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Review

Can time-lapse parameters predict embryo ploidy? A systematic review

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KEY MESSAGE

Studies reporting an association between morphokinetic parameters and embryo ploidy status are controversial and do not support the predictive value of time-lapse analysis for embryo aneuploidy screening.

A B S T R A C T

Embryo morphology assessment performs relatively poorly in predicting implantation. Embryo aneuploidy screening (PGS) has recently improved, but its clinical value is still debated, and the development of a cheap non-invasive method for the assessment of embryo ploidy status is a highly desirable goal. The growing implementation of time-lapse devices led some teams to test the effectiveness of morphokinetic parameters as predictors of embryo ploidy, with conflicting results. The aim of this study was to conduct a comprehensive review of the literature on the predictive value of morphokinetic parameters for embryo ploidy status. A systematic search on *PubMed* was conducted using the following key words: time-lapse, morphokinetic, aneuploidy, IVF, preimplantation genetic screening, PGS, chromosomal status. A total of 13 studies were included in the analysis. They were heterogeneous in design, patients, day of embryo biopsy, statistical approach and outcome measures. No single or combined morphokinetic parameter was consistently identified as predictive of embryo ploidy status. In conclusion, the available studies are too heterogeneous for firm conclusions to be drawn on the predictive value of time-lapse analysis for embryo aneuploidy screening. Hence, morphokinetic parameters should not be used yet as a surrogate for PGS to determine embryo ploidy *in vitro*.

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https://doi.org/10.1016/j.rbmo.2018.01.001
1472-6483/

Introduction

The ultimate objective of assisted reproduction techniques is to offer patients the highest healthy live birth rate and the lowest multiple pregnancy rate. Morphology is the most common method used for evaluating embryo quality *in vitro*; however, it performs poorly in identifying the embryo with the highest implantation potential, even at the blastocyst stage (Gardner et al., 2015). This prevents many IVF teams implementing a largely single embryo transfer policy (Kushnir et al., 2017). Embryo morphology assessment has little predictive power for implantation because of its weak association with embryo ploidy status, which is the most critical factor for sustained implantation in IVF (Gardner et al., 2015). Embryo aneuploidy screening, also known as preimplantation genetic screening (PGS), allows the identification of embryo chromosomal status. Several technical improvements over the past decade have led to the identification of trophectoderm biopsy and array comparative genetic hybridization (aCGH) or next-generation sequencing as the technique of choice for PGS (Gardner et al., 2015). Although shown to be efficient and clinically relevant in some studies, this technique suffers from some limitations. Indeed, it raises regulatory issues in some countries (Harper et al.,2014), it can be considered invasive, it requires specific technical skills, it can take up to 24 h before obtaining the result according to the technique, and it still remains expensive (Gardner et al., 2015; Sermon et al., 2016). Therefore, the development of a non-invasive, rapid, and cheaper method for assessing embryo ploidy status would represent a breakthrough in the field of IVF (Gardner et al., 2015). The recent implementation of time-lapse devices in more IVF laboratories, allowing continuous embryo monitoring in stable culture conditions, has raised hopes among many embryologists. Although the clinical value of this strategy has been validated in some studies (Petersen et al., 2016; Rubio et al., 2014), literature reviews have provided various results (Armstrong et al., 2015; Chen et al., 2017), leading to ongoing debate on this topic (Harper et al., 2017). Among the numerous studies reported on time-lapse, some have evaluated the association between morphokinetic parameters and embryo ploidy to evaluate if time lapse could be the awaited non-invasive method for embryo aneuploidy screening. These studies provided discordant conclusions. They were conducted in various settings, with heterogeneous design, procedures and populations, ultimately failing to yield a firm conclusion.

Therefore, the aim of this study was to conduct a comprehensive review of the literature on the predictive value of morphokinetic parameters for embryo ploidy status.

Materials and methods

We conducted a systematic search on *Medline* of all articles related to time-lapse (or morphokinetic) analysis of human preimplantation embryo development and its association with aneuploidy evaluated with PGS technology published up to April 2017 using the *Pubmed* database with the following keywords: time-lapse, morphokinetic, aneuploidy, IVF, preimplantation genetic screening, PGS and chromosomal status.

This search was conducted according to Prisma guidelines (http://www.prisma-statement.org/), and only full-length articles in English dealing with clinical observations in humans were included. The principal summary measure was the predictive value of time-lapse parameters for embryo ploidy. Comparison with a control group was not mandatory. No statistical tests were carried out with these data. All references were screened, and eligibility assessed by two independent reviewers (AR and JL). A third author (TF) checked the final list of references and made the final decision in case of disagreement.

The following data were extracted from the selected articles: study design, number of couples, clinical indication for PGS, number of embryos, embryo stage for biopsy, PGS technique, time-lapse device, embryo culture atmosphere, morphokinetic parameters studied, euploidy rate, clinical outcome measure, adjustment with patients' characteristics, relevant morphokinetic variables identified, statistical approach and main conclusion.

Results

A total of 161 studies were screened for eligibility. All records were screened, and 148 were excluded. A total of 15 full-text articles were assessed in detail for eligibility, among which two were excluded because they were conducted in preimplantation genetic diagnosis cycles rather than in PGS cycles, thus not allowing full information on embryo ploidy status to be obtained. Finally, 13 were selected for data collection on the predictive value of morphokinetic analysis for human embryo ploidy (Balakier et al., 2016; Basile et al., 2014; Campbell et al., 2013a, 2013b; Chavez et al., 2012; Chawla et al., 2015; Del Carmen Nogales et al., 2017; Kramer et al., 2014; Minasi et al., 2016; Mumusoglu et al., 2017; Patel et al., 2016; Rienzi et al., 2015; Yang et al., 2014) (**Table 1**).

Most studies were retrospective. Only two were prospective, with one conducted on embryos donated for research (Chavez et al., 2012) and the other one on clinical cycles (Yang et al., 2014). The number of couples and IVF–PGS cycles included in these studies varied significantly, ranging from 25 (Campbell et al., 2013a) to 444 (Minasi et al., 2016), and from 25 (Campbell et al., 2013a) to 530 (Minasi et al., 2016), respectively. Similarly, the number of embryos included in the analysis was heterogeneous in these studies, ranging from 53 (Chavez et al., 2012) to 928 (Minasi et al., 2016).

The clinical indication for PGS varied notably among these studies, even if most of them were conventional PGS cases, i.e. advanced maternal age, recurrent implantation failure and recurrent miscarriage. Only one study was conducted in PGS cycles for sex selection (Chawla et al., 2015) and one in couples with previous aneuploidy conceptions (Yang et al., 2014). Two studies included cases of PGS for severe male factor infertility in addition to conventional PGS indications (Balakier et al., 2016; Campbell et al., 2013a). Clinical indication for PGS could not be found in two studies (Campbell et al., 2013b; Minasi et al., 2016).

Embryo biopsy was carried out at cleavage stage in five studies (Basile et al., 2014; Chavez et al., 2012; Chawla et al., 2015; Del Carmen Nogales et al., 2017; Patel et al., 2016) and at the blastocyst stage in eight studies (Balakier et al., 2016; Campbell et al., 2013a, 2013b; Kramer et al., 2014; Minasi et al., 2016; Mumusoglu et al., 2017; Rienzi et al., 2015; Yang et al., 2014). When performed at the cleavage stage, no morphokinetic data were provided on subsequent embryo development, except in one study (Patel et al., 2016).

All studies but one (Chavez et al., 2012) were carried out with the Embryoscope® as time-lapse device. Although unlikely, whether the type of time-lapse device used could influence the eventual association of morphokinetic parameters with embryo ploidy status is not

Table 1 – Principal characteristics of the studies reporting on the value of morphokinetic parameters as predictors of embryo ploidy. Studies are listed in chronological order.

	Study design	Number of couple/ cycles	Clinical indication for PGS	Number of embryos	Embryo stage for biopsy	PGS technique	Time- lapse device	Atmosphere
Chavez et al. (2012)	Prospective on donated zygotes	45/NA	NA	53	Day 2	aCGH	custom-built miniature microscope system	6% CO2, 5% O2
Campbell et al. (2013a)	Retrospective	25/25	AMA, RIF, recurrent miscarriage, severe male factor	98	Blastocyst	aCGH or SNP array	Embryoscope®	5.5% CO2, 5% O2
Campbell et al. (2013b)	Retrospective/ validation study	69/69	Unknown	88	Blastocyst	aCGH or SNP array	Embryoscope®	5.5% CO2, 5% O2
Basile et al. (2014)	Retrospective	87/125	RIF and recurrent miscarriage	504	Day 3	aCGH	Embryoscope®	Not described
Kramer et al. (2014)	Retrospective/ validation study	25/25	Recurrent miscarriage, AMA, others	149	Blastocyst	aCGH	Embryoscope®	6% CO2, 5% O2
Yang et al. (2014)	Prospective	NA	RPL, RIF, PCA	285	Blastocyst	aCGH	Embryoscope®	6% CO2, 5% O2
Chawla et al. (2015)	Retrospective	132/132	Sex selection	460	Day 3	aCGH	Embryoscope®	Not described
Rienzi et al. (2015)	Retrospective/ validation study	138/138	AMA, RIF, recurrent miscarriage	455	Blastocyst	aCGH	Embryoscope®	6% CO2, 5% O2
Minasi et al. (2016)	Retrospective	444/530	Unknown	1730/928 cultured in time-lapse	Blastocyst	aCGH	Embryoscope®	6% CO2, 5% O2
Balakier et al. (2016)	Retrospective	296 (113 with PGS)/296 (113)	AMA, PCOS, male factor and others	2441/607 with PGS	Blastocyst	aCGH	Embryoscope®	6% CO2, 5% O2
Patel et al. (2016)	Retrospective	26/29	AMA, RIF, recurrent miscarriage	167	Day 3	aCGH	Embryoscope®	Not described
Mumusoglu et al. (2017)	Retrospective/ validation study	103/103	AMA, PGD	415	Blastocyst	aCGH	Embryoscope®	6.8% CO2, 5% O2
Del Carmen Nogales et al. (2017)	Retrospective	112/112	AMA, RIF and recurrent miscarriage	485	Day 3	aCGH	Embryoscope®	Not described

(*continued on next page*)

Table 1 – (*continued*)

	Euploidy rate (%)	Clinical outcome measures	Morphokinetic parameters studied	Relevant morphokinetic variables	Adjusted with patients' characteristics	Statistical approach	Conclusion
Chavez et al. (2012)	24.5	NA	All up to day 2	cc2, s2	No	Mean comparison	Cell-cycle parameters could be diagnostic of ploidy and have clinical relevance.
Campbell et al. (2013a)	38.8	NA	All up to blastocyst stage	tSB, tB	No	Mean comparison; Fisher's test; decision-tree model	Late time-lapse parameters increase the probability of selecting euploid embryos.
Campbell et al. (2013b)	NA[a]	CPR and LBR	All up to blastocyst stage	tSB, tB	No	Decision-tree model	Late time-lapse parameters increases the probability of selecting euploid embryos.
Basile et al. (2014)	28.3	Implantation rate and CPR	All up to day 3	t5, t5–t2, cc3	No	Mean comparison; quartiles; logistic regression; ROC curve; decision tree	Time-lapse-based algorithm increases the probability of selecting euploid embryos.
Kramer et al. (2014)	43	NA	All up to blastocyst stage	None	No	Chi-squared ; ANOVA, ROC curve	Failure of Campbell's model. Time-lapse parameters cannot be used to select euploid blastocysts
Yang et al. (2014)	46	Implantation rate, OPR	All up to blastocyst stage	None	No	Mean and frequency comparison	Time-lapse increases the probability of non-invasively selecting normal embryos.
Chawla et al. (2015)	42.8	NA	All up to day 3	t5–t2, cc3	No	Mean and frequency comparison; logistic regression; ROC curve	Time-lapse increases the probability of non-invasively selecting normal embryos.
Rienzi et al. (2015)	40.9	OPR and LBR	All up to blastocyst stage	None	Yes	Bivariate generalized mixed models, linear logistic model	Failure of Campbell and Basile's models. Time-lapse parameters Cannot be used to select euploid blastocysts.
Minasi et al. (2016)	34.9	CPR	All up to blastocyst stage	tSB, tB, tEB, tHB	Yes	Mixed logistic models; mixed linear regression	Late time-lapse parameters are different in euploid and aneuploidy embryos but do not improve clinical outcome.
Balakier et al. (2016)	49.8	Implantation rate, CPR and LBR	All up to blastocyst stage plus multinucleation at two- and four-cell stages	NA	Yes	Mean comparison, logistic regression	High implantation rate, even for embryos with multinucleation at the two-cell stage.
Patel et al. (2016)	24.5	NA	All up to blastocyst stage	t5–t2, cc3	No	Mean comparison; chi squared; quartiles; logistic regression; ROC curve	Time-lapse-based algorithm (Basile et al., 2014) increases the probability of selecting euploid embryos but should not replace PGS.
Mumusoglu et al. (2017)	41.7	NA	All up to blastocyst stage	t9, tM, tSB, tB, tEB	Yes	Clustered data analysis	Failure of most models and late time-lapse parameters to predict euploidy.
Del Carmen Nogales et al. (2017)	38.1	NA	All up to day 3	t3, t5–t2	No	Mean comparison; chi squared; quartiles; logistic regression analysis	Time-lapse is useful to discard embryos with high risk of complex aneuploidies.

[a] Validation study conducted in non-PGS cycles.

aCGH, array comparative genetic hybridization; AMA, advanced maternal age; ANOVA, analysis of variance; CPR, clinical pregnancy rate; LBR: live birth rate; NA, not applicable; OPR, ongoing pregnancy rate; PCA, previous aneuploidy conceptions; PCOS, polycystic ovary syndrome; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening; RIF, recurrent implantation failure; ROC, receiver operatory characteristic; SNP, single nucleotide polymorphism.

known, as no comparative study has yet been conducted. Although embryo culture atmosphere was not reported in four studies (Basile et al., 2014; Chawla et al., 2015; Del Carmen Nogales et al., 2017; Patel et al., 2016), it was carried out under low oxygen tension in the nine remaining studies.

All studies on PGS technique were based on aCGH, allowing the evaluation of all chromosomes. Only two studies from the same group reported using both aCGH and single nucleotide polymorphism array (Campbell et al., 2013a, 2013b). Euploidy rate was reported in 12 studies (not applicable in Campbell et al., (2013b)), which was conducted in non-PGS cycles) and ranged from 24.5% (Chawla et al., 2015) to 49.8% (Balakier et al., 2016), with a trend towards higher euploidy rate when biopsy was carried out at the blastocyst stage than at the cleavage stage.

Six studies included clinical outcome measures after a PGS cycle (Balakier et al., 2016; Basile et al., 2014; Campbell et al., 2013b; Minasi et al., 2016; Rienzi et al., 2015; Yang et al., 2014). Most of them used clinical pregnancy rate; some also used implantation rate or live birth rate.

Concerning the morphokinetic parameters studied, all studies reported morphokinetic parameters up to embryo biopsy, including pronuclei appearance and fading, cellular cleavage timings and intervals, compaction and blastocyst formation and expansion. One study also reported multinucleation at the two-cell and four-cell stages (Balakier et al., 2016). Among the 13 selected studies, 11 aimed at identifying relevant morphokinetic variables, which could be significantly different between euploid and aneuploidy groups, and finally help in selecting euploid embryos for transfer, whereas two consisted of external validation of previously published models (Campbell et al., 2013b; Kramer et al., 2014). Studies conducted in early cleavage embryos mostly identified intervals between cleavages rather than cleavage timings as relevant for identifying euploid embryos (Basile et al., 2014; Chavez et al., 2012; Chawla et al., 2015; Del Carmen Nogales et al., 2017; Patel et al., 2016). Some studies conducted at the blastocyst stage identified late morphokinetic parameters, i.e. compaction or blastulation stages, but not early ones (cleavage stages) as relevant predictors of embryo ploidy (Campbell et al., 2013a; Minasi et al., 2016; Mumusoglu et al., 2017). Not all studies, however, conducted at the blastocyst stage reported significant morphokinetic differences between euploid and aneuploid embryos (Rienzi et al., 2015; Yang et al., 2014).

In addition to the studies aimed at identifying predictive morphokinetic markers, other investigators have conducted external validation of some previously published morphokinetic models. The model by Campbell et al. (2013a) was evaluated externally by Kramer et al. (2014) and by themselves in a separate cohort (Campbell et al., 2013b). Patel et al. (2016) tested the performance of the model by Basile *et al.* (2014). Rienzi et al. (2015) and Mumusoglu et al. (2017) tested the performance of both Campbell's and Basile's models, both concluding that the models failed to predict embryo euploidy.

Statistical approach varied greatly among these 13 studies, depending on the main outcome measure and study design. Most studies performed basic univariate analysis to compare morphokinetic parameters in euploid and aneuploid embryos. Most studies also carried out logistic regression analysis to identify some independent predictors of embryo ploidy, eventually integrated in a predictive model. The sensitivity and specificity of the model was then evaluated with receiver operator characteristic curve analysis when appropriate (Basile et al., 2014; Chawla et al., 2015; Kramer et al., 2014; Patel et al., 2016). Importantly, few authors emphasized the possible bias of considering embryos as individuals in statistical analysis, as all embryos originating from the same patient are influenced by those patient-specific characteristics and are, therefore, not independent entities ('cohort effect'). Therefore, these investigators strongly recommended the adjustment of statistical analysis and its results with patient characteristics (Kirkegaard et al., 2016; Mumusoglu et al., 2017).

Finally, most, but not all, investigators reported significant differences in morphokinetic pattern between euploid and aneuploid embryos, but the clinical significance of these results was absent to modest (**Table 1**). Although the conclusions raised by investigators varied significantly, all concluded that time-lapse should not be considered as an appropriate non-invasive method for embryo ploidy assessment.

Discussion

This comprehensive review of the literature on the effectiveness of time-lapse as a predictor of embryo ploidy highlights the large heterogeneity of the studies published to date, concluding that neither a unique morphokinetic nor combined parameters could predict embryo ploidy with enough sensitivity, specificity, or both, to be used clinically for embryo selection.

First, most studies reviewed here were carried out retrospectively and within a single clinic, with different sample sizes. Although this does not necessarily lessen their value, there is a need for large multi-centre studies to enhance the overall quality of the evidence generated.

The second question raised in this review concerns the type of time-lapse device. Although this should theoretically not lead to a significant difference in measuring morphokinetic parameters, it should be noted that all studies, bar one, were conducted with the Embryoscope®, the first and most widely implemented time-lapse device to date, thus providing a certain inter-study homogeneity on technical aspects. Whether the use of different approaches, as well as devices and analytical methods, in the field of time-lapse could account for the conflicting findings found within the literature is hard to determine and quantify precisely. This should be explored in further studies. The issue of inter-operator variability in annotating morphokinetic parameters could eventually be raised, thus encouraging the development of automated annotation tools (Castello et al., 2016; Molder et al., 2015). Although this variability has been shown to be low (Sundvall et al., 2013), it is unclear how widely guidelines for annotation practice (Ciray et al., 2014) are followed and how consistent time-lapse users are in their operating procedures. Whether more recent time-lapse devices with automated detection of cell cleavages will provide different results and lead to different conclusions still needs to be tested.

Although the clinical indication for PGS varied notably among the studies, the main indications were advanced maternal age, recurrent implantation failure and recurrent miscarriage. It is, therefore unlikely that differences in clinical indications would explain the discrepancy in conclusions of the studies cited here. Some patient characteristics, however, have been shown by some investigators to be critical for interpretating morphokinetic studies, as embryos from the same patient tend to cluster (Kirkegaard et al., 2016; Mumusoglu et al., 2017). This point will be discussed further in the discussion.

The most significant difference between the studies reviewed here was the stage at which embryo biopsy was carried out. Indeed, embryo biopsy was carried out at the cleavage stage in five studies (Basile

et al., 2014; Chavez et al., 2012; Chawla et al., 2015; Del Carmen Nogales et al., 2017; Patel et al., 2016), whereas embryo biopsy was carried out at the blastocyst stage in eight studies (Balakier et al., 2016; Campbell et al., 2013a, 2013b; Kramer et al., 2014; Minasi et al., 2016; Mumusoglu et al., 2017; Rienzi et al., 2015; Yang et al., 2014). The respective advantages and disadvantages of these two strategies have been debated in recent years (Scott et al., 2013; Sermon et al., 2016). Trophectoderm biopsy, however, has gained increasing interest, and is more widely used, as it is considered to optimize the whole procedure when fewer embryos are available, but with higher implantation potential than cleavage stage biopsy (Sermon et al., 2016). Moreover, it allows the biopsy of several cells and probably allows a better management of embryo mosaicism (Capalbo et al., 2013). Whether trophectoderm biopsy is more relevant than cleavage stage biopsy for PGS was not the topic of this review. Recent data, however, obtained in arrested embryos cultured in time-lapse device and extensively analysed by genome-wide SNP genotyping in both polar bodies and karyomapping of disaggregated embryonic cells, suggest that genomic imbalance and partial genome loss occurring during early cleavage affects embryonic gene expression and blocks the morula to blastocyst transition (Ottolini et al., 2017). This reinforces the value of trophectoderm biopsy compared with performing biopsy pre-zygote genome activation at the cleavage stages of development. The present comprehensive review of the literature could eventually be repeated and specifically focus on morphokinetic follow-up up to the blastocyst stage followed by trophectoderm biopsy when more studies are available.

Various technical approaches can be used for PGS. Here, all studies were based on aCGH, with two of them also using single nucleotide polymorphism array Campbell et al. (2013a, 2013b). Whether the implementation of new technologies for embryo aneuploidy screening, such as next-generation sequencing, brings new insights into the association between morphokinetic parameters and embryo ploidy should be explored in further studies.

Embryo culture conditions could constitute a bias in assessing morphokinetics. Indeed, low oxygen tension has been shown to result in significantly different morphokinetic patterns (Kirkegaard et al., 2016) than atmospheric ones. Although this was not reported in four studies, most of them included in this review were conducted under low oxygen tension.

Six studies included clinical outcome measures after PGS cycle (Balakier et al., 2016; Basile et al., 2014; Campbell et al., 2013b; Minasi et al., 2016; Rienzi et al., 2015; Yang et al., 2014). Interpreting these data, however, remains hazardous, as none of them was specifically designed to determine the relevance of morphokinetic parameters in predicting clinical outcome after PGS cycle.

Concerning the type of morphokinetic parameters analysed, studies with trophectoderm biopsy obviously included additional data compared with those conducted in cleavage stage embryos. These studies mostly concluded that intervals between cellular cleavages were more relevant than cleavage timings for the selection of euploid embryos (Basile et al., 2014; Chavez et al., 2012; Chawla et al., 2015; Del Carmen Nogales et al., 2017; Patel et al., 2016). This value of cellular intervals was previously suggested in clinical studies conducted in IVF cycles aimed at identifying morphokinetic predictors of implantation (Meseguer et al., 2011). Not all studies carried out at the blastocyst stage reported significant morphokinetic differences between euploid and aneuploid embryos (Rienzi et al., 2015; Yang et al., 2014), but most did (Campbell et al., 2013a; Minasi et al., 2016; Mumusoglu et al., 2017). Interestingly, these studies did not confirm the value of these early parameters as relevant predictors of embryo ploidy (Campbell et al., 2013a; Minasi et al., 2016; Mumusoglu et al., 2017). As genetic events, such as mitotic errors, genomic imbalance or genome loss, occur during late embryo development after embryo genomic activation (Capalbo et al., 2013; Ottolini et al., 2017), this might account for this apparent loss of predictive value of early morphokinetic parameters for embryo ploidy when evaluated at the blastocyst stage. This, however, remains to be confirmed in longitudinal studies with cleavage stage and blastocyst biopsy successively performed.

Finally, the recently raised issue of statistical approach and adjustment for patients' characteristics to take clustering effect into account in time-lapse studies (Kirkegaard et al., 2016) was also questioned in three studies included in this review (Minasi et al., 2016; Mumusoglu et al., 2017; Rienzi et al., 2015), and, particularly, in one of them (Mumusoglu et al., 2017). The concept of this approach is that embryos generated from one couple should not be considered individually. Instead, the statistical approach should consider intra-patient clustering effect to determine the extent to which the morphokinetic variation observed is independent of patient's clinical or cycle characteristics (Kirkegaard et al., 2016). In the study by Mumusoglu et al. (2017), 16–47% of the observed variation of morphokinetic parameters was found to be patient-related. Interestingly, the investigators concluded that considering embryos as individuals in statistical analysis could represent a major bias, leading to overestimated statistical associations and potentially incorrect conclusions, especially in heterogeneous populations. This was also highlighted in a commentary published in 2014 (Ottolini et al., 2014), in which the authors comment on the studies reported by Campbell et al. (2013a), Campbell et al. (2013b). The authors of this commentary particularly questioned the reported association between morphokinetic parameters and implantation, as no female age was provided, and insisted on the importance of confounding factors such as age in this non-age-controlled cohort. This was further debated by Campbell et al. (2014), who stated that age was not the likely causal factor of observed delays in blastulation.

Conclusion

This comprehensive review of the literature demonstrates that morphokinetic parameters should not yet be used as a surrogate for PGS to determine chromosomal status of the preimplantation embryo. More large-scale studies, conducted in homogeneous populations with standard culture and biopsy protocol, using relevant statistical approaches adjusted to patients' characteristics, are needed to gain insight into the putative association between embryo morphokinetic parameters and ploidy, ultimately improving IVF clinical outcome.

ARTICLE INFO

Article history:
Received 8 August 2017
Received in revised form 3 January 2018
Accepted 4 January 2018
Declaration: The authors report no financial or commercial conflicts of interest.

Keywords:
Time-lapse
Morphokinetic
Aneuploidy
Preimplantation genetic screening

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