Preimplantation genetic screening: who benefits?

Hey-Joo Kang, M.D., Alexis P. Melnick, M.D., Joshua D. Stewart, M.D., Kangpu Xu, Ph.D., D.V.M., and Zev Rosenwaks, M.D.

The Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medical College, New York, New York

Objective: To compare IVF outcomes between women undergoing frozen transfers of blastocysts verified as euploid by preimplantation genetic screening (PGS) with patients undergoing fresh nonbiopsied blastocyst transfers.
Design: Retrospective cohort study.
Setting: Academic medical center.
Patient(s): All patients undergoing IVF-PGS cycles between January 2010 and November 2014 were included (n = 274). Patients were compared with a control group consisting of all fresh blastocyst transfers that occurred during the same period (n = 863).
Intervention(s): Patients underwent IVF-PGS with 24-chromosome screening. Patients with euploid embryos had transfer of one to two embryos in a subsequent frozen ET cycle.
Main Outcome Measure(s): Implantation, clinical intrauterine gestation (CIG), miscarriage, biochemical pregnancy (BC), and live birth (LB) rates were compared.
Result(s): Odds ratios (ORs) were estimated for outcomes in women undergoing PGS versus controls. Among patients ≤37 years old, there were no differences in CIG and LB rates for single (adjusted ORs [aORs], 1.20 [95 %confidence interval {CI}, 0.66–2.21]; 1.21 [95% CI, 0.66–2.2]) and double ETs (aORs, 1.09 [95% CI, 0.54–2.18]; 0.87 [95% CI, 0.44–1.7]). BC and miscarriage rates were also similar. For patients >37 years old, CIG and LB rates were increased for single (aORs, 3.86 [95% CI, 1.25–11.9]; 8.2 [95% CI, 2.28–29.5]) and double ETs (aORs, 9.91 [95% CI, 2.0–49.6]; 8.67 [95% CI, 2.08–36.2]) with no difference in BC and miscarriage rates. A per-retrieval analysis of the >37 group failed to demonstrate any difference in CIG or LB rates.
Conclusion(s): Among patients ≤37, IVF-PGS does not improve CIG, LB, and miscarriage rates. IVF-PGS in women >37 improved CIG and LB rates. However, per cycle, the PGS advantage in this age group does not persist. (Fertil Steril® 2016;106:597–602. ©2016 by American Society for Reproductive Medicine.)
Key Words: IVF, trophectoderm biopsy, preimplantation genetic screening, blastocyst transfer

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The goal of preimplantation genetic screening (PGS) is the transfer of a single euploid embryo aiming at achieving a healthy singleton pregnancy. Initially, PGS was performed principally on day 3 embryos, whereby a single blastomere was biopsied and analyzed with fluorescence in situ hybridization (FISH). This was followed 2 days later with a blastocyst transfer. After several retrospective studies in the 1990s suggested promising improvements in implantation and pregnancy rates after PGS, this screening procedure was widely adopted. More recently, several randomized controlled studies produced evidence that day 3 biopsy with PGS is detrimental to IVF outcomes, partially due to its invasive nature and to embryo mosaicism (1–4).

It is generally accepted that the most common reason for failed implantation in IVF is embryo aneuploidy. Recent refinements in blastocyst culture techniques as well as in molecular diagnostic technology, along with the observation that a biopsy at the blastocyst stage is less detrimental to embryo survival compared with day 3 biopsy, have led to renewed interest in implementing PGS at the blastocyst stage.

Particular IVF patient cohorts—older women or those with recurrent miscarriages due to aneuploidy—may benefit from PGS. However, whether universal application of this technology to all patients undergoing IVF is appropriate is a matter of enduring controversy (5–7). Advocates for universal PGS tout improvements in implantation rates leading to increased single ETs as well as decreased miscarriage rates. Other investigators cite potential disadvantages such as increased cost

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Reprint requests: Alexis P. Melnick, M.D., the Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine of Weill Cornell Medical College, 1305 York Avenue, New York, New York10021 (E-mail: alm2036@med.cornell.edu).

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and invasiveness. Furthermore, adopting routine use of PGS would result in a transfer-free cycle for those patients whose embryos fail to reach the blastocyst stage. The literature to date is lacking in sufficient data comparing PGS with appropriately selected controls. The goal of this study was to compare IVF outcomes between women undergoing frozen transfers of euploid blastocysts after PGS with patients undergoing fresh blastocyst transfers absent PGS to determine whether routine application of this technology proves beneficial.

MATERIAL AND METHODS

Cycle Selection

This study was approved by the Weill Cornell Medical College Institutional Review Board. All IVF cycles performed at the Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine from January 2010 to November 2014 were reviewed for inclusion. Inclusion criteria were all cycles in which one or more embryos underwent biopsy for 24-chromosome screening. The control group consisted of all patients with a fresh blastocyst transfer during the same period. Cases of severe male factor as the primary etiology for infertility and preimplantation genetic diagnosis cycles for single gene defects were excluded.

Stimulation Protocol

Controlled ovarian hyperstimulation (COH), oocyte retrieval, and ET were performed per our standard protocols (8, 9). Patients were either down-regulated with a GnRH agonist (Lupron; Abbott Pharmaceuticals) followed by stimulation with gonadotropins (Follistim, Merck; Gonal-F, EMD-Serono; and/or Menopur: Ferring) or were stimulated with gonadotropins until criteria were met for pituitary suppression with a GnRH antagonist (0.25 mg Ganirelix acetate, Organon; 0.25 mg Cetrotide, EMD-Serono). GnRH agonist luteal suppression was started 8 days after an LH surge in the cycle before COH. For GnRH-antagonist cycles, Ganirelix or Cetrotide was administered at either a lead follicle diameter of 13 mm or an E_2 level exceeding 300 pg/mL. For women with suspected diminished ovarian reserve, estrogen priming was initiated 10 days post-LH surge to suppress early recruitment in the luteal phase. All protocols were selected according to age, weight, ovarian reserve, and prior response to COH. Patients were monitored with serial E_2 measurements and transvaginal ultrasounds. HCG (3,300–10,000 IU; Profasi, EMD-Serono; Novarel, Ferring Pharmaceuticals; or Pregnyl, Schering-Plough), GnRH agonist (Lupron; Abbott Pharmaceuticals), or a combination of low-dose hCG (1,500 IU) and GnRH agonists were administered when two follicles reached 17 mm in diameter. Retrieval was performed in the standard fashion 35–36 hours after hCG administration. Patients in the control group underwent ET 5 days after oocyte harvest. Luteal support for the control group was in the form of 50 mg IM P nightly and was begun 1 day post oocyte retrieval.

For the PGS group, once trophectoderm biopsy results confirmed as least one euploid embryo, patients were scheduled for a frozen ET cycle. For patients with regular menstrual cycles, transfers were performed 5 days after a serum-confirmed LH surge. In some patients, twice daily vaginal P supplementation (Endometrin, Ferring pharmaceuticals) was started 1 day post-ET at the discretion of the patient's physician. Patients with oligomenorrhea were prepped with luteal Lupron and estrogen patches until the endometrial stripe reached a thickness of at least 7 mm, after which evening IM P was started. ET was performed after five doses of IM P. Embryos were thawed and transferred using a Wallace catheter (Marlow/Cooper Surgical).

Laboratory Conditions

Embryos were cultured using either standard incubation or via the EmbryoScope (Vitrolife, Denmark) time-lapse system. Embryos were evaluated on the morning of day 5, and trophectoderm biopsy was performed on either day 5 or day 6 depending on embryonic development. Grading criteria were previously described by Gardner et al. with some minor modifications (10). Embryos receiving a grade of at least 2B-B- on day 5 were biopsied; the remaining embryos were cultured to day 6 before biopsy. Before cell removal, embryos were immobilized with a holding pipette, and a few laser pulses (ZILOS-tk Laser) were used to perforate the zona pellucida. A biopsy pipette with internal diameter of 20 μm was used to aspirate three to five cells, and the biopsy specimen was removed with gentle traction and laser pulsation. The biopsied specimens were rinsed in several drops of wash buffer and then loaded into 0.2 mL polymerase chain reaction (PCR) tubes with about 2 mL of lysis buffer. Samples were labeled and transferred to the genetic lab for analysis. Specimens were analyzed using either 24-chromosome single nucleotide polymorphism array by Natera (11) or at the Weill Cornell PGS laboratory with the Illumina (BlueGnome) 24SureV3 chip (aCGH). All biopsied blastocysts were vitrified within 1–2 hours after trophectoderm biopsy.

Outcome Variables Assessed

Our primary outcome was clinical intrauterine gestational rates. Secondary outcomes included live-birth rates, missed/spontaneous abortions in the first trimester, biochemical pregnancy rates, and implantation rates. The clinical intrauterine gestation rate was defined as the number of cycles with at least one viable fetus (as evidenced by ultrasound of fetal cardiac activity) per transfer. Live-birth rate/ongoing pregnancy rate was defined as the number of cycles resulting in at least one live-born child delivered at greater than 24 weeks' gestation of all transfers performed. Implantation rate was defined as the number of gestational sacs on transvaginal ultrasound divided by the total number of embryos transferred per each patient. Biochemical pregnancy rate was defined as the proportion of cycles resulting in a transient elevation in hCG level without ultrasound confirmation of a gestational sac per transfer. Miscarriage rate was defined as the number of first trimester missed or spontaneous abortions in the first trimester per transfer. Outcomes were compared between patients undergoing PGS with subsequent frozen transfer and controls undergoing fresh transfer. The groups