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Review

Paving the way for a gold standard of care for infertility treatment: improving outcomes through standardization of laboratory procedures

William Schoolcraft [a], ***Marcos Meseguer*** [b], ***The Global Fertility Alliance*** *,[1]

[a] *Colorado Center for Reproductive Medicine, Englewood, CO, USA*

[b] *Instituto Valenciano de Infertilidad (IVI) Valencia, INCLIVA-Universidad de Valencia, Valencia, Spain*

William Schoolcraft is founder and Medical Director of the Colorado Center for Reproductive Medicine, having completed his medical training at the University of Kansas and a OBGYN residency at UCLA. He pioneered blastocyst culture and transfer and has published widely on the treatment of poor responders, comprehensive chromosome screening and vitrification.

KEY MESSAGE

The best possible outcomes for IVF patients depend on optimization of many variables and procedures. A systematic approach to establishing standardized, universally-adopted best practices incorporating technological laboratory advancements should enable a gold standard of care with high-quality gametes and embryos leading to improved take-home healthy baby rates.

A B S T R A C T

Infertility affects over 70 million couples globally. Access to, and interest in, assisted reproductive technologies is growing worldwide, with more couples seeking medical intervention to conceive, in particular by IVF. Despite numerous advances in IVF techniques since its first success in 1978, almost half of the patients treated remain childless. The multifactorial nature of IVF treatment means that success is dependent on many variables. Therefore, it is important to examine how each variable can be optimized to achieve the best possible outcomes for patients. The current approach to IVF is fragmented, with various protocols in use. A systematic approach to establishing optimum best practices may improve IVF success and live birth rates. Our vision of the future is that technological advancements in the laboratory setting are standardized and universally adopted to enable a gold standard of care. Implementation of best practices for laboratory procedures will enable clinicians to generate high-quality gametes, and to produce and identify gametes and embryos of maximum viability and implantation potential, which should contribute to improving take-home healthy baby rates.

* Corresponding author.
E-mail address: alan.thornhill@igenomix.com (A Thornhill).
[1] Authors comprised Diego Ezcurra, Tammie Roy and Alan Thornhill*.

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Introduction

Assisted reproductive technologies have evolved over five decades, with several key advances, most notably the introduction of IVF (Steptoe and Edwards, 1978; Wang, 2011; Zhao et al., 2011). Despite these advances, IVF success is not guaranteed, with almost half of the patients treated remaining childless, even after multiple cycles of treatment (Centres for Disease Control and Prevention, National ART Summary Report, 2013). The live birth rates associated with IVF are surprisingly low, although they have improved slowly over time. There are wide variations in outcomes even within the same country. For example, the most recent validated and verified statistics published for IVF in the USA demonstrate a clinical pregnancy rate (per cycle started) of 21.6% at one clinic and 67% at another. Of note, these results were reported for women under 35 years of age and by clinics within 100 miles of each other (Centres for Disease Control and Prevention, Fertility Clinic Success Report, 2013). Despite the availability of new technologies and a mandatory quality system approach, results from the UK's fertility regulator (Human Fertilization and Embryology Authority [HFEA]) showed only a 1% annual increase in live birth rates after fresh embryo transfer for the reporting years 2009–11 (Human Fertilization Embryology Authority, 2013). Finally, the multiple birth rate after IVF within the developed world is vastly different, with reported rates of around 6% in Finland and Sweden, and 23% in the UK (Royal College of Obstetricians and Gynaecologists, 2011). This brief selection of examples serves to demonstrate that even with shared expertise, a vast array of literature to consult, and near global accessibility to the latest technologies and consumables, these disparities in outcomes persist and are difficult to explain as the result of purely demographic differences between patient populations. Low live birth rates can be influenced by various factors including a lack of technological proficiency at each stage of the multistep IVF process (Bhattacharya et al., 2013; Egea et al., 2014; Sunkara et al., 2014). Moreover, the financial barrier inflicted by the high cost of IVF results in a fragmented market favouring couples with sufficient financial means. Clearly the outcomes at a given centre are influenced by the patient population treated – whether that be the result of random presentation, self-selection, centre selection policies based on specific inclusion and exclusion criteria, or regulatory, legal or funding guidelines. Furthermore, it is evident that the best outcomes require appropriate and timely diagnosis of infertile patients in order to recommend and administer the appropriate and optimal ovarian stimulation and subsequent treatment. In this review, however, we focus on how technological advances in laboratory practices can address some of the challenges in IVF. Innovation in, and standardization of, laboratory practices and equipment can help optimize outcomes and improve the success rate of the current IVF treatment paradigm, paving the way for a 'gold standard' of care. To reach this standard, the benefits and limitations of existing procedures and novel technologies must be comprehensively and objectively assessed before appropriate, step-wise change can be implemented.

Subjective assessments, a major source of variability

Treatment failure can occur due to a number of factors. The complexity of the multistep IVF process results in a myriad of components that can have a detrimental influence on the outcome and directly impact live birth rates. The success of the complex process of implantation is influenced by maternal and embryonic factors, but mostly relies on cross-talk between a healthy viable embryo and a receptive endometrium (Braude, 2013). As such, generation and identification of healthy viable embryos, and evaluation of endometrial receptivity, are key. A major limitation in the characterization of endometrial receptivity and embryo implantation potential is the current lack of repeatable, easy, practical, non-invasive, cost-efficient and objective biomarkers. Currently, embryo selection is primarily based on single-point subjective morphological features, which fail to adequately discriminate between viable and non-viable embryos (with respect to both genetic and non-genetic cytoplasmic factors). This can result in the transfer of cytoplasmically or chromosomally abnormal (aneuploid) embryos that have been shown to be associated with a reduction in success (Braude, 2013; Meldrum, 2016; Meldrum and de Ziegler, 2016). Although screening tests for aneuploidy exist, the use of these tests alone or in combination with morphology varies between clinics. In addition, consensus is currently lacking regarding what type of patient may benefit from screening tests for aneuploidy, because the method is not 100% accurate and proper clinical evidence is considered by some to be insufficient (Sermon et al., 2016). Furthermore, we currently lack a reproducible test to accurately identify oocyte (hence embryo) cytoplasmic quality. Tests such as mitochondrial scoring (Diez-Juan et al., 2015; Wells et al., 2014) or oocyte viscoelastic property analysis (Yanez et al., 2016) have been suggested as a solution to this issue.

Current areas of focus for optimization of IVF laboratory techniques and procedures

There are several steps in the IVF process that could be optimized through the implementation of currently available technology. Standardizing work processes can reduce variation in IVF outcomes on both an individual and centre-wide level.

Culture media (and extended culture)

Commercialized culture media has improved IVF success and is a vital factor influencing IVF outcome, affecting pre- and post-implantation stages (Chronopoulou and Harper, 2015). Extended embryo culture prolongs growth, enables more advanced embryos to be selected, and has been linked to improved IVF success in young patients with a low body mass index (Braga et al., 2012). As with any embryo selection technique, extended culture to the blastocyst stage may shorten time to pregnancy (with higher pregnancy rates per transfer and implantation rate; Bontekoe et al., 2014; Braga et al., 2012), but does not improve cumulative pregnancy rate (De Vos et al., 2016; Glujovsky et al., 2016). Further research is required to establish optimum culture conditions for embryo development and the optimal time for transfer (Bontekoe et al., 2014).

The proliferation of commercially available culture media has seen significant improvements and optimizations in recent years and now consists of two different approaches to embryo culture: sequential, where embryos are moved part way through the culture period to a medium with a different composition; and single-step, in which embryos are held in the same dish throughout and culture medium is not replenished at any point.

In sequential culture, the different requirements of an early versus late-stage embryo are considered. For example, the energy source

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