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REVIEW

The clinical benefit and safety of current and future assisted reproductive technology

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Abstract Since the first birth by IVF was achieved in 1978, the techniques involved in assisted reproductive technology have grown at an enormous rate. However, new technology has rarely been robustly validated before clinical use and developing scientific understanding of the available techniques has done little to alter their use. Furthermore, there are inconsistencies in the available clinical studies and endpoints. The benefits of some technologies already established for routine use are currently dubious and there are clear ethical concerns with providing them to patients when their scientific basis is not clear. As the uptake of assisted reproductive technology increases and newer technologies continue to push the boundaries of science, it is important to consider the clinical benefits and safety of all assisted reproductive technologies. This review will discuss aspects of some of the more recent techniques, including sperm DNA-damage tests, intracytoplasmic morphologically selected sperm injection, amino acid and metabolomics profiling, preimplantation genetic screening and time-lapse imaging, and those that may have substantial impacts on the field of reproductive medicine in the future including artificial gametes, ovarian transplantation and gene therapy.

KEYWORDS: assisted reproductive technology, embryo selection, IVF, preimplantation genetic screening, sperm DNA damage, time-lapse imaging

Introduction

Since the first IVF birth in 1978 (Steptoe and Edwards, 1978), the field of assisted reproductive technology has evolved at a rapid rate. Now, in 2012, clinics can achieve pregnancies in couples where there are no spermatozoa in the ejaculate, efficiently freeze human gametes and embryos, and perform whole chromosome scanning of the preimplantation embryo. Despite being impressive achievements, historically, new technology has rarely been robustly validated before clinical use in humans (Harper et al., 2012). Ideally, new technology should be first evaluated in a suitable animal model, and only when safety has been

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confirmed should it be applied to humans. Even then, newly introduced techniques should only be used routinely after randomized controlled trials (RCT) have confirmed that the technique is of benefit and that all safety issues have been addressed. As new technologies continue to push the boundaries of scientific knowledge, an appreciation of their clinical benefit and safety will become even more paramount.

This review begins by critically discussing some of the techniques already being used in clinical practice and to what end their use is supported by a strong scientific basis. Whether improvements in scientific understanding since their introduction have altered their clinical benefit and safety, and whether this information has been incorporated into clinical practice, is also considered. Some technologies that are beginning to be introduced or could have substantial impacts on reproductive medicine in the future will also be discussed. In an attempt to learn from previous mistakes, a particular focus will be placed on whether these developing technologies will provide a clear clinical benefit in addition to adhering to safety and ethical concerns.

Ongoing developments: gamete and embryo selection

Sperm DNA-damage tests

The main aim of assisted reproductive technology is to artificially achieve a pregnancy when natural conception has failed. The number of viable embryos may intuitively be improved if the most suitable gametes are involved in fertilization. Male fertility has long been assessed on conventional parameters including motility, morphology and concentration. While these parameters are important considerations, it is now understood that these alone provide only a limited diagnostic and prognostic value and an improved marker of sperm quality is desirable (Lefievre et al., 2007; Chen et al., 2009). It is intuitive that the genomic integrity of the spermatozoa is important for its cellular functions, including the ability to promote embryonic development and health after fertilization, and therefore methods to assess genomic integrity could have important clinical applications.

As early as 1980, it was reported that an appreciation of sperm DNA integrity could be a useful indicator of male fertility (Evenson et al., 1980), and an ever-increasing interest in DNA damage has followed. However, to what degree such DNA fragmentation tests are currently beneficial has now been called into question (Zini and Sigman, 2009; Barratt et al., 2010). Fundamentally, the precise nature and location of the damage detected by DNA-damage assays are, in many cases unclear, as is indeed the case for the most utilized clinical assay, the sperm chromatin structure assay (SCSA) (Aitken et al., 2009; Bungum et al., 2011). Further still, the unique packaging of sperm chromatin raises the question as to whether assay reagents are capable of accessing all areas of the genome, further complicating the correct interpretation of assay results. Several DNA-damage assays are now available for research and clinical purposes, including the SCSA (Evenson et al., 1999), sperm chromatin dispersion test (SCD) (Fernandez et al., 2003), terminal deoxynucleotidyl transferase-mediated dUDP nick-end labelling (TUNEL) (Gorczyca et al., 1993), the comet assay (Singh et al., 1989) and the sperm comet assay (Simon et al., 2010). However, the lack of validation and standardization of these numerous assays is becoming clear. While some have stated that the results from the SCSA and SCD display a high concordance, discrepancies in the absolute values of DNA fragmentation generated by these assays may lead to confusion when comparing reports using different techniques (Fernandez et al., 2005; Balasuriya et al., 2011). Others have stated that the SCSA and TUNEL assay measure different aspects of DNA damage, and therefore each may provide information of different clinical relevance (Henkel et al., 2010). It is therefore not acceptable to regard these various assays as providing comparable information. Lastly, clearly defined thresholds to distinguish fertile from infertile men on the basis of several assays have not been developed (Simon et al., 2010), and concerns over the high intra-individual variation of results, at least with the SCSA, have been raised (Erenpreiss et al., 2006). Since the SCSA has been exposed to more scrutiny than other assays (Sakkas and Alvarez, 2010), it is possible that results from these other assays will also be complicated by individuals displaying varying levels of damage in a temporal manner. It is therefore currently inappropriate to place a large emphasis on the results of single DNA-damage assays, despite such tests often being used in such a manner.

In addition to these concerns, the clinical effect that DNA damage has on outcomes and post-natal health is currently conflicting. As some studies have reported that DNA-damage assays, in particular the SCSA, can predict the success of natural conception and intrauterine conception (Evenson and Wixon, 2006; Bungum et al., 2007), it has been suggested that DNA-damage assays could be offered to all patients prior to treatment in an effort to better decide whether more invasive techniques (IVF, intracytoplasmic sperm injection (ICSI)) would be more appropriate. While this certainly would be beneficial, more evidence is required before such a routine use could be supported. Recent evidence has suggested that the association between sperm DNA damage and failure to achieve pregnancy during IVF or ICSI cycles is not strong enough to suggest DNA-damage assays have a broad clinical indication (Collins et al., 2008; Zini and Sigman, 2009; Barratt et al., 2010; Zini, 2011). While more robustly designed clinical studies will be needed to verify this statement, a recent paper noting that sperm DNA fragmentation had no clinical effect when good-quality oocytes were used raises the likelihood that an assessment of sperm DNA damage is not relevant in all cases (Meseguer et al., 2011b). Concern surrounding DNA damage has led to the suggestion that sperm DNA damage could be promutagenic, with the potential to cause molecular mutations leading to post-natal disease (Aitken et al., 2001). While animal models have raised concerns about the long-term health and behaviour of offspring conceived with spermatozoa containing damaged DNA (Fernández-Gonzalez et al., 2008), there is no conclusive evidence that DNA damage in spermatozoa is a significant risk to the post-natal health of humans, It should however be noted that it has been suggested that current studies have been underpowered to detect