The journey toward personalized embryo selection algorithms

Fully submerged in the computer age, nowadays we have access to vast amounts of information in all areas. In parallel, the tools and methods that make it possible to exploit, analyze, and understand this information have equally evolved, raising the possibility, and almost the obligation, of taking full advantage of stated information to improve processes and maximize results. As a consequence of this, we are faced with the possibility of personalizing processes and offering the optimal variant of a product to every person. We can see this every day when we receive personalized advertisements in social media that perfectly match our interests and situation. This trend of personalization is even reaching medicine and health care in general. All this is thanks to the training of artificial intelligence algorithms with the great amount of information available. This is a reality that is no different in the field of assisted reproduction.

We manage extensive information about demographic and personal characteristics of patients, their habits, causes of infertility, ovarian stimulation strategy, embryo culture systems, and so on. On the other hand, the established use of time-lapse imaging systems provides us with detailed information about the whole development of the embryo, not only at the morphological level but also about the exact timing at which the embryos reach every developmental milestone. Not only can we consider morphokinetics as numerical data, but it is possible to analyze complete videos of embryonic development as a whole, to determine the morphological characteristics in an automatic and objective way and even extrapolate to abstract variables that the human eye is unable to discern. Thanks to this technology, we have been able to relate the variability in these parameters to embryo viability and their capacity to give rise to a pregnancy and a healthy live birth.

Numerous studies have resulted in the development of embryo selection algorithms (ESAs) that are capable of predicting embryo viability based on their morphological and morphokinetic characteristics. However, we must not forget that each of these algorithms has been developed from a defined set of embryos with a specific context of characteristics, referring to both the patient population to which they belong and the process of fertilization and culture in the laboratory, which is necessarily different from any other set. It is for this reason that the application, both retrospective and prospective, of these algorithms in different sets of embryos, with their different contexts, does not always render the same results, with a loss of predictive capacity. In other words, we could say that the framework of each data subset provides a series of confounding variables that can affect the very parameters used in these algorithms, even before reaching the endometrial receptivity barrier, that were not taken into account originally.

Within this context, the descriptive article presented by Barrie et al. (1) sheds some light on the matter by performing an extensive statistical study with the aim of determining the effect of numerous possible confounding factors on main morphokinetic parameters collected by a time-lapse imaging system such as the EmbryoScope. Multivariate regression found a significant effect on several morphokinetic parameters of variables related to the patient, such as age and body mass index (BMI), or the fertilization technique used. This article demonstrates, once again, that some features of the patient affect embryo quality and morphokinetics, whereas others affect endometrial receptivity and then may interfere with the prediction abilities of any ESAs. Therefore, it is necessary to distinguish between these types of confounders, because those that affect morphokinetics may not be actual confounders by themselves but might be affecting embryo quality.

Because of the multivariate effects of patient features that Barrie et al. refer to, if we limit investigations to search for effects on the typical dependent variables (morphology and clinical results), we may not find significant results, as we are unknowingly introducing other variables that have their own effects at different levels. We can take BMI as an example. An article by Bellver et al. from 2010 (2) concluded that BMI does not seem to affect embryonic morphology. However, if we expand the range of dependent variables (in this case using morphokinetics), we can see some effects (3), concluding that the parameters found to be affected by BMI vary between studies, which only confirms what Barrie et al. suggest in their article: these different results may be due to the variability of each population, or, more specifically, the multifactorial effect of their whole set of defining characteristics. Similarly, other authors have also evaluated the effect of yet other variables, including smoking habits (4) and the type of medium used for embryo culture (5), on the morphokinetics of embryo development, finding significant differences as well.

We are aware that the ideal goal is to generate an ESA applicable in all cases. Nevertheless, this idea raises the need to deepen the study of the effect of this whole set of characteristics on embryo quality by themselves before being able to use ESAs in a generalized way. This further study should not be limited to the morphokinetic level but should also include morphology and classical endpoint variables, creating a prism with even more dimensions to better understand the entire embryonic development. Fortunately, thanks to the increasing computing and data analysis capacity of artificial intelligence tools, we are ready to take that further step at data exploitation.

In summary, future research focused on generating ESAs should include variables related to embryonic development and those belonging to the wide range of characteristics that surround patients, as well as clinical and laboratory procedures, taking advantage of the computational power that machine learning provides. Thus, it will be possible to

somehow normalize each prediction for each patient and specific context, taking one more step toward a global standard and even personalized reproductive medicine.

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