Journal of Assisted Reproduction and Genetics (2020) 37:495–496
https://doi.org/10.1007/s10815-020-01759-w

COMMENTARY

Novel insights into the genetics of early human development: PGT as a catalyst for reform

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Published online: 26 March 2020

"The idea is to try to give all the information to help others to judge the value of your contribution; not just the information that leads to judgment in one particular direction or another."

Richard Feynman.

Setting priorities at times like these seems a purposeless task for those of us engaged in the business of reproductive medicine. As we remain mired in the depths of the coronavirus pandemic, collecting all the information we can about the virus and how it spreads is the imperative at hand as experts around the globe seek to limit the already devastating consequences of Covid-19. While our thoughts and hopes go out to all those affected by this crisis, perhaps it is time to reflect on one of the more controversial issues frequenting the pages of so many journals in our field over the past 10 years. JARG has been no different from our sister publications in meeting the challenges posed by the field of genetic testing, especially in the context of what we now refer to as PGT-A.

Our current issue brings the JARG readership closer to the conversation we should have been having all along. Buttressed by contributions from a diverse collection of authors representing a spectrum of perspectives, this month's treatment takes the matter of PGT-A through a dynamic range of interpretations and recommendations. What emerges is an acknowledgement of the rightful place PGT-A has assumed in clinical practice in sharp contradistinction to the advances made in the basic biology underlying early human development. Any worthwhile information gathering effort aimed at diagnosing, treating, and managing our common cause of infertility should in the end bring a sense of pause and reflection on what we have learned that we may not have known before.

The biology of early human embryo development has come a long way from the Carnegie collection of the 1940s. The centerpiece upon which much of our understanding is based is understandably the chromosome [1]. And through it all, testing for chromosomes, mutations, and many unanticipated genomic *variations on the theme* brought the relevance of our genetic inheritance in normal and disease states to the forefront of human ARTs in an era that witnessed the arrival of a plurality of gametes and embryos. The hard choices of what gamete pairs or embryos would become a child now rested firmly in the hands of ART practitioners.

That PGT-A may be only scratching the surface of what could go wrong in a human embryo to cause miscarriage or a malformation was being queried by some. For example, Adashi and McCoy drew attention to the prevalence of zygotic mitotic errors and their mosaic nature relative to the well-known zygotic penetrance exhibited by errors during meiosis [2] . Moreover, many of the peculiarities of cell behavior noted through the application of time lapse imaging of human embryos, exposed on a broad scale deviations in cell cycle progression and cell division behaviors once reserved for the most abnormal of cells within tumors [3]. Based on several years of imaging mammalian embryo behavior, with great spatial and temporal precision, we now know with a measure of certainty the these behaviors are not unique to human embryos but rather represent measures of great plasticity and dynamism during the initial cell cycles of human development deviating from the norm of what somatic cells would be expected to do [4].

For more than a decade now, we ART aficionados have been looking in on the embryo during this vulnerable phase of its preimplantation existence. With the widespread adoption of time lapse imaging, we have witnessed an enormous range of cellular behaviors and intracellular and intercellular dynamics not imaginable before this window opened. From this perspective alone we have learned much about human embryos. When combined with a rich history of genetic testing and analysis, and careful tracking of fates enabled by a progressively extended period of culture and observation, we have learned much about the biology of the human embryo, much more than we seem to credit our field for.

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Listening to what the embryo was trying to say, we took aim on chromosomes-counting them, confirming what earlier studies had shown that beyond the realm of meiotic aneuploidies, the mitoses exhibited by the early embryo were highly error prone in chromosome segregating capabilities! The result-*viva la mosaicism*.

And with this realization came a series of studies linking what we saw in time lapse in the form of tripolar spindles and 1–3 cell divisions and the downstream consequences chromosome imbalances often leading to developmental arrest [5]. As mentioned above, it turns out that we are not alone as a species in making matters of cytoskeletal remodeling and genetic gymnastics a property of early development underlying at least one dimension of mosaicism that has gathered so much attention over the recent past [6].

Had we looked with the greater resolution afforded by high throughput sequencing, an emerging field in genetics having to do with genome mosaicism would have captured our attention [7]. Genome mosaicism coupled with the maturing field of single cell analysis, reinforced the notion of heterogeneity or mosaicism as the norm within embryos, tissues, organs and whole organisms. Add to recognition of the prevalence of mosaicism the many mechanism now appreciated to generate this and other forms of genetic diversity not adhering to the laws of Mendelian inheritance [6], like meiotic drivers [8], and we are left with a sense of gratitude for what ARTs has contributed to our evolving understanding of the complexities of early human development.

How ARTs impact offspring health later in life has been an information gathering objective since the initial days of IVF. As we move to the future in adopting and implementing well-intentioned technologies like PGT-A and others introduced to our readership in this issue, we should remain mindful of just how critical these earliest days of human development are with respect to acquired genetic predispositions to disease later in life [9].

References

1. Griffin DK, Ogur C. Chromosomal analysis in IVF: just how useful is it? Reproduction. 2018;156(1):F29–50.
2. Adashi EY, McCoy RC. Technology versus biology: the limits of pre-implantation genetic screening: better methods to detect the origin of aneuploidy in pre-implantation embryos could improve the success rate of artificial reproduction. EMBO Rep. 2017;18(5):670–2.
3. Coticchio G, Mignini Renzini M, Novara PV, Lain M, De Ponti E, Turchi D, et al. Focused time-lapse analysis reveals novel aspects of human fertilization and suggests new parameters of embryo viability. Hum Reprod. 2018;33(1):23–31.
4. Vazquez-Diez C, Paim LMG, FitzHarris G. Cell-size-independent spindle checkpoint failure underlies chromosome segregation error in mouse embryos. Curr Biol. 2019;29(5):865–73 e3.
5. McCoy RC, Newnham LJ, Ottolini CS, Hoffmann ER, Chatzimeletiou K, Cornejo OE, et al. Tripolar chromosome segregation drives the association between maternal genotype at variants spanning PLK4 and aneuploidy in human preimplantation embryos. Hum Mol Genet. 2018;27(14):2573–85.
6. Vazquez-Diez C, FitzHarris G. Causes and consequences of chromosome segregation error in preimplantation embryos. Reproduction. 2018;155(1):R63–76.
7. Lupski JR. Genetics. Genome mosaicism–one human, multiple genomes. Science. 2013;341(6144):358–9.
8. Zanders SE, Unckless RL. Fertility costs of meiotic drivers. Curr Biol. 2019;29(11):R512–R20.
9. Liu P, Yuan B, Carvalho CMB, Wuster A, Walter K, Zhang L, et al. An organismal CNV Mutator phenotype restricted to early human development. Cell. 2017;168(5):830–42 e7.