Comprehensive chromosome screening with synchronous blastocyst transfer: time for a paradigm shift☆

Recently, the nature of assisted reproductive technology (ART) laboratory investigation has been shifting. Traditionally, it has focused on optimizing the culture milieu or assuring fertilization; now, a variety of new technologies are available to assess the reproductive potential of individual embryos. Perhaps most prominent has been the resurgence of embryonic aneuploidy screening. The validation of 24-chromosome testing platforms has led to a variety of studies demonstrating higher implantation and delivery rates. These findings are now translating to changes in the paradigm of ART practice.

Caution is prudent in times of change, and methodical analyses are needed. Evaluation logically focuses on efficacy in terms of enhanced implantation and delivery rates. Other factors, such as safety, cost, and accessibility also deserve thoughtful consideration. Evaluations of these endpoints should take into account the caliber of the data supporting the "new paradigm," in parallel with the data supporting the current "standard of care," and both should be evaluated with the same level of rigor.

Several investigators have recently expressed concerns about the implementation of comprehensive chromosomal screening (CCS) in clinical practice. Fortunately, an ever-growing literature is available to provide clinicians and scientists with the information they need to evaluate many of the critical issues. Some of the major issues and questions include:

1. Efficacy of 24-chromosome embryonic aneuploidy screening. Multiple studies provide class I data demonstrating higher implantation and delivery rates following 24-chromosome aneuploidy screening. In distinct contrast to fluorescent in-situ hybridization-based preimplantation genetic screening studies in which every randomized controlled trial (RCT) showed either no improvement or active detriment, every RCT involving 24-chromosome screening has demonstrated benefit (1–3).
2. What magnitude of improvement in clinical outcomes is necessary to justify screening? Answering this question inevitably involves a subjective decision that will be made by patients after counseling by the clinicians caring for them. Given that aneuploidy rates vary from 25% in women in their late twenties to 85% for those in their mid-forties, the opportunity for enhancing outcomes will be greatly affected by the age of the female partner and her intrinsic ovarian responsiveness. It is unlikely that improvements will be made in direct proportion to the aneuploidy rate, as many other factors affect delivery rates. Women with high embryonic arrest rates are unlikely to attain the full benefit of screening. Still, the magnitude of the enhanced outcomes seen in the RCTs is substantial.
3. The cost of CCS may be burdensome. Although substantial costs are associated with CCS, even in proportion, they are lower than the costs of additional ART cycles. A definitive cost-effectiveness study has not been published to date. Although enhanced delivery rates should translate to fewer treatment cycles, that question must await more detailed analyses before conclusions may be drawn. Additionally, savings attributable to decreased pregnancy losses and the care provided to ongoing aneuploid gestations would need to be considered. Given that, and the impact on transfer order discussed below, it is unlikely that cost effectiveness will limit implementation of embryonic aneuploidy screening.
4. Implementation of CCS may actually increase the risk for multiple gestations unless transfer order is reduced. That very fact has already been established in a randomized controlled trial (2). In fact, it is a mathematical certainty. As implantation rates increase, if there is no decrease in transfer order, then multiple gestation rates will inevitably rise. However, it is not reasonable to assume that transfer order would remain the same. For the first time, there are class I data demonstrating eSET after CCS is as effective as double-embryo transfer of unscreened embryos (2). All prior RCTs comparing elective single-embryo transfer (eSET) versus double-embryo transfer found poorer per-transfer outcomes with eSET. If CCS is used, that is no longer true. Equivalent delivery rates are maintained while virtually eliminating the risk of twins. The paradigm using CCS and eSET produced an average gain in birth weight of approximately 650 grams. No other single intervention in obstetrics has produced such a dramatic enhancement in birth weight, which is known to be highly correlated with the health of the child. Of course, the transfer of two screened embryos would further increase pregnancy rates, but at the cost of quite elevated twin rates; thus, it should be discouraged. Armed with these data, utilization of eSET in our program has risen from less than 6% to approximately 60% over a 4-year interval.
5. Embryo cryopreservation is essential to the application of CCS. This is an excellent point, as it is true in many, but not all, programs. Analyses can be completed in as little as 4 hours, and several programs now have testing laboratories within their facilities. However, that may not be necessary. Data from RCTs demonstrate equivalent delivery rates following the transfer of fresh or vitrified CCS screened blastocysts (2). Furthermore, data now demonstrate meaningfully better obstetrical outcomes in conceptions following the transfer of cryopreserved embryos.
6. Some subpopulations may not benefit from aneuploidy screening. The studies to date have focused on infertile normal responders. No class I data address the impact of CCS in women who are low responders or have recurrent pregnancy loss. An RCT to determine the impact of CCS in women at risk for low response to gonadotropin stimulation has been registered (NCT01977144) and is currently underway. Within the general ART population, individuals who might typically be considered candidates for two-embryo transfer should be offered CCS. Given that the eSET rate was 8.8% in the recently released 2012 Society for Assisted Reproductive Technology (SART) data, it would appear that this type of screening is appropriate

for very large numbers of patients. Even those patients who desire eSET attain increased delivery rates if the euploid embryos are selected for transfer. Although many of these patients already have excellent delivery rates, it is difficult to imagine a scenario in which the increases in implantation rates seen in the RCTs done to date would not be a compelling reason to screen.

7. The need to culture to the blastocyst stage to safely biopsy embryos increases the number of futile cycles because of embryonic arrest prior to blastulation. This issue is extremely important and represents a widely held belief, but it is not supported by data. In this case, two important facts may have been disregarded: (1) The in vivo environment on day 3 is not physiologic given that human embryos are not in the endometrial cavity on the third day of development. Moreover, significant differences exist between the intra-endometrial and intra-tubal environments at that time. The real question is which of the two nonphysiologic environments (intra-endometrial versus in vitro laboratory) allow a given embryo to attain its highest reproductive potential. To date, the RCTs favor extended culture to the blastocysts. Definitive studies in low responders have not yet been done; (2) This mode of reasoning also completely disregards the issue of synchrony. Data, as opposed to speculation, now indicate that active management of the time of transfer improves outcomes in those patients whose embryos are slow to blastulate (4). Of course, it is not possible to know on day 3 when any single embryo will blastulate. By failing to place embryos into extended culture, clinicians and embryologists lose the opportunity to determine if the embryos blastulate synchronously with endometrial development. This lost opportunity removes the ability to transfer vitrified embryos the following month when synchrony may be assured. Therefore, day-3 transfer might actually result in a reproductively competent embryo failing to implant. This outcome is of particular concern in patients with diminished ovarian reserve with very few embryos. Hopefully, class I data will become available to resolve this issue in the near future.
8. The use of CCS allows some programs to manipulate their data and create inaccuracies in the SART/Centers for Disease Control and Prevention reporting system. Factors that are important to the fidelity of the reporting system are important and legitimate concerns. The prior reporting system was not designed to reliably capture outcomes from cycles requiring deferment of transfer to the following month. Fortunately, the leadership at SART has recently restructured the system to achieve greater clarity and accuracy. This adjustment is not the first adjustment for the SART/Centers for Disease Control and Prevention reporting system, and it is unlikely to be the last. The key point is that the system remains committed to fair and accurate reporting and has done an excellent job in addressing this issue. Perhaps most important, implementation of new technologies or procedures should not be based on consideration of the reporting system, but rather on optimizing patient outcomes.

Implementation of CCS in normal responders positively affects outcomes and for the first time empowers practical eSET without compromising clinical outcomes. This procedure will positively affect many patients. Some caution should remain. The data in low responders and in women with recurrent loss are insufficient to draw definitive conclusions.

CCS will not eliminate all clinical failures. Many other challenging problems remain to be resolved. Still, these are exciting times as embryonic aneuploidy screening moves clinical care ever closer to that "holy grail" of one embryo–one healthy baby.

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