J Assist Reprod Genet (2014) 31:1113–1114
DOI 10.1007/s10815-014-0325-x

EDITOR'S COMMENTARY

Relevant and irrelevant translational discovery and male infertility: the case of the Y chromosome and more!

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Published online: 31 August 2014

Finger-pointing and blame-passing retain the distinction as favorite pastimes of constituencies whose members beg to proffer opinions of a contrasting or debatable character. While widely recognized as the sum and substance of political discourse, assigning fault and flaw in medical disciplines spans the bench-to-bedside mentality upon which meaningful, and useless, discoveries are served up to members of the biomedical research community intent on identifying new cures or treatments for human disease, and/or the mechanistic bases of the complex biological processes underlying disease etiology. The evolution of ARTs for manipulating reproductive performance in animals, including we hominids, will continue the blame game as long as betterments and refinements are sought out by the clinicians and scientists vested in a deeper understanding of reproductive physiology.

Transcending, or is it descending, the ladder from human behavior down to gametes, it has become tradition to assign failures to fertilize to either the egg or sperm. This month, JARG focusses on the male side of the coin. We launch our coverage on the topic of male infertility with a comprehensive review from Ashok Agarwal and his colleagues that takes our readership through the current status of the genetic and epigenetic determinants of spermatogenesis in the human, including a critical evaluation of the methods presently in use to bypass sperm deficits using ARTs (A multi-faceted approach to understanding male infertility: gene mutations, molecular defects and assisted reproductive techniques (ART), DOI 10.1007/s10815-014-0280-6). The authors draw immediate and special attention to the fact that as our knowledge base deepens regarding the genetic and molecular causes of male infertility, caution must be maintained and encouraged in the practice of ARTs given the likelihood that offspring produced from intrinsically maligned sperm will bear properties of disease states themselves, compromising reproductive and general health in future generations.

Reinforcing the theme of male infertility is a study that notes the prevalence of failed fertilization in human ARTs and seeks ways to eradicate such an outcome in traditional and ICSI cycles. Hence, total fertilization failure (TFF) is expected in 5-10 % of all IVF cycles, and even after ICSI 30 % of oocytes fail to initiate development. Is there a way to overcome this by increasing oocyte number is the question posed by Kahyaoglu and colleagues in this issue (Total fertilization failure: is it the end of the story? DOI 10.1007/s10815-014-0281-5). Once again, the take-home message is that "more" is not better and the reasons for finger-pointing at the egg or sperm are reviewed in some detail.

In drawing attention to the widely adopted use of ICSI for IVF, and IUI as the first and direct treatment strategy for infertile couples, two studies are presented in which methodologies used to enrich the "best of the best" sperm. Finding better ways to enrich normal sperm relative to those bearing abnormal morphological features was the subject of studies by Xue and team where they compare swim up versus density gradient separation approaches in the context of the DNA fragmentation index (Efficacy of swim up versus density gradient centrifugation in improving sperm deformity rate and DNA fragmentation index in semen samples from teratozoospermic patients, DOI 10.1007/s10815-014-0287-z). Finally, from the University of Texas Southwestern Medical Center in Dallas comes the report from Tan and colleagues

Capsule With detailed genomic maps and epigenetic landscapes being uncovered in pathognomic and idiopathic cases of male infertility, insights into the immediate and distal responsibilities of the Y chromosome for the physiology of human reproduction are becoming better understood. And with the recent findings that in mice as few as two genes on the Y chromosome are necessary and sufficient for term development, the use of ROSI and other ARTs may require reconsideration as to their safety and efficiency.

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that sets realistic cutoff values for semen parameters that predict pregnancy success in IUI cycles (Predictive value of postwashed total progressively motile sperm count using CASA estimates in 6871 non-donor intrauterine insemination cycles, DOI 10.1007/s10815-014-0306-0).

While much to do has been made of the development and application of "OMICS" in the field of human ARTs, the translational relevance of such approaches has yet to be established. Of the newer technologies being evaluated for their use in identifying metabolomic biomarkers of male infertility, NMR analysis of seminal fluids offers some promise as demonstrated by the work of Jayaraman et al. (Identification of biochemical differences between different forms of male infertility by nuclear magnetic resonance (NMR) spectroscopy, DOI 10.1007/s10815-014-0282-4). In the end, the role of the Y chromosome in sex determination, testis development, and function in adult life has been the overarching focus in the field of male reproductive physiology and genetics.

For those Y chromosome aficionados in the audience, a report earlier this year must have come as some surprise and for the sake of closure, reminds us of the ongoing debate regarding the translation of studies in animals to human biology.

From the group of Monika Ward at the Institute for Biogenesis Research of the University of Hawaii comes the startling finding that the essence for production of sperm capable of supporting term development in mice is reducible to but two genes located on the Y chromosome (Yamauchi et al., 2014, Two Y genes can replace the entire Y chromosome for assisted reproduction in the mouse, Science 343:69–72, DOI 10.1126/science1242544). This remarkable series of experiments takes advantage of several transgenically manipulated mouse lines in which the Y chromosome has been reduced from 78 Mb to approximately 2 Mb encoding only seven genes. Although these mice are infertile, intratesticular retrieval of round spermatids was possible even amidst the largely aberrant phenotypes noted in the seminiferous tubules. Germ cells from these mutant animals were then used to perform round spermatid injection (ROSI) into mature oocytes which, in a low number of cases, developed into 2-cell embryos that were transferred into fallopian tubes of recipient animals that subsequently gave birth to live offspring. ROSI efficiency with sperm from miniY chromosome mice was lower than that obtained with spermatids from normal XY bearing males and the offspring produced with truncated Y chromosomes were healthy and fertile upon further mating. These studies reveal a level of complexity in the Y chromosome that begins to explain many of the male infertility phenotypes known to afflict humans in relation to clinically recognized dysmorphisms typically managed with traditional ICSI. Moreover, the fact that many of the mutant mouse round spermatids used in this study were documented to have a diploid composition owing to expected failures in the completion of meiosis-2, the demonstrable restoration of diploid zygotes at the 2-cell stage implies the existence of, at least in the mouse, an early conceptus-based mechanism for rectifying triploidy! While the authors of this study in a rarely recognized admittance of a lack of relevance to human biology are to be commended, they proceed to explain how the composition of the human Y chromosome differs from that of the mouse and how these findings would have to be properly contextualized before translation to human ARTs.

The broader implications for human ARTs are noteworthy. Although it retains its experimental status, ROSI stands as a logical therapeutic strategy for the treatment of non-obstructive azoospermia. And even in cases where genetic deficiencies indicate the likelihood of ICSI with diploid sperm resulting from a failure to complete meiosis, the studies in mice suggest that zygotic correction from a triploid to diploid chromosome constitution occurs with low efficiency and produces genetically balanced and healthy offspring. Such assurances at the time of embryo transfer would be obtainable using PGS. In the meantime, it will be of utmost importance to follow the health of ROSI-ICSI children to gain insight into the safety and efficiency of melded ARTs and the extraordinary means by which human embryos manage extreme cases of genetic imbalance derivative of this and other ART procedures.