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ARTICLE

Failure mode and effects analysis of witnessing protocols for ensuring traceability during PGD/PGS cycles

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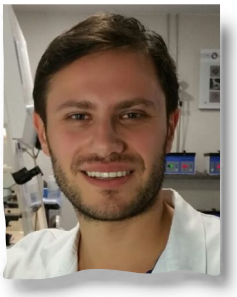

Danilo Cimadomo works as a molecular biologist at the GENERA centers for reproductive medicine and at the GENETYX molecular biology laboratory, where he collaborated in the implementation of qPCR-based blastocyst stage PGD/PGS policy. Currently, he is a PhD student at the University of Roma, Sapienza. He participated in two projects awarded with the Grant for Fertility Innovation in 2013 and 2015 focusing on miRNAs as potential mediators of a blastocyst-endometrial dialogue. His interests mainly cover PGD/PGS, and the research of novel techniques and/or criteria to increase our predictive power upon blastocyst implantation potential in IVF.

Abstract Preimplantation genetic diagnosis and aneuploidy testing (PGD/PGS) use is constantly growing in IVF, and embryo/biopsy traceability during the additional laboratory procedures needed is pivotal. An electronic witnessing system (EWS), which showed a significant value in decreasing mismatch occurrence and increasing detection possibilities during standard care IVF, still does not guarantee the same level of efficiency during PGD/PGS cycles. Specifically, EWS cannot follow single embryos throughout the procedure. This is however critical when an unambiguous diagnosis corresponds to each embryo. Failure Mode and Effects Analysis (FMEA) is a proactive method generally adopted to define tools ensuring safety along a procedure. Due to the implementation of a large quantitative PCR (qPCR)-based blastocyst stage PGD/PGS programme in our centre, and to evaluate the potential procedural risks, a FMEA was performed in September 2014. Forty-four failure modes were identified, among which six were given a moderate risk priority number (>15) (RPN; product of estimated occurrence, severity and detection). Specific corrective measures were then introduced and implemented, and a second evaluation performed six months later. The meticulous and careful application of such measures allowed the risks to be decreased along the whole protocol, by reducing their estimated occurrence and/or increasing detection possibilities.

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KEYWORDS: FMEA, misdiagnosis, mismatch, PGD, preimplantation genetic screening (PGS), traceability

Introduction

Preimplantation genetic diagnosis and aneuploidy testing (PGD/PGS) is a technique aimed at identifying embryos, either not affected by a monogenic disease or euploid, within a cohort of blastocysts produced by a couple during an IVF cycle. At present, PGD/PGS implementation in IVF is constantly growing and several centres are starting to provide this treatment for their patients (Coonen et al., 2015; Dahdouh et al., 2015a, 2015b; Lee et al., 2015; Ubaldi et al., 2015). Recently, we published a risk assessment analysis outlining how the introduction of an electronic witnessing system (EWS) in our clinical practice has significantly reduced the estimated occurrence of mistakes, while increasing detection for all the most error-prone steps throughout standard IVF cycles (Rienzi et al., 2015), an interesting topic that has been debated in literature (Parmegiani et al., 2015; Sakkas et al., 2015). However, since April 2013 we introduced quantitative PCR (qPCR)-based trophectoderm biopsy for both monogenic diseases and chromosomal structural and/or numerical disorders diagnosis (Capalbo et al., 2015a; Treff and Scott, 2013; Treff et al., 2012). The IVF cycles requiring this analysis involve specific critical procedures that potentially expose the patients to additional hazards, whose classification, and methods for forecast and prevention have to be defined meticulously (Harper et al., 2010). This is especially important due to the fact that the EWS guarantees an electronic patient-based traceability, but it lacks an embryo-based one. In PGD/PGS cycles single embryo identification acquires a pivotal importance since each tube containing the biopsy has to be unambiguously linked to its corresponding embryo. Since its first implementation in our centre, PGD/PGS use had a 2.3-fold increase from 195 cycles in 2013 to more than 450 in 2014 (Ubaldi et al., 2015). Mandatory recommendations within the European Commission Directives (2004/23/EC; 2006/86/EC), dealing with traceability and witnessing systems to ensure patient safety, acquire even a higher importance then when applied to PGD/PGS cycles, especially in centres performing such a high number of procedures. Based on the need for a proper risk assessment analysis for several steps along the whole PGD/PGS protocol, we adopted Failure Mode and Effects Analysis (FMEA). FMEA is an efficient proactive method to define the risks along a procedure. It requires expert operators to collaborate in a multidisciplinary fashion, aiming at the acquisition of knowledge and consciousness about traceability and witnessing processes.

This study reports our PGD/PGS cycles-based FMEA from blastocyst culture up to qPCR-based diagnosis and unaffected/euploid embryo warming, passing through several critical steps such as trophectoderm fragment tubing, cryopreservation and analysis.

Materials and methods

Study design

This study was conducted at the GENERA centre for reproductive medicine, Clinica Valle Giulia, in Rome. This is a centre that introduced qPCR-based blastocyst stage PGD/PGS in April 2013 (Capalbo et al., 2015a). GENERA collaborates since its implementation with GENETYX molecular genetics laboratory in Marostica (VI). A specific team from both centres was formed for this proactive risk assessment. The timeline of the study is summarized in **Figure 1**. In particu-

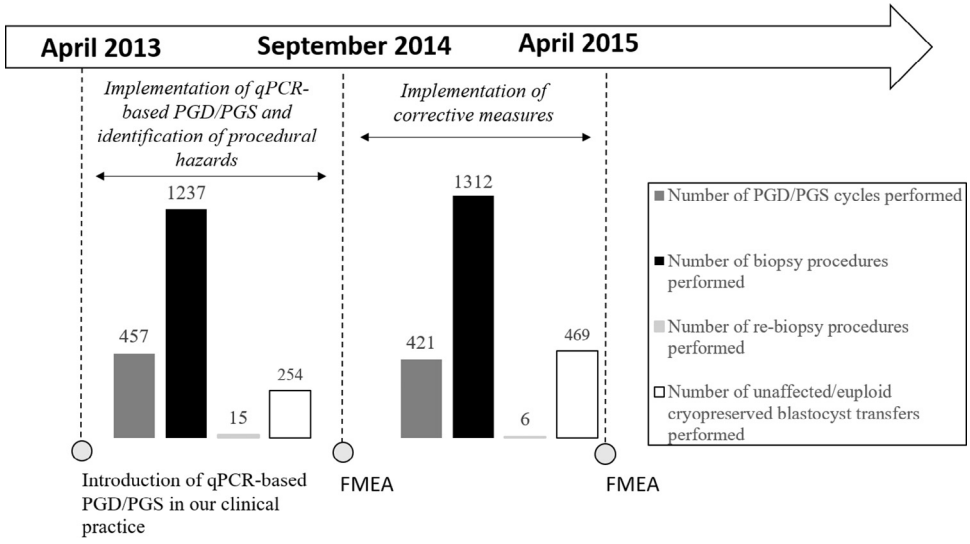

Figure 1 Design and timeline of the study. qPCR-based blastocyst stage PGD/PGS was introduced in April 2013. A FMEA was performed in September 2014 through which we defined critical procedures and related failure modes. Corrective measures were then arranged and prospectively evaluated between September 2014 and April 2015. PGD/PGS = preimplantation genetic diagnosis and aneuploidy testing; FMEA = Failure Mode and Effects Analysis.