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ARTICLE

Impact of blastocyst biopsy and comprehensive chromosome screening technology on preimplantation genetic screening: a systematic review of randomized controlled trials

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Abstract Embryonic aneuploidy is highly prevalent in IVF cycles and contributes to decreased implantation rates, IVF cycle failure and early pregnancy loss. Preimplantation genetic screening (PGS) selects the most competent (euploid) embryos for transfer, and has been proposed to improve IVF outcomes. Use of PGS with fluorescence-in-situ hybridization technology after day 3 embryo biopsy (PGS-v1) significantly lowers live birth rates and is not recommended for use. Comprehensive chromosome screening technology, which assesses the whole chromosome complement, can be achieved using different genetic platforms. Whether PGS using comprehensive chromosome screening after blastocyst biopsy (PGS-v2) improves IVF outcomes remains to be determined. A systematic review of randomized controlled trials was conducted on PGS-v2. Three trials met full inclusion criteria, comparing PGS-v2 and routine IVF care. PGS-v2 is associated with higher clinical implantation rates, and higher ongoing pregnancy rates when the same number of embryos is transferred in both PGS and control groups. Additionally, PGS-v2 improves embryo selection in eSET practice, maintaining the same ongoing pregnancy rates between PGS and control groups, while sharply decreasing multiple pregnancy rates. These results stem from good-prognosis patients undergoing IVF. Whether these findings can be extrapolated to poor-prognosis patients with decreased ovarian reserve remains to be determined.

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Introduction

After the birth of the world's first IVF baby in the UK, Louise Brown (Steptoe and Edwards, 1978), and despite numerous advances in the field of reproductive medicine, the likelihood of achieving a live birth in couples undergoing assisted reproduction techniques remains low, ranging from 30–35% in young patients to less than 5–8% in patients older than 41–42 years of age (Gunby et al., 2011; Stern et al., 2013). A growing body of evidence suggests that the dramatic decline in IVF success rates with advanced female age is mainly caused by embryonic aneuploidy (Hardarson et al., 2008; Harton et al., 2013; Kroon et al., 2011; Munne et al., 1995). To improve IVF clinical outcomes, preimplantation genetic screening (PGS) has been proposed to infertile couples seeking assisted reproduction technique treatments (Brezina et al., 2013; Gianaroli et al., 1999; Moutou et al., 2014; Munne et al., 1993; Rubio, 2013). The process of PGS consists of selecting the most competent (euploid) embryos for transfer, through aneuploidy screening after embryo biopsy (Fragouli and Wells, 2012; Kaser and Ginsburg, 2014; Munne, 2002; Wells, 2010). Indications for PGS use in IVF include advanced maternal age (Gianaroli et al., 1999; Hanson et al., 2009; Kuliev and Verlinsky, 2003; Milan et al., 2010; Munne et al., 1995, 1998; Orris et al., 2010; Platteau et al., 2005; Rubio et al., 2013a; Schoolcraft et al., 2009), repeated implantation failure (Blockeel et al., 2008; Greco et al., 2014; Rubio et al., 2013a), recurrent spontaneous abortion (Munne et al., 2005; Shahine and Lathi, 2014) and severe male factor infertility (Harper and Sengupta, 2012; Rodrigo et al., 2014). Recently, PGS has also been used to improve embryo selection in elective single embryo transfer (SET) cycles (Schoolcraft and Katz-Jaffe, 2013; Yang et al., 2012).

Previous data from randomized controlled trials (RCTs) with fluorescence-in-situ hybridization (FISH)-based PGS technology used on one or two blastomere cells from day 3 embryo biopsy (PGS-v1) showed a deleterious effect and lower live birth rates compared with no PGS (Hardarson et al., 2008; Jansen et al., 2008; Mastenbroek et al., 2007, 2011). Since then, many centres and recommendations have discouraged the PGS-v1 practice (Ginsburg et al., 2011; Mastenbroek et al., 2011). The main drawback of this technique is the embryo-stage biopsy, which might confer a lower implantation rate than non-biopsied embryos (Munne et al., 2010b; Scott et al., 2013b). A number of other drawbacks are associated with FISH analysis: it is limited to a restricted number of chromosomes, only up to 12 probes are used and repeat hybridization is necessary if more than six are used (Munne et al., 2010a). Finally, the entire chromosomal complement of a single blastomere cell from day-3 embryo biopsy cannot be easily evaluated with FISH technology (Munne et al., 2010a).

Recently, a paradigm-shift in PGS practice has been observed with embryo-stage biopsy. Blastocyst-stage biopsy is being extensively used in PGS (Harton et al., 2013; Schoolcraft et al., 2010; Scott et al., 2013a). This new form of embryo biopsy has been shown to carry no deleterious effect on embryo development and might be the ideal way of achieving the goal of PGS (Scott et al., 2013b). New genetic testing technologies, which assess the whole chromosome complement (24 chromosomes), are known as comprehensive chromosome screening (CCS) (Handyside, 2013). Complete chromosome analysis can nowadays be carried out with different genetic platforms, such as array comparative genomic hybridization (CGH) (Fiorentino et al., 2011; Gutierrez-Mateo et al., 2011; Munne, 2012; Schoolcraft et al., 2010), Single nucleotide polymorphism microarrays (Schoolcraft et al., 2011), quantitative polymerase chain reaction (qPCR) (Treff and Scott, 2013), as well as next-generation sequencing (Treff et al., 2013b; Wells, 2014).

Although the use of PGS coupled with CCS technology on multiple trophectoderm cells from blastocyst biopsy (PGS-v2) has dramatically increased in numerous assisted reproduction technique centres (Fragouli and Wells, 2012; Moutou et al., 2014), the level of evidence suggesting the usefulness of this new technique needs to be assessed in further detail. Hence, in the present study, a systematic review is conducted of RCTs dealing specifically with the clinical outcomes associated with PGS-v2 compared with embryo selection based on standard morphology criteria (Gardner et al., 2000; Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011). The primary outcome of the present study is to evaluate the effect of PGS-v2 on implantation rates and ongoing pregnancy rates in IVF, and to assess the accuracy of this method for embryo selection.

Materials and methods

Search strategy

PubMed (http://www.pubmed.gov) and databases for registration of RCTs (http://www.clinicaltrials.gov) were searched until the end of May 2014 with no date limitations, and no language restriction using the following Boolean search criteria: '([preimplantation genetic screening OR PGS] AND [comprehensive chromosome screening OR CCS] OR [PGS AND embryo selection] OR [array comparative genomic hybridization OR aCGH] OR [quantitative real-time PCR OR qPCR] OR [embryo selection]). The following limiting categorical terms were used: human, clinical trial, randomized controlled trial, title/abstract.

The Cochrane Central was then searched using the following Boolean search criteria ([preimplantation genetic screening OR PGS] AND [comprehensive chromosome screening OR CCS] OR [PGS AND embryo selection] OR [array comparative genomic hybridization OR aCGH] OR [quantitative real-time PCR OR qPCR] OR [embryo selection]). Similar searches were carried in other databases, namely, EMBASE, Scopus, Web of Science, and Google Scholar. The reference lists and bibliographies of included studies were then searched for other salient and pertinent manuscripts. Finally, manual searches of studies belonging to research teams having prior