ORIGINAL ARTICLE: GENETICS

Comprehensive chromosome screening improves embryo selection: a meta-analysis

Elias M. Dahdouh, M.D., M.Sc.,[a,b,c] Jacques Balayla, M.D.,[c] and Juan Antonio García-Velasco, M.D., Ph.D.[d]

[a] Assisted Reproduction Center, CHU Sainte-Justine, University of Montreal, Canada; [b] PROCREA Clinics, Montreal, Canada; [c] Department of Obstetrics and Gynecology, University of Montreal, Montreal, Canada; and [d] Instituto Valenciano de Infertilidad (IVI) Madrid and Rey Juan Carlos University, Madrid, Spain

Objective: To study whether preimplantation genetic screening with comprehensive chromosome screening (PGS-CCS) improves clinical implantation rates (IR) and sustained IR (beyond 20 weeks) compared with routine care for embryo selection in IVF cycles.
Design: Meta-analysis of randomized controlled trials (RCTs) and observational studies (OSs).
Setting: University-affiliated teaching hospital.
Patient(s): Infertile couples undergoing IVF.
Intervention(s): PGS-CCS with the use of different genetic platforms performed on polar body (PB), cleavage embryo, or blastocyst following embryo biopsy.
Main Outcomes Measure(s): Clinical IR and sustained IR in RCTs as well as OSs comparing PGS-CCS and routine care were determined after a complete review of the literature. Pooled estimates of risk ratios (RRs) with their 95% confidence intervals (CIs) according to a fixed-effects model with the use of the Mantel-Haenszel method were calculated after the meta-analysis. Forest plots are provided for comparative purposes.
Result(s): Out of 763 citations identified, 29 articles met initial eligibility criteria and were further analyzed. Of these, only three RCTs and eight OSs met full inclusion criteria, allowing direct comparison of PGS-CCS and routine IVF care based on embryo morphology selection. In the RCTs, all embryo biopsies were performed on day 5–6 of embryo development. In the OSs, biopsies were performed on different stages of embryo development, including PB, day 3, or day 5–6. Meta-analysis of the RCTs (3 studies; n = 659) showed that PGS-CCS was associated with a significantly higher clinical IR, with a pooled RR of 1.29 (95% CI 1.15–1.45), as well as a significantly higher sustained IR, with a pooled RR of 1.39 (95% CI 1.21–1.60). Similar findings were shown in the OSs, where the pooled RR for clinical IR was 1.78 (95% CI 1.60–1.99; 7 studies; n = 2,993) and for sustained IR was 1.75 (95% CI 1.48–2.07; 4 studies; n = 1,124). Statistical heterogeneity (I^2) was minimal for RCTs and substantial among OSs.
Conclusion(s): PGS with the use of CCS technology increases clinical and sustained IRs, thus improving embryo selection, particularly in patients with normal ovarian reserve. Results from ongoing RCTs conducted on different patient populations (e.g., decreased ovarian reserve) and different embryo stage biopsy (e.g., PB, day 3) may further clarify the role of this technology. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Preimplantation genetic screening, comprehensive chromosome screening, embryo selection, elective single embryo transfer

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/dahdouhe-pgs-ccs-embryo-selection/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

In vitro fertilization (IVF) is a well established reproductive technique used in couples for the treatment of infertility (1). IVF is a complex procedure, which includes a number of different steps: ovarian stimulation, egg retrieval, embryo culture, and finally embryo transfer (2–5). Its success depends on multiple factors, namely, embryo status (genetic complement), endometrial receptivity, and an adequate embryo transfer technique (6–8). Unfortunately, a high proportion of embryos may be aneuploid, and the transfer of these is associated with decreased implantation rates (IRs), high miscarriage rates, and decreased live birth rates (9–13). To bypass the high embryo aneuploidy rate, reproductive endocrinologists have traditionally transferred multiple embryos with the aim of achieving at least one single live birth (14). This

Received July 9, 2015; revised and accepted August 26, 2015.
E.M.D. has nothing to disclose. J.B. has nothing to disclose. J.A.G.-V. has nothing to disclose.
Reprint requests: Elias M. Dahdouh, M.D., M.Sc., Assisted Reproduction Center, Department of Obstetrics and Gynecology, CHU Sainte-Justine, University of Montreal, 3175 Chemin de la Côte-Sainte-Catherine, Montreal, Quebec H3T1C5, Canada (E-mail: elias.dahdouh@umontreal.ca).

Fertility and Sterility® Vol. ■, No. ■, ■ 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.08.038

practice has been associated with a high rate of multiple pregnancies, which carries a number of risks to the health of both mother and fetus (15–18). Because of this major drawback, techniques of embryo selection (ES) have been developed to select the best available one or two embryos to transfer into the uterus (19–21). Ideally, the best single embryo carrying the highest implantation potential (euploid embryo) should be selected for transfer, and this would lead to a lower multiple pregnancy rate, making IVF with elective single-embryo transfer (eSET) a more attractive procedure for many assisted reproductive technology (ART) clinics (22–24).

Morphologic evaluation remains the criterion standard and most commonly used method for ES. This type of selection carries many limits and has been associated with conflicting reproductive results, despite adopting standard criteria for oocyte and embryo morphology assessment (25, 26). Other methods of ES aiming to improve the clinical outcomes and to bypass the technical limitations encountered by the morphologic embryo assessment have been developed in the past decades (6, 27). These techniques have been introduced into clinical practice and show promise, but they still need to be proven as effective and to be available at affordable cost before their widespread use (28). These include embryonic morphokinetic evaluation with the use of time-lapse imaging by new microscopy systems and embryo assessment based on the analysis of embryo metabolism, among others (20, 21, 29, 30).

The most biologically plausible and promising means of ES remains the assessment of the genetic component of the embryo following embryo biopsy, a process known as preimplantation genetic screening (PGS) (6, 31, 32). The first reported pregnancies after PGS with the use of fluorescence in situ hybridization (FISH) technique occurred in 1995, and its clinical use has dramatically increased since then (9). PGS has been applied in IVF for different indications where the risk of embryo aneuploidy is high, notably advanced maternal age (AMA) (9, 33–41), repeated implantation failure (RIF) (35, 42, 43), recurrent miscarriage (44, 45), and severe male factor infertility (46, 47). Recently, PGS has been used to improve embryo selection in eSET cycles (24, 48).

However, most of the randomized controlled trials (RCTs) on PGS using FISH technology after cleavage-embryo biopsy showed no increase in live birth rates, and even a deleterious effect on IVF outcomes (49). Therefore, many centers and recommendations have discouraged its use (49, 50). The reasons for the latter results might be attributed to the FISH technology itself, or to the stage of the embryo biopsy, which may have adverse effects on embryo development (51–53). It is now evident that the combination of FISH with day-3 embryo biopsy does not confer any advantage to infertile couples and that it may even lower their chance of conceiving. A new genetic technique known as comprehensive chromosome screening (CCS), which analyzes the whole chromosome complement, has been developed and used recently in PGS cycles (46, 54–56). This technique has been applied on different stages of embryo biopsies, including polar body (PB), cleavage-stage, and blastocyst-stage embryos (32, 55, 57). In addition, CCS can be achieved with the use of different genetic platforms, including metaphase comparative genomic hybridization (mCGH), array comparative genomic hybridization (aCGH), single-nucleotide polymorphism (SNP) microarray, quantitative polymerase chain reaction (qPCR), and most recently, and next-generation sequencing (NGS) (32, 58–62). These have been extensively tested and validated in PGS cycles and show promising early clinical results. However, whether PGS-CCS improves embryo selection in IVF remains unclear and a matter of debate. As such, the aim of the present study was to perform a meta-analysis on all published studies on PGS-CCS compared with routine care in ES, and to perform an in-depth evaluation of the available evidence of this new form of PGS.

MATERIALS AND METHODS

Search Strategy

We performed an English-language Medline, Embase, Google Scholar and Cochrane database search, as well as Pubmed and RCT registry (www.clinicaltrials.gov) searches, up to the end of May 2015 with no date limitations and the use of the following boolean search criteria: "((Preimplantation Genetic Screening OR PGS) AND (Comprehensive Chromosome Screening OR CCS) OR (PGS AND embryo selection) OR (embryo selection) OR (elective single embryo transfer)." No limiting categoric terms were used other than restricting the search to human studies. 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 previous publications on PGS were undertaken and pertinent studies retrieved. This review was modeled on the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement, and the flow chart depicting the search strategy is illustrated in Figure 1.

Study Selection

The three authors independently examined the electronic search results for reports of possibly relevant trials, which were retrieved and analyzed in further detail. Published observational studies (OSs) and RCTs were eligible for inclusion if they compared women undergoing IVF with the use of PGS-CCS and women undergoing IVF with standard care and no PGS. All studies were assessed according to predetermined quality criteria. Validity of RCTs was assessed in terms of method of randomization, presence of a power calculation, unit of analysis used, use of an intention-to-treat analysis, and presence or absence of blinding. We did not find the need to contact any authors in an attempt to retrieve missing data, given that data to carry out the present meta-analysis were complete. We made no distinction between fresh or frozen cycle transfer; oocyte, blastomere, or blastocyst biopsy; and type of CCS technology used.

Statistical Analysis

The effect of CCS technology was assessed for two main indications separately. Our first outcome of interest was clinical IR, defined as the number of gestational sacs with or without Q1