to methods of embryo grading and transfer using a combination of relevant terms [embryo, mammalian, embryo transfer, grade, grading, morphology, biomarkers, SART, and *in vitro* fertilization (IVF)] was performed. The inclusion and exclusion in this review were dictated by the aim and scope of the study. Two investigators independently assessed the studies and extracted information. A total of 61 articles were reviewed.

Very few studies have evaluated the efficacy of the SART embryo grading method. The present study suggests the necessity for revision of the current SART grading system. The system, as it is now, lacks criteria for describing the cohort specific best embryo and thus is of limited use in single embryo transfer. The study foresees heightened descriptive efficiency of the SART system by implementing the proposed changes.

Strengths and weaknesses of the SART embryo grading were identified. Ideas for selecting the best cohort-specific embryo have been discussed, which may trigger methodological improvement in SART and other embryo grading systems.

Keywords: Embryo, SART, Grading, Transfer

Citation: Hossain A, Phelps J, Agarwal A, Sanz E, Mahadevan M. A review of the society for assisted reproductive technology embryo grading system and proposed modification. Int J Fertil Steril. 2016; 10(2): 141-147.

Introduction

Embryo selection for embryo transfer (ET) is a crucial step of *in vitro* fertilization (IVF). Selecting the best embryo for achieving pregnancy from an embryo cohort has been a challenge for embryologists

Received: 31 May 2015, Accepted: 30 Aug 2015

(1). In the early use of IVF for infertility treatment, morphological assessment of embryo quality was the method for choosing embryos and remains the mainstay of embryo selection today (1-3), but different morphological methods for grading IVF-generated



Royan Institute International Journal of Fertility and Sterility Vol 10, No 2, Jul-Sep 2016, Pages: 141-147

^{*}Corresponding Address: Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, The University of Texas Medical Branch at Galveston, 301 University Blvd, Galveston, Texas 77555-0587, USA Email: amhossai@utmb.edu

embryos have been developed over time (4-12). Recently, biochemical and time-lapse analyses of embryo quality have been under investigation, but they are not yet fully ready for clinical application (13-16). Information about the efficiency and usefulness of these grading methods is important for improving ET success.

Embryologists also recognize the necessity of developing a unifying standard method of grading embryos (17-19). The European Society of Human Reproduction and Embryology (ESHRE) is working to develop one such unifying embryo grading method (17, 18, 20, 21). Some European countries such as the United Kingdom and Spain have already started to utilize a national standardized grading method (19, 22, 23). Likewise, embryologists in the United States under the banner of the Society for Assisted Reproductive Technology (SART) took the initiative to establish a uniform embryo grading method (1, 24, 25). The SART task force devised a grading system, applying a 3-point grading scale of "good, fair, and poor" in 2006 (24, 25). The present study is a review of the current SART 3-point embryo grading method. The objective of this review was to find whether the SART method is fulfilling embryologists' needs in selecting embryos for transfer. The review makes some suggestions which we believe will improve the SART embryo grading method's usefulness for selecting the best embryo(s) for transfer.

Materials and Methods

In this retrospective study, a review of the literature relevant to SART embryo grading system was conducted to assess its strengths and limitations. Information on evaluation of human embryo quality in general, and the SART method of evaluation in particular, was used. Several strategies were adopted to identify the pertinent articles. First, a multifaceted search performed for the period of 2000 to 2014 generated a total of 113 citations (Fig.1). The search utilized combinations of the following terms and subject headings: embryo, mammalian, ET, grade, grading, morphology, morphological parameters, biomarkers, SART, and IVF. Special emphasis was given to articles dealing with the efficiency of the SART grading system. Reference lists of relevant articles were searched manually to find additional reports which led us to select several articles prior to 2000. Proceedings of selected scientific meetings, book chapters, and monographs on embryo assessment were also reviewed. Articles found not relevant to the aim and scope of the present study were excluded from the review. Articles on the other embryo grading methods were included only if found pertinent to the scope of the study. Some of the search-generated items were excluded stepwise from the study if they were i. Duplicates (n=7) or ii. Irrelevant after reading the title and abstract (n=34) or the entire article (n=11).



Fig.1: Flow chart showing selection and exclusion of articles in the systematic review. SART; Society for Assisted Reproductive Technology.

Int J Fertil Steril, Vol 10, No 2, Jul-Sep 2016 142

Institutional review board approval was not requested, as this was a review of published literature and not human research.

Results

Characteristics of the studies retrieved and reviewed

The literature search had 2 components. The first component, which specifically focused on the SART grading method, produced 22 articles, of which 9 were not relevant to the objective of the study. The review findings of the remaining 13 articles are shown below under the section "Synopsis of the SART grading system". Two authors (A.H. and M.M.) independently reviewed the articles and reached similar conclusions. Another 48 articles covering other grading methods and advances in IVF technologies, specifically those that had an association with embryo evaluation, comprised the second component of the search. This second set of 48 articles was reviewed, and the extracted information was collated with the first set (13 articles) to prepare the other sections of the manuscript (Fig.1).

Synopsis of the SART grading system

The review found that the SART members realized the necessity of developing a unifying standard method of grading embryos, and SART established a task force to explore such a possibility (24). In 2005, the task force developed a 3-point grading system using "good, fair, and poor" as grades. Three preconditions-must be simple, must have a basis in scientific inquiry, and must be easily adoptable in laboratories-guided the SART scheme. The grading utilized morphologic features applicable to 3 growth phases: cleavage, morula, and blastocyst (24, 25). Compared to other grading methods, the SART method was found to have 2 unique attributes. First, the SART system uses words, such as "good, fair, and poor," as grades, while other methods apply alphabet letters (A/a, B/b, C/c) and numerals (1/I, 2/II, 3/III) or their combinations as grades (1, 17, 18, 24, 26). Second, implementation of the SART grading system is endorsed by the nationally recognized organization that created it, while the majority of grading methods lack the advantage of being supported by a professional organization (18, 24, 26).

The voluntary collection of embryo data employing the SART method began in 2006 and became mandatory in 2010 (24, 25). The task force claimed an association between implantation and SART grades based on the initial set of SART embryo data. This relationship of SART grades and implantation was first reported at the 2009 American Society of Reproductive Medicine (ASRM) meeting and then in a number of journal articles (27-30). In the consensus workshop on embryo assessment sponsored by ALPHA scientists (an organization of scientists in reproduction) and ESHRE, a member of the SART task force made a presentation that highlighted the SART's stand on standardized embryo grading (18).

The Centers for Disease Control (CDC) has been responsible for publishing the SART embryo data since 2009 (31-33). The American Association of Bioanalysts (AAB) implemented a proficiency test, based on the SART method of grading, to standardize the grading skills of embryologists (34). Both the CDC and AAB remain committed to sharing the SART embryo grading outcomes with the public (31, 32, 34). Apart from those conducted by SART, CDC, and AAB, there were no evaluation studies, clinical trials, comparative analyses, or review studies on the SART grading system. The only studies outside of SART that made comments on the SART system were those of our group (35, 36). Our study found SART grading applicable to all developmental stages from oocyte to blastocyst.

Limitations of the SART grading system and potential resolution

The SART system sorts the embryos of a cohort into 3 groups: good, fair, or poor (24, 25). Since many IVF procedures produce a large number of embryos, obtaining several good embryos in each cohort is likely, and the same is true for the fair and poor categories (31, 36, 37). The dilemma, however, is determining which good embryo(s) to select for ET when several of the same grade are in the pool. The SART system does not have any provision for further discriminating the single best embryo from the available good embryos (24, 25). Secondly, the SART method selects embryos based on static observation (1, 24). This type of single snapshot examination may miss or overlook in-depth details, making the grading insufficient (38-41). Hossain et al.

| Table 1: Potential upgrades for SART embryo grading method | | | | | | |
|--|------------------------------------|---|-------------------------------|-----------------------------|--------------------|----------------------------------|
| Current SART grading method | | Proposed changes in the SART grading method | | | | |
| | | Option 1 | | | Option 2 | |
| Existing grades | Number of em- bryo in the grade | Possible grades | Number of embryo in the grade | Embryo ranking in the grade | Possible grades | Number of embryo in the grade |
| Good | 0 to M | Good | 0 to M | R1, R2, R3, etc. | Best | 0 to 1 |
| Fair | 0 to M | Fair | 0 to M | R1, R2, R3, etc. | Better | 0 to 1 |
| Poor | 1 to M | Poor | 1 to M | R1, R2, R3, etc. | Good | 0 to M |
| | | | | | Fair | 0 to M |
| | | | | | Poor | 1 to M |

SART; Society for Assisted Reproductive Technology, M; Stands for multiple and R1, R2, R3, etc.; Represent rank 1, rank 2, and rank 3, etc., respectively.

Recent publications demonstrate that new knowledge and technological advancements that have occurred in the field, particularly in the assessment of embryo viability and implantation, are powerful enough for refining SART's embryo selection strategy to overcome the challenge of embryo selection for ET (6, 42-49). Specifically, knowledge on sequential assessment, time-lapse monitoring, and profiling by "-omics" technology has grown significantly and shows great promise to add a new dimension to the embryo evaluation (7, 50-57). In addition to this literature-based projection, we have come up with specific ideas of our own to make the SART system a better fit to tackle the challenge of embryo selection for transfer (Table 1). In our proposal, we advocate for 2 different upgrades to the SART grading method (Table 1).

Discussion

The SART grading system was based on 3 preconditions: must be simple, must have a basis in scientific inquiry, and must be easily adoptable in laboratories. Such preconditions were imposed for better standardization and easy execution of the system globally. The goal apparently has been achieved as SART grading became one of the most widely practiced grading methods.

In the era of highly efficient ovulation induction, yields of multiple embryos in all 3 SART grades-good, fair, and poor-became common (32, 33, 36). The SART method classifies the embryos into 3 broad groups instead of selecting the best embryo for ET. By identifying embryos as good, fair, and poor, the SART system prepares a list of transfer-suitable embryos, not a rank-ordered list

of embryo(s) for transfer. Ideally, the number of embryos for ET should be narrowed down to 1 embryo (32, 58, 59)-the best in the cohort-which is not achieved using the SART system.

Our vision of the SART upgrade has been briefly outlined in Table 1. It presents 2 alternate suggestions to overcome the above indicated limitations of the SART system in embryo selection for ET. This proposal provides a guiding principle to rank a sequential list of embryos in the cohort. In option 1 of the proposal (Table 1), we suggest grading the embryos as "good, fair, and poor," as it is currently done by the SART method; however, we recommend adding a second tier of ranking for the graded embryos. For example, in the event of ET, the embryos in the "good" group should be ranked further for selection for ET. If the "good" group has no embryo or has an insufficient number of embryos, the embryos of the lower group should be ranked for ET. The target is to find the best embryo in the cohort. In the alternate plan (option 2), the SART system could be expanded to 5 grades instead of the current 3. Increasing the number of grades from 3 to 5 and simultaneously restricting the number of embryos to 1 in the top 2 grades (best and better) would compel the embryologist to serially tag the embryos, particularly the top 2. Emphasis is placed on 2 embryos because 1-2 embryos are commonly used in ET (21, 32, 33, 37). In either plan (option 1 or option 2), in lieu of the one-time evaluation, the cumulative grade obtained by sequential monitoring, manual or electronic, should be favored for individualizing the cohort-specific embryos. The SART method utilizes a set of parameters (cell number,

fragmentation, and symmetry) for grading the cleaving embryos and another set of parameters (expansion, inner cell mass [ICM], and trophectoderm [TE]) for blastocyst grading (24, 25). Many other studies, including our own, whose primary focus were embryo grading, found the following growth phase-specific morphological parameters ideal for embryo evaluation: zona pellucida (ZP), perivitelline space (PS), ooplasm, and polar body (PB) for oocyte; ZP, PS, pronucleus, and cytoplasm for zygote; number, quality, symmetry, fragmentation, and compaction of blastomeres in the cleaving embryos; and size (expansion), ICM, and TE for blastocysts (3, 4, 6, 9, 10, 12, 18, 23, 36, 39). In our proposed upgrade, we emphasize continuous monitoring of the cohort members in the pool by employing the above mentioned growth phase-specific morphological parameters so that the cohort members can be ranked reflecting the differences in their quality, specifically their vigor and implantation potential. Although time-lapse and "-omics" technologies may have advantages in monitoring and ranking the embryos, many laboratories lack these advance technologies. These laboratories have to sharpen their embryo ranking skills based on the methodological resources available to them. No matter what method a laboratory applies in evaluation of embryos, conventional or advanced, the primary goal-ranking the embryos in the cohort-can eventually be achieved by the embryologist's embryo monitoring skills. Based on this optimism, we suggest embryo ranking in both of our proposed upgrade options. Embryo selection for ET will hopefully be better served by the proposed changes in SART grading simply because they require the embryologist to rank the embryos in the respective cohort. Future studies will cultivate this important concept of ranking embryos to develop a comprehensive upgrade plan for the SART system.

Selecting the best embryo for transfer could perhaps be achieved if the SART system would rank the embryos the way students in a class are ranked based on cumulative assessments. A successful embryo ranking would improve the ability to assess the relative vivacity and implantation potential of individual embryos within a cohort, perhaps lessening the need to transfer more than 1 embryo. With accurate embryo ranking, it is not unreasonable to assume that if the best ranked embryo cannot result in implantation, the lower-ranked embryos will be less likely to implant in an equitable uterine environment. Thus, if validated embryo ranking can be achieved, the practice of transferring lower quality embryos with the thought of improving pregnancy rates may become less common.

The primary aim of embryo ranking should be to discriminate the viability and implantation potential among embryos of a cohort (6, 42, 44, 45, 48, 53, 55). Two concepts are becoming increasingly evident from recent studies: i. Improved understanding of embryo implantation is necessary to enhance success in selecting the best embryo, (1, 5, 12, 18, 40, 52-54, 57, 60) and ii. Sequential assessment has an advantage over single assessment in finding the best embryo (8, 11, 38, 42, 51). In addition, recent studies also suggest that advanced high-technology IVF techniques, compared to conventional IVF, are more effective for investigating the viability and implantation potential of embryos (3, 12, 26, 46, 49). In the near future, 2 of these advanced IVF techniques, 1 using timelapse monitoring technology (3, 16, 46, 49, 57, 61) and the other using "-omics" technology, (14, 43, 48, 52-54) may become capable of efficiently discriminating the embryo viability and implantation.

Conclusion

The present study shows the strengths and weaknesses of the SART grading system. SART grading was established for the noble mission of developing a unifying standard method of grading human embryo. It has helped immensely in standardizing grading systems among clinics. The joint effort of SART and AAB in developing an embryo gradingrelated proficiency test homogenizes the embryo grading skills of the embryologists. However, with the shift in clinical practice to transfer fewer embryos, the current SART system falls short in fulfilling its ultimate goal-selecting the right embryo for ET. Apart from SART itself, we found no evaluation studies or clinical trials on the efficiency of the SART grading method. The authors of this manuscript humbly suggest that the time for upgrading the current SART grading system to include a more descriptive ranking of embryos is due. Our proposed additions to the current SART grading system are simple and can be implemented by any IVF laboratory without the need for additional equipment. Moreover, it would better permit a descriptive process to delineate the best embryos Hossain et al.

for transfer rather than a cohort of embryos.

Acknowledgements

There was no funding to support and conflict of interest in this systematic review.

References

- 1. Ceyhan ST, Jackson KV, Racowsky C. Selecting the most competent embryo. In: Carrell DT, Racowsky C, Schlegel PN, Van Voorhis BJ, editors. Biennial review of infertility. New York: Humana Press; 2009; 1: 143-169.
- Boiso I, Veiga A, Edwards RG. Fundamentals of human 2. embryonic growth in vitro and selection of high-quality embryos for transfer. Reprod Biomed Online. 2002; 5(3): 328-350.
- Ciray HN. The scientific basis for utilizing conventional 3. embryo selection parameters: re-visiting fragmentation, blastomere and nuclear symmetry and time spent in cytokines. J Clin Embryol. 2012; 15(4): 82-94.
- Cummins JM, Breen TM, Harrison KL, Shaw JM, Wilson 4. LM, Hennessey JF. A formula for scoring human embryo growth rate in vitro fertilization: its value in predicting pregnancy and in comparison with visual estimates of embryo quality. J In Vitro Fert Embryo Transf. 1986; 3(5): 284-295
- 5. Gardner DK, Lane M, Stevens J, Schlenker T, Schoolcraft WB. Blastocyst score affects implantation and pregnancy outcome: towards a single blastocyst transfer. Fertil Steril. 2000; 73(6): 1155-1158.
- Scott L, Alvero R, Leondires M, Miller B. The morphology 6. of human pronuclear embryos is positively related to blastocyst development and implantation. Hum Reprod. 2000; 15(11): 2394-2403.
- Fisch JD, Rodriguez H, Ross R, Overby G, Sher G. The 7. graduated embryo score predicts blastocyst formation and pregnancy rate from cleavage-stage embryos. Hum Reprod. 2001; 16(9): 170-1975. De Placido G, Wilding M, Strina I, Alviggi E, Alviggi C,
- 8. Mollo A, et al. High outcome predictability after IVF using a combined score for zygote and embryo morphology and growth rate. Hum Reprod. 2002; 17(9): 2402-2409.
- Milki AA, Hinckley MD, Gechardt J, Dasig D, Westphal LM, Behr B. Accuracy of day 3 criteria for selecting the best embryos. Fertil Steril. 2002; 77(6): 1191-1195. 9
- Zollner U, Zollner KP, Hart G, Diet J, Steck T. The use of a detailed zygote score after IVF/ ICSI to obtain good quality 10 blastocysts: the German experience. Hum Reprod. 2002; 17(5): 1327-1333.
- 11. Neuber E, Mahutte NG, Arici A, Sakkas D. Sequential embryo assessment outperforms investigator-driven morphological assessment at selecting a good quality blastocyst. Fertil Steril. 2006; 85(3): 794-796.
- Holte J, Berglund L, Milton K, Garello C, Gennarelli G, 12. Revelli A, Bergh T. Construction of an evidence-based integrated morphology cleavage embryo score for implantation potential of embryos scored and transferred on day 2 after oocyte retrieval. Hum Reprod. 2007; 22(2): 548-557.
- Botros L, Sakkas D, Seli E. Metabolomics and its applica-13 tion for non-invasive embryo assessment in IVF. Mol Hum Reprod. 2008; 14(12): 679-690.
- 14. Scott RT, Treff NR. Assessing the reproductive competence of individual embryos: a proposal for the validation of new "-omics" technologies. Fertil Steril. 2010; 94(3): 791-794.

- 15. Harper J, Magli MC, Lundin K, Barratt CL, Brison D. When and how should new technology be introduced into the IVF laboratory? Hum Reprod. 2012; 27(2): 303-313.
- 16. Thornhill A. Reply: time-lapse parameters could not predict pregnancy: a hasty conclusion? Hum Reprod. 2014; 29(1): 185-186.
- 17. Zollner U, Zollner KP, Steck T, Dietl J. Pronuclear scoring. Time for international standardization. J Reprod Med. 2003; 48(5): 365-369.
- ALPHA Scientists in Reproductive Medicine and ESHRE 18. Special Interest Group of Embryology. The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. Hum Reprod. 2011; 26(6): 1270-1283.
- Stylianou C, Critchlow D, Brison DR, Roberts SA. Embryo 19. morphology as a predictor of IVF success: an evaluation of the proposed UK ACE grading scheme for cleavage stage embryos. Hum Fertil (Camb). 2012; 15(1): 11-17. Gianaroli L, Plachot M, Magli MC. Atlas of embryology.
- 20. Hum Reprod. 2000; 15(Suppl 4): 79.
- de Mouzon J, Goossens V, Bhattacharya S, Castilla JA, Ferraretti AP, Korsak V, et al. Assisted reproductive tech-21. nology in Europe, 2006: results generated from European registers by ESHRE. Hum Reprod. 2010; 25(8): 1851-1862.
- Torello MJ, Ardoy M, Calderon G, Cuadros J, Herrer R, Moreno JM, et al. Criterios ASEBIR de vaoracion morfo-22. logica de Oocitos, Embriones tempranos y Blastocistos. Proceedings of the 3rd ASEBIR Congress; 2005 Nov 17-18; ASEBIR; Zaragoza; 2005.
- Cutting R, Morroll D, Roberts SA, Pickering S, Rutherford 23. A, BFS and ACE. Elective single embryo transfer: guidelines for practice British Fertility Society and Association of Clinical Embryologists. Hum Fertil (Camb). 2008; 11(3): 131-146.
- Racowsky C, Vernon M, Mayer J, Ball GD, Behr B, Pomeroy KO, et al. Standardization of grading embryo 24. morphology. Fertil Steril. 2010; 94(3): 1152-1153.
- 25. Racowsky C, Vernon M, Mayer J, Ball GD, Behr B, Pomeroy KO, et al. Standardization of grading embryo morphology. J Assist Reprod Genet. 2010; 27(8): 437-439
- 26. Machtinger R, Racowsky C. Morphological systems of human embryo assessment and clinical evidence. Reprod Biomed Online. 2013; 26(3): 210-221.
- Racowsky C, Stern JE, Gibbons WE, Barry B, Pomeroy 27. KO, Biggers JD. National collection of embryo morphology data into SARTCORS: associations among cell number, fragmentation and blastomere symmetry on day 3 (d3) with live birth rate. Fertil Steril. 2009; 92 Suppl 3: 0-278.
- Vernon MW, Stern JE, Ball GD, Wininger JD, Mayer JF, Racowsky C. Utility of the national embryo morphology 28. data collection by SART: Correlation between morphologic grade and live birth rate. Fertil Steril. 2009; 92 Suppl 3: P-270.
- Racowsky C, Stern JE, Gibbons WE, Behr B, Pomeroy 29 KO, Biggers JD. National collection of embryo morphology data into society for assisted reproductive technology clinic outcomes reporting system: associations among day 3 cell number, fragmentation and blastomere symmetry, and live birth rate. Fertil Steril. 2011; 95(6): 1985-1989.
- 30. Vernon M, Stern JE, Ball GD, Wininger D, Mayer J, Racowsky C. Utility of the national embryo morphology data collection by SART: Correlation between day-3 morphologic grade and live-birth outcome. Fertil Steril. 2011; 95(8): 2761-2763
- 31. CDC. Assisted reproductive technology-2010 assisted reproductive technology national summary report and 2010

Int J Fertil Steril, Vol 10, No 2, Jul-Sep 2016 146

assisted reproductive technology fertility clinic success rates report. Available from: http://www.cdc.gov/ART/ART2010. (6 Aug 2013).

- CDC. Multiples and Assisted Reproductive Technology-Considering Elective Single Embryo Transfers. Available from: www.cdc.gov/art/preparingforart/eset.htm. (6 Aug 2013).
- 33. SART. Available from: www.sart.org/. (6 Aug 2013).
- AAB (American Association of Bioanalysts). Proficiency test results on embryo grading. Available from: www.aabpts.org. (6 July 2013).
- Hossain A. Potential for empowering, and broadening the application of SART embryo grading system. Proceedings of American Association of Bioanalysts' annual meeting; 2012 May 17-19; Las Vegas, NV; 2012.
- Hossain A. Potential for empowering and broadening the application of the START embryo grading system. J Clin Embryol. 2012; 15(3): 54-66.
- ASRM and SART. Criteria for number of embryos to transfer: a committee opinion. Fertil Steril. 2013; 99(1): 44-46.
- Urman B, Yakin K, Ata B, Balaban B. How can we improve current blastocyst grading systems? Curr Opin Obstet Gynecol. 2007; 19(3): 273-278.
- Bar-Yoseph H, Levy A, Sonin Y, Alboteanu S, Levitas E, Lunenfeld E, et al. Morphological embryo assessment: reevaluation. Fertil Steril. 2011; 95(5): 1624-1628.
- Meseguer M, Rubio I, Cruz M, Basile N, Marcos J, Requena A. Embryo incubation and selection in a time-lapse monitoring system improves pregnancy outcome compared with a standard incubator: a retrospective cohort study. Fertil Steril. 2012; 98(6): 1481-1489.
- Herrero J, Meseguer M. Selection of high potential embryos using time-lapse imaging: the era of morphokinetics. Fertil Steril. 2013; 99(4): 1030-1034.
- Nagy ZP, Dozortsev D, Diamond M, Rienzi L, Ubaldi F, Abdelmassih R, et al. Pronuclear morphology evaluation with subsequent evaluation of embryo morphology significantly increases implantation rates. Fertil Steril. 2003; 80(1): 67-74.
- Katz-Jaffe MG, Gardner DK. Embryology in the era of proteomics. Theriogenology. 2007; 68(Suppl 1): S125-130.
- Katz-Jaffe MG, Gardner DK. Symposium: Innovative techniques in human embryo viability assessment. Can proteomics help to shape the future of human assisted conception? Reprod Biomed Online. 2008; 17(4): 497-501.
- Vergouw CG, Botros LL, Roos P, Lens JW, Schats R, Hompes PG, et al. Metabolomic profiling by near-infrared spectroscopy as a tool to assess embryo viability: a novel, non-invasive method for embryo selection. Hum Reprod. 2008; 23(7): 1499-1504.
- Basile N, Meseguer M. Time-lapse technology: evaluation of embryo quality and new markers for embryo selection. Expert Rev Obstet Gynecol. 2012; 7(2): 175-190.
- Ciray HN, Aksoy T, Goktas C, Ozturk B, Bahceci M. Timelapse evaluation of human embryo development in single versus sequential culture media--a sibling oocyte study. J Assist Reprod Genet. 2012; 29(9): 891-900.

- Gardner DK, Wale PL. Analysis of metabolism to select viable human embryos for transfer. Fertil Steril. 2013; 99(4): 1062-1071.
- NIH (national institutes of health). Clinical Validation of Embryo Cinematography. Available from: http://clinicaltrials.gov/ct2/show/study/NCT01549262?term=nct0154926 2&rank=1. (6 Aug 2013).
 Steer CV, Mills CL, Tan SL, Campbell S, Edwards RG.
- Steer CV, Mills CL, Tan SL, Campbell S, Edwards RG. The cumulative embryo score: a predictive embryo scoring technique to select the optimal number of embryos to transfer in in vitro fertilization and embryo transfer programme. Hum Reprod. 1992; 7(1): 117-119.
 Neuber E, Rinaudo P, Trimarchi JR, Sakkas D. Sequential
- Neuber E, Rinaudo P, Trimarchi JR, Sakkas D. Sequential assessment of individually cultured human embryos as an indicator of subsequent good quality blastocyst development. Hum Reprod. 2003; 18(6): 1307-1312.
- Brison DR, Houghton FD, Falconer D, Roberts SA, Hawkhead J, Humpherson PG, et al. Identification of viable embryos in IVF by non-invasive measurement of amino acid turnover. Hum Reprod. 2004; 19(10): 2319-2324.
 Katz-Jaffe MG, Gardner DK, Schoolcraft WB. Proteomic
- Katz-Jaffe MG, Gardner DK, Schoolcraft WB. Proteomic analysis of individual human embryos to identify novel biomarkers of development and viability. Fertil Steril. 2006; 85(1): 101-107.
- Dominguez F, Gadea B, Esteban FJ, Pellicer A, Simon C. Comparative protein-profile analysis of implanted versus non-implanted human blastocyst. Hum Reprod. 2008; 23(9): 1993-2000.
- Lemmen JG, Agerholm I, Ziebe S. Kinetic markers of human embryo quality using time-lapse recordings of IVF/ ICSI-fertilized oocytes. Reprod Biomed Online. 2008; 17(3): 385-391.
- Montag M, Liebenthron J, Köster M. Which morphological scoring system is relevant to human embryo development? Placenta. 2011; 32(Suppl 3): S252-256.
- Chen AA, Tan L, Suraj V, Reijo Pera R, Shen S. Biomarkers identified with time-lapse imaging: discovery, validation, and practical application. Fertil Steril. 2013; 99(4): 1035-1043.
- Ziebe S, Petersen K, Lindenberg S, Andersen AG, Gabrielsen A, Andersen AN. Embryo morphology on cleavage stage: how to select the best embryos for transfer after in vitro fertilization. Hum Reprod. 1997; 12(7): 1545-1549.
 Van Royen E, Mangelschots K, De Neubourg D, Valken-
- Van Royen E, Mangelschots K, De Neubourg D, Valkenburg M, Van de Meerssche M, Ryckaert G, et al. Characterization of a top quality embryo, a step towards single embryo transfer. Hum Reprod. 1999; 14(9): 2345-2349.
- Heitmann RJ, Hill MJ, Richter KS, DeCherney AH, Widra EA. The simplified SART embryo scoring system is highly correlated to implantation and live birth in single blastocyst transfers. J Assist Reprod Genet. 2013; 30(4): 563-567.
- ASRM. Embryo development: new technologies and science. Postgraduate course number 5. Proceedings of the ASRM annual meeting; 2012 Oct 19-25; Birmingham, Alabama, USA; ASRM; 2012.