



Letter to Editor

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Human blastomere rotation in early cleavage embryos is not associated with reduced implantation: Evidence from time–lapse videography

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Dear Editor,

Time-lapse videography of human embryos allows for the easy visualization of the embryos without removing them from the protective environment of the incubator[1], the measurement of various morphokinetic (quantitative) parameters[2], and the identification of abnormalities of growth (qualitative parameters) such as direct cleavage[3], reverse cleavage[4] and intercellular contact of blastomeres[5]. This extensive viewing gives the opportunity to apply algorithms to predict implantation based upon morphokinetic parameters[2,6] or a combination of qualitative and quantitative measures[7]. However, one major limitation is the poor transferability of algorithms between laboratories[8] presumably because embryos exhibit plasticity when grown in different laboratories[9]. Qualitative parameters are more reproducible markers of embryo quality between laboratories given their binary nature[9], (*i.e.* present or absent), and so any qualitative parameter associated with reduced implantation may prove useful in an algorithm.

Keywords:

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Blastomere rotation
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Embryo rolling, also known as blastomere rolling or movement, involves blastomeres moving around each other creating a rotation but without dividing. In a recent set of proposed guidelines on the nomenclature and annotation of dynamic human embryo monitoring by time-lapse[10], embryo rolling was listed as an additional annotation that might be indicative of irregular cleavage events, although no evidence was presented on its clinical usefulness. More recently, blastomere movement was categorized into 3 types and their occurrence at the 2-cell stage was shown to be independent of pregnancy outcomes[11]. It is still unclear in terms of the impact of such movement or rolling in the spatial perspective apart from the temporal perspective. A retrospective analysis of time-lapse recordings was therefore undertaken to determine if the degree of blastomere rolling is associated with a reduced implantation rate, and to evaluate whether blastomere rolling may be a useful time-lapse videography parameter for the inclusion in an algorithm to predict implantation potential.

A retrospective audit was undertaken by using de-identified cycle information from *in vitro* fertilization (IVF) or intracytoplasmic sperm injection treatment cycles at Fertility North (Perth, Western Australia, Australia). The 155 women ranged from 24.3 to 44.5 years in age, with a mean age of 34 years, and all had signed a

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consent (FNC1) for the use of stored data to be used for practice management and quality assurance. This form had been approved by the Joondalup Health Campus Human Research Ethics Committee becoming effective on 17th February 2017. Cycles included in the analysis were the women's first IVF cycle and only if the woman was having a single embryo transfer of an embryo showing no evidence of direct or reverse cleavage. All women had embryo transfer on day 3, and those women who required extended culture with a blastocyst transfer were excluded. After insemination *via* either conventional IVF or intracytoplasmic sperm injection, fertilized oocytes were then placed into the Embryoscope™ incubator (Vitrolife, Denmark) and cultured until day 3, with images being taken every 10 min at 7 focal planes on each embryo, as previously described[7]. Embryos for transfer were viewed retrospectively using the EmbryoViewer software (Vitrolife, Sweden), and blastomere movement was tracked up until it was removed from the incubator for transfer. Successful implantation of the embryo was confirmed by the detection of a fetal heartbeat at 7 weeks of gestation. Quantification of embryo rolling activity was performed manually by one scientist (Emma P Langdon) using a measuring device with a quadrant grid placed over the circumference of the embryo on the screen. Embryos were assessed at the 2-cell and 4-cell stages, and rolling activity was graded as (a) 0° being no rolling; (b) rolling of 1°-90° and (c) rolling between 90° and 180°. Rolling was significantly more prevalent in 2-cell embryos (34/155, 21.9%) than 4-cell embryos (5/155, 3.2%; $\chi^2=24.67$, $P<0.001$). For 2-cell embryos, there was no difference in implantation rates ($\chi^2=0.0478$, $P>0.05$) when there was 0° (51/121, 42.1%), 1°-90° (12/27, 44.4%) or >90° (3/7, 42.9%) rotation. The low level of rotation in 4-cell embryos made statistical analysis unreliable, and only one embryo showed rolling at both stages. Using multivariate logistic regression analysis (odds ratio and 95% confidence interval), there was no effect upon implantation of blastomere angle of rotation at 2-cell (1.167, 0.630-2.163; $P=0.624$) or 4-cell (5.494, 0.586-51.540; $P=0.136$) or embryo grading with conventional criteria (1.145, 0.562-2.333; $P=0.750$), but maternal age had a negative effect (0.923, 0.858-0.994; $P=0.034$). Interestingly, maternal age appeared to show a trend towards significance in affecting the incidence of rolling ($P=0.057$), as the mean age of women with rolling embryos was higher than those with non-rolling embryos [(35.4 ± 4.7) years old *vs* (33.7 ± 4.5) years old].

In summary, embryo rolling has been suggested in a contemporary European guideline[10] as being an annotation worth recording with time-lapse videography. Unfortunately, the present study has shown that embryo rolling is not a useful indicator of implantation potential either for embryo selection or deselection. This lack of predictive value means it should not be considered as a parameter for inclusion in an algorithm to rank the implantation potential of human embryos.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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