Over a decade of experience with preimplantation genetic diagnosis

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The three respondents provide additional support for preimplantation genetic diagnosis (PGD) having the pivotal place it now has in prenatal genetic diagnosis: chromosomal abnormalities (e.g., unbalanced translocations), Mendelian disorders, and HLA typing for transfer of compatible, genetically normal embryos. Transferring euploid embryos has decreased the clinical abortion rate and increased the implantation rate in assisted reproductive technologies (ART), but it has not necessarily improved the live-birth rate. Safer embryo biopsy, more extensive diagnostic efforts (i.e., microarray analysis), and more refined patient selection may be required before shifting from preselection of embryos based solely on morphological parameters to transfer of only aneuploidy-free embryos. (Fertil Steril 82:302–3, 2004; ©2004 by American Society for Reproductive Medicine.)

The responses of our colleagues underscore the scientific community’s belief that PGD has moved from investigational to clinical application. The experience of de Boer et al. (1) illustrates well the successful results in newer programs. Politically, PGD shows burgeoning acceptance across the political spectrum, as evidenced by the diverse panelists at a January 8, 2004, symposium hosted by the Genetics and Public Policy Institute (www.dnapolicy.org). Former Speaker of the House Newt Gingrich, former Clinton White House Chief of Staff John Podesta, and former National Institutes of Health Director Bernadine Healy opportunistically displayed consensus. Still, Trounson as well as Hill point out that key issues must be addressed. Indeed, the public still considers PGD to be in its early epoch.

Our colleagues agree with the common indications for PGD: chromosomal abnormalities (e.g., parental translocation), Mendelian disorders, and HLA testing for transfer of compatible embryos. In addition, de Boer et al. (1) and Hill (2) clearly share our enthusiasm for aneuploidy testing to increase live-birth rates in assisted reproductive technology (ART). All agree with the plausibility of this strategy, given that morphologically normal embryos may be aneuploid, unable to survive yet depriv ing the patient of an opportunity for a successful pregnancy. Transferring blastocysts, as de Boer et al. (1) espouse, is fashionable with or without PGD; however, this approach does not guarantee a euploid blastocyst because mosaicism persists in the blastocyst.

Logic would dictate that transferring euploid embryos to improve ART success applies to couples with multiple spontaneous abortions, repeated IVF failures, or just advanced maternal age. Data show decreased clinical abortions and increased implantation rates. While it is frustrating that less improvement in the live-birth rate is observed, results are improved over cycles undergone before the use of PGD. There are several possible explanations.

[1] Benefit is biologically and stochastically possible only in selected groups, such as women over 38 years old in whom some requisite number of embryos is available for testing. [2] The chromosome-specific probes currently used do not alone suffice. Perhaps microarray technology for full karyotyping can improve pregnancy rates. [3] The lower than desired live-birth rate could reflect the unappreciated deleterious effects of embryo biopsy. What is the biopsy “learning curve”? Would, as Trounson opines, better media improve outcome? Might this also mitigate the perturba-
tions of imprinting, this year’s Cassandra (perhaps with validity)?

What does the future hold? First, properly designed studies should identify those women in whom pregnancy rates can be improved by transferring euploid embryos. At the same time, cohort registry data will define risks, if any. In the aggregate, we can then determine precisely who will benefit from PGD for aneuploidy to improve ART live-birth rates. But surely there will be other novel directions. Why not test for expression of genes connoting a high likelihood of implantation? Then the Venn diagrams of IVF and PGD will further overlap if not show synonymy.

References