The practice of in vitro fertilization according to the published literature

The "holy grail" of in vitro fertilization is identifying a single embryo that produces a healthy baby. Currently, we have the ability to select a single euploid embryo for transfer. This can be achieved without harming the embryo if the biopsy is done at the blastocyst stage. Blastocysts can be frozen with high survival rates and then transferred in a thaw cycle. The implantation of frozen thawed embryos has been shown to be superior to those transferred into an endometrium that is under the influence of the stimulated environment. Frozen embryo transfer cycles have been shown to yield safer and healthier deliveries and fewer ectopic pregnancies.

In the past, success rates have instead been maintained at the great cost of transferring multiple embryos in the hope that one would result in a delivery. The practice of transferring multiple embryos is especially prevalent in older patients and in patients with a poor prognosis. The problems of multiple gestations, premature delivery, and ovarian hyperstimulation are tolerated as necessary side effects. Using embryo morphology and now, perhaps, time-lapse microscopy, as a non-invasive assessment of viability to pick the "right embryo," our field has progressed. Despite the inherent limitations of these techniques, miscarriage and multiple gestations, as well as aneuploidy, are still judged by many to be acceptable side effects.

The transition from day-3 embryo transfer to blastocyst transfer was supported by many studies, and improved implantation rates have been documented (1). Despite these data, many still insist that embryos that could not reach the blastocyst stage in culture could still make viable pregnancies had they been replaced on day 3. However, not one peer-reviewed article has been published to support this popular thesis. Instead, one article proves the thesis that extended culture selects against aneuploidy (2). Therefore, adherence to day-3 transfer, rather than transfer of a blastocyst, makes transfer of a chromosomally abnormal embryo more likely. In addition, randomized controlled trials of day-3 transfer of 1 versus 2 embryos all demonstrate lower pregnancy rates with single-embryo transfer.

With regard to embryos faring better in the uterus, it is important to note that human embryos are not in the uterus on day 3, but rather in the oviduct. The environment of the uterus on day 3, post-ovulation is not ideal to support embryo development. In all eutherian mammals studied to date, other than the human, the replacement of embryos at the cleavage stages (days 1–3) to the uterus is not associated with high pregnancy rates. The majority of such embryos die. In contrast, when animal embryos are replaced in the uterus, postcompaction high pregnancy rates can be attained.

With the development of physiologically based sequential culture media, it is now possible to culture viable human blastocysts in the in vitro fertilization (IVF) laboratory. In 9 prospective randomized trials using sequential culture media, 5 reported a significant increase in implantation rates when embryos were transferred at the blastocyst stage on day 5 rather than at the cleavage stage. Three of the trials reported no difference in implantation rate with respect to day of transfer, whereas one clinic reported a lower implantation rate when day-5 transfer was used. Therefore, the literature favors the use of blastocyst transfer to increase the implantation rate of human embryos conceived through IVF. By increasing the implantation rate through blastocyst transfer, it is possible to decrease the number of embryos transferred.

The concern that there are cycles in which no embryos survive when culturing to blastocyst, even though embryos could have been transferred on day 3, is a valid criticism, but it is rare and occurs less than 5%–6% of the time in established labs. The assumption that an embryo that is viable on day 3 but does not make a blastocyst would have made a viable pregnancy is unsubstantiated. Indeed, there are many cycles with no euploid blastocysts, that is, a cycle where only miscarriage or no pregnancy would occur. Both of these circumstances have been described as futile cycles, and yet they are no more futile than a cycle in which the transfer was done on day 3 followed by luteal support with either a miscarriage or negative pregnancy test as the outcome. Indeed, it is clear that euploid embryo transfer has a lower miscarriage rate, and avoiding miscarriage has clear psychological, financial, and medical advantages.

When discussing safety, the issue of multiple gestations is paramount. The risks to the mother (the most severe of which includes preeclampsia/eclampsia) must be recognized as a major reproductive health issue that now has a potential solution that cannot be ignored. Twin pregnancies are not safer than singleton pregnancies. A well-designed randomized controlled trial has shown that elective single-embryo transfer of a euploid blastocyst provides the same success as double-embryo transfer of untested blastocysts. Although success rates were similar in the two groups, the rate of twinning in the double-embryo transfer group was significantly higher (53.4%), as opposed to the single-euploid embryo transfer group (0%). When one considers the risks of multiple gestations (increased rates of prematurity, cerebral palsy, and perinatal death), this provides a compelling argument for transfer of a single-euploid embryo. Further, the issue of cost has been a major concern for both patient and provider. Cost needs to be considered with monetary, health, safety, and outcome metrics. A study from Canada showed that 17% of admissions in their intensive care unit were multiple gestations directly resulting from assisted reproductive technology. They described that if a mandatory single-embryo transfer policy were to take effect, it would have saved 3,082 patient days and 270 patient ventilator days (3). Although it is difficult to mandate single-embryo transfer, genetic screening of embryos allows elective single-embryo transfer to become a viable and attractive option for the infertility patient.

Despite several randomized controlled trials documenting its efficacy, there have been many papers that criticize the widespread use of preimplantation genetic screening of blastocysts using comprehensive chromosomal screening. Although cost considerations are paramount, none of the cost analyses include the reduced cost of multiple gestations, miscarriage, frozen aneuploid embryos, and pregnancy termination that preimplantation genetic screening affords. The

emotional and monetary costs of spontaneous abortion cannot be ignored. It has been shown that many spontaneous abortions in the first trimester are caused by chromosomal abnormalities, even in patients age less than 40 years. This makes genetic testing of embryos a particularly attractive proposition. A reduced miscarriage rate from an IVF cycle has significant merit. Initial efforts with preimplantation genetic screening, however, involved day-3 blastomere biopsy, which in fact proved to be somewhat harmful, and ultimately this technique has fallen out of favor. Since then, multiple publications have shown the superiority and safety of day-5 trophectoderm biopsy with comprehensive chromosomal screening as compared with contemporary IVF (4).

Subsequently, randomized controlled trials have shown superior implantation rates and live birth rates in those who underwent trophectoderm biopsy and chromosomal screening compared with those who did not. If the goal is the delivery of a single, euploid healthy baby, then genetic screening of embryos followed by single, thawed, euploid embryo transfer seems to have the greatest potential for achieving this goal (5). In fact, irrespective of genetic testing, frozen (programmed or natural) embryo transfer was shown to have statistically decreased risks of ectopic pregnancy, antepartum hemorrhage, preterm birth, small for gestational age, low birth weight, and perinatal mortality. The combination of genetic screening, via a proven and safe method of trophectoderm biopsy, along with transfer during a frozen/programmed embryo-transfer cycle, provides hope for the future of assisted reproduction. Care can be individually suited to the patient with regard to age and ovarian reserve status. It may not yield success for all patients, but our obligation to first do no harm will be served by transferring fewer aneuploid embryos, making fewer multiple pregnancies, ectopic pregnancies, electively terminated chromosomally abnormal pregnancies, miscarriages, and premature babies.

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REFERENCES

1. Scholtes MC, Zeilmaker GH. A prospective, randomized study of embryo transfer results after 3 or 5 days of embryo culture in in vitro fertilization. Fertil Steril 1996;65:1245–8.
2. Adler A, Lee HL, McCulloh DH, Ampeloquio E, Clarke-Williams M, Wertz BH, et al. Blastocyst culture selects for euploid embryos: comparison of blastomere and trophectoderm biopsies. Reprod Biomed Online 2014;28:485–91.
3. Janvier A, Spelke B, Barrington KJ. The epidemic of multiple gestations and neonatal intensive care unit use: the cost of irresponsibility. J Pediatr 2011;159:409–13.
4. Scott RT Jr, Upham KM, Forman EJ, Zhao T, Treff NR. Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial. Fertil Steril 2013;100:624–30.
5. Schoolcraft WB, Treff NR, Stevens JM, Ferry K, Katz-Jaffe M, Scott RT Jr. Live birth outcome with trophectoderm biopsy, blastocyst vitrification, and single-nucleotide polymorphism microarray-based comprehensive chromosome screening in infertile patients. Fertil Steril 2011;96:638–40.