Improving IVF Results: How Far Can We Tamper with Human Biology?

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7.1 Introduction

The use of assisted reproductive technology (ART) procedures to treat infertile couples has significantly increased in the United States since its inception in the late 1970s. According to the Society for Assisted Reproductive Technology (SART), a total of 87,089 fresh, non-donor, in vitro fertilization (IVF) cycles were performed in 2013, and it is projected that IVF utilization rates will continue to climb [1]. However, despite significant advancements in the field, the process of human reproduction remains inefficient. Previous work analyzed the number of embryos transferred compared to the number of live births between 1995 and 2001 and showed that the overwhelming majority of embryos produced during IVF cycles (about 85%) and chosen for transfer failed to result in a live born infant [2]. Recently, the same analysis, but for the years 2004 and 2013, demonstrated that out of the total number of embryos replaced (1,808,082), the total number of live born infants was 358,214, for an overall (across all ages and across the 10 years) "embryo wastage" rate of 80% [3]. Similarly, notwithstanding multiple oocytes are retrieved for IVF, the overall live birth rates per oocyte during ART are low (5–10%) and have not changed significantly since the start of IVF almost 40 years ago [4–6].

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7.2 How to Decrease the "Embryo Wastage" Rates

The transfer of fewer embryos is certainly one mechanism to reduce the embryo wastage rates. Examining the trend in mean number of embryos transferred over the last 20 years, the reduction in the mean number of embryos transferred is striking. In fact, in 1995 the overall mean number of embryos transferred during IVF was 3.9 [2] and has steadily decreased from an average of 2.75 in 2004 to 2.04 in 2013, and this trend, seen across all age groups, was significant [3]. Despite the reduction in the mean number of embryos replaced, the transfers resulting in a live birth have significantly increased each year across all age groups with the exception of the group of women age greater than 42. In 2004, the overall embryo wastage rate, meaning the number of embryos that did not lead to a live birth, was 83%, which decreased to 76.5% in 2013, and this trend was statistically significant ($p < 0.001$).

When age groups were analyzed individually, "embryo wastage" rates decreased ($p < 0.05$) across all age groups, and it was more pronounced in the younger women, particularly for the group of women under the age of 35, where "embryo wastage" decreased from 76.1% in 2004 to 65.2% in 2013 ($p < 0.001$) [3]. In women over the age of 42, the "embryo wastage" rate only marginally decreased and remained relatively high from 2004 to 2013 (98.0% to 97.2%, respectively), and in this age group, there was also the smallest change in the mean number of embryos transferred (3.3 in 2004 to 2.8 in 2013). Data analysis further showed that the average number of embryos transferred per year, averaged across all age groups, positively correlated with the "embryo wastage" rate (Spearman coefficient = 0.988, $p < 0.001$). This illustrates that as the number of embryos transferred decreased, the percentage of non-implanting embryos also decreased without having an impact on the pregnancy rates. This pattern has been consistent since 1995 and is further proof that only a few embryos, if any, are competent for live birth per cohort in each ART cycle [2, 3, 7]. In other words, it is possible to decrease the wastage rate, but this is not due to an improved oocyte or embryo biology but merely to a reduction in the mean number of embryos transferred (i.e., a smaller denominator in the equation of total live births divided by the total number of embryos transferred).

7.3 Biological Questions and Embryo Selection

Many unanswered biological questions remain: (1) Why so many human oocytes and embryos retrieved and produced during IVF do not result in a live birth? (2) Why most menstrual cycles in the human do not yield a competent oocyte or a viable embryo? (3) Why the use of IVF has not changed this biological law of nature?

Over the years, it has become apparent that IVF can maximize a reproductive cycle but there is a biological limit imposed on the fraction of human eggs retrieved after stimulation, to the percent of human eggs that can produce a live baby [8]. In fact, even with the application of the currently best methods available in clinical practice or in the embryology laboratories, not every IVF cycle (like not every menstrual cycle in nature [9, 10]) will yield a competent oocyte/embryo for live birth.

We can only strive to maximize pregnancy and live birth rates per transfer by identifying whether in that specific reproductive cycle there is or there is not an embryo of high potential for a birth. However, this is just a matter of selection, not true "improvement." In fact, no selection method will ever increase live birth rates per started cycle (due to the intrinsic biological limits of human reproduction) [8].

An approach slowly gaining more acceptance is for all the embryo transfers to be at the blastocyst stage of growth, which means growing the embryos in vitro up to day 5 or 6 of development before transfer. If the embryos arrest before day 5 or day 6, given today's greatly improved laboratory conditions, it probably means that, in that particular cycle, they were not viable and not destined to become a live birth [8]. The recent Cochrane literature supports improved pregnancy rates per transfer with blastocyst as opposed to cycle day 3 transfers [11]. If we were to do all transfers at the blastocyst stage, we would improve the live birth rates when calculated per transfer (since there will be fewer, unnecessary, transfers), although no patients should be deceived into thinking it will improve their overall chance for pregnancy.

There are a number of other methods being promoted for the assessment of embryo viability and competence for a live birth. However, they are invasive, not completely reliable, costly, and likely result in the non-transfer/discard of some viable embryos. If one proposes PGS (preimplantation genetic screening) for all blastocysts, there is now sufficient data to demonstrate that PGS is neither sensitive nor specific enough to select all euploid embryos, and there is accumulating data to demonstrate that this could ironically even lower live birth rates [12–18]. Indeed offering sophisticated embryo PGS testing (via array CGH or SNP or qPCR or next-generation sequencing—NGS) has been shown be impacted by high rates of trophectoderm embryo mosaicism [12–15], making the diagnostic accuracy very challenging with the risk of discarding some normal embryos that were incorrectly diagnosed as abnormal. Therefore, the overall pregnancy rate might be decreased rather than increased [15–17]. Recently the use of PGS has been shown to be ineffective also in improving pregnancy rates on intent to treat analysis (IVF with PGS versus expectant management) in patients with recurrent pregnancy loss [18].

Another method is the selection of embryos by time-lapse imaging of morphokinetic and morphological parameters, based on the assumption that a continuous observation of embryo's growth can be predictive of embryos with the highest capacity to implant. However, this methodology comes with vastly increased costs and the risk of deselecting embryos still able to produce live births. One study in fact has reported the birth of healthy children after transfer of blastocysts originating from embryos with abnormal morphokinetic cleavage patterns that should have been not transferred if the time-lapse indications were needed. These authors concluded that only the transfer of viable embryos after 5–6 days of cultured (blastocysts) provides optimal embryo selection [19]. Likewise, another very recent randomized control trial, comparing time-lapse-selected embryos versus those selected by morphology alone, showed that the addition of time-lapse morphokinetic data did not improve clinical reproductive outcomes [20, 21]. But again, all these methods are only selection, and not true improvement of oocytes or embryos biological quality [8].

Therefore, the easiest, noninvasive, and least expensive way to increase the pregnancy rate and live baby rate per transfer without lowering the live baby rate per patient is the adoption of exclusive blastocyst-stage transfers (day 5 or 6 embryos). Blastocyst transfers are not associated with any likelihood of discarding normal embryos that were wrongly diagnosed as abnormal (as with PGS because of trophoblast mosaicism, or judged abnormal as per morphokinetic parameters). By utilizing only blastocyst-stage embryos for transfer, the live baby pregnancy rates per transfer across all ages will quickly surge (since the same number of pregnancies will be calculated out of a smaller denominator), and also the implantation rates will increase since fewer embryos will be transferred [8].

There will be some cases with no transfers, and so clinicians may worry, what will be the patient reaction to not having a transfer? With proper counseling, patients will be thankful for knowing early in the process that the cycle was not successful because there were no transferable embryos, if none developed to the blastocyst stage. This will save unnecessary emotional stress, reduce "false hopes," avoid unnecessary supplementation of progesterone, reduce costs, and allow patients to move sooner to another cycle or to alternative plans. A question that cannot be answered at this time with unequivocal certainty is whether some patients may still benefit of day 3 embryo transfers instead of day 5, on the assumption that the laboratory conditions might impair the further development of an embryo. If there is any doubt in the physician's mind for a particular group of patients (particularly those with three or fewer embryos), then they could opt for a cycle day 3 transfer at the first cycle of IVF, and if it fails, then blastocyst culture would be used for selection in a subsequent cycle. So as long as viable embryos are not mistakenly discarded as with the current imprecise trophectoderm biopsy results and morphokinetic parameters, the shorter time to pregnancy will be of benefit.

In summary, despite today's greatly improved laboratory conditions and the individualization of stimulation protocols, the process of IVF is still inefficient with low live birth rates per embryos produced and per oocytes retrieved. This is because the majority of human oocytes harvested and the majority of embryos produced are chromosomally or genetically abnormal. The ability to confidently identify gametes and embryos with the greatest reproductive potential would not improve overall live baby rate, but it would improve the success rate per transfer and lessen the agony of waiting for what turns out to be a negative pregnancy test.

Of course, better than improved embryo selection is to actually improve live baby rates per oocyte and per stimulated cycle. A carefully conducted "big data" multivariate regression analysis has ironically linked high FSH overdosage in ovarian stimulation to lower success [22]. Tampering too much with nature in this case actually has lowered IVF success. So perhaps the best advance now for IVF is to take a step backward rather than forward, recognizing the inherited deficiency of the human oocyte and just maximizing natural selection accuracy.

A recent paper [23] noted that the intrinsic fertility of the oocyte as ascertained by natural cycle IVF with single-embryo transfer does not decline until the age of 34 years. In fact, the fecundity rate of about 25% is maintained until this time. This work also showed that during natural cycles the intrinsic fertility of the oocyte,

assessed by live baby per oocyte collected, is much higher (five times higher) than when there is ovarian stimulation strongly arguing in favor of considering a much lower stimulation for IVF cycles to reduce oocyte wastage [23].

References

1. Society for Assisted Reproductive Technologies (SART). www.sart.org. 2015.
2. Kovalevsky G, Patrizio P. High rates of embryo wastage with use of assisted reproductive technology: a look at the trends between 1995 and 2001 in the United States. Fertil Steril. 2005;84:325–30.
3. Ghazal S, Patrizio P. Embryo wastage rates remain high in assisted reproductive technology (ART): a look at the trends from 2004-2013 in the United States. JARG. 2017;34(2):159–66.
4. Patrizio P, Bianchi V, Lalioti MD, Gerasimova T, Sakkas D. High rate of biological loss in assisted reproduction: it is in the seed, not in the soil. Reprod Biomed Online. 2007;14:92–5.
5. Patrizio P, Sakkas D. From oocyte to baby: a clinical evaluation of the biological efficiency of in vitro fertilization. Fertil Steril. 2009;91:1061–6.
6. Martin JR, Bromer JG, Sakkas D, Patrizio P. Live babies born per oocyte retrieved in a subpopulation of oocyte donors with repetitive reproductive success. Fertil Steril. 2010;94:2064–8.
7. Doherty L, Martin JR, Kayisli U, Sakkas D, Patrizio P. Fresh transfer outcome predicts the success of a subsequent frozen transfer utilizing blastocysts of the same cohort. Reprod Biomed Online. 2014;28(2):204–8.
8. Patrizio P, Silber S. Improving IVF: is there a limit to our ability to manipulate human biology? JARG. 2017;34(1):7–9.
9. Hertig TA. Human trophoblast: normal and abnormal. Am J Clin Pathol. 1967;47(3):249–68.
10. Opitz JM, Fitzgerald JM, Reynolds JF, Lewin SO, Daniel A, Ekblom SL, Phillips S. The Montana fetal genetic pathology program and a review of prenatal death in human. Am J Med Genet Suppl. 1987;3:93–112.
11. Glujovsky D, Blake D, Farquhar C, Bardach A. Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology. Cochrane Database Syst Rev. 2012;(7):CD002118.
12. Greco E, Minasi MG, Fiorentino F. Healthy babies after intrauterine transfer of mosaic aneuploid blastocysts. N Engl J Med. 2015;373:2089–90.
13. Orvieto R, Shuly Y, Brengauz M, Feldman B. Should pre-implantation genetic screening be implemented to routine clinical practice? Gynecol Endocrinol. 2016;32(6):506–8. (e-pub Feb 12, 2016).
14. Scott RT, Galliano D. The challenge of embryonic mosaicism in preimplantation genetic screening. Fertil Steril. 105(5):1150–2. (e-pub Feb.10, 2016).
15. Gleicher N, Vidali A, Braverman J, Kushnir VA, Barad DH, Hudson C, et al. Accuracy of preimplantation genetic screening (PGS) is compromised by degree of mosaicism of human embryos. Reprod Biol Endocrinol. 2016;14(1):54.
16. Kang HJ, Melnick AP, Stewart JD, Xu K, Rosenwaks Z. Pre-implantation genetic screening: who benefits? Fertil Steril. 2016;106(93):597–602.
17. Orvieto R, Gleicher N. Should pre implantation genetic screening (PGS) be implemented to routine IVF practice? J Assist Reprod Genet. 2016;33(11):1445–8. (e pub Sept.15).
18. Murugappan G, Shahine LK, Perfetto CO, Hickok LR, Lathi RB. Intent to treat analysis of in vitro fertilization and preimplantation genetic screening versus expectant management in patients with recurrent pregnancy loss. Hum Reprod. 2016;31:1668–74.
19. Stecher A, Vanderzwalmen P, Zintz M, Wirleitner B, Schuff M, Spitzer D, Zech NH. Transfer of blastocysts with deviant morphological and morphokinetic parameters at early stages of in-vitro development: a case series. Reprod Biomed Online. 2014;28(4):424–35.
20. Goldman LR, Goldberg J, Falcone T, Austin C, Desai N. Does the addition of time-lapse morphokinetics in the selection of embryos for transfer improve pregnancy rates? A randomized controlled trial. Fertil Steril. 2016;105(2):275–85.

21. Wu YG, Lazzaroni-Tealdi E, Wang Q, Zhang L, Barad DH, Kushnir VA, et al. Different effectiveness of closed embryo culture system with time-lapse imaging in comparison to standard manual embryology in good and poor prognosis patients: a prospectively randomized pilot study. Reprod Biol Endocrinol. 2016;14(1):49–54.
22. Baker VL, Brown MB, Luke B, Smith GW, Ireland JJ. Gonadotropin dose is negatively correlated with live birth rate: analysis of more than 650,000 assisted reproductive technology cycles. Fertil Steril. 2015;104:1145–52 e5.
23. Silber S, Kato K, Aoyama N, Yabuuchi A, Skaletsky H, Fan Y, Liao C, et al. Intrinsic fertility of human oocytes. Fertil Steril. 2017;107(5):1232–7.