The effects of governmental interventions on clinical practice and research in reproductive medicine and reproductive biology

The term “reproductive medicine” refers to maintenance of normal reproductive functions in women and men, aside of nutritional maintenance, allowing for the most basic of all biological functions—successful reproduction and maintenance of the human species. “Reproductive biology,” in turn, is the study of these reproductive processes, allowing for the development of therapeutic interventions based on better understanding of physiological processes underlying normal reproductive function.

Some history

Since the purpose of human reproductive processes is the creation of new human life, clinical practice as well as research in this arena has always been surrounded by public controversy, ethical disagreements and varying degrees of government interventions. A number of key events come to mind: It all started in 1944, after John Rock, MD (at the time a Clinical Professor of Ob/Gyn at Harvard Medical School in Boston, MA, and his research assistant, Miriam Menkin, announced in SCIENCE that, after six years of work, they had observed in vitro fertilization (IVF) and initial embryo cleavage.

The next noteworthy event took place in 1973 (5 years before the first IVF baby was born in the UK) when the Chairman of the Ob/Gyn Department at Columbia University in New York City stormed into the laboratory of Landrum Brewer Shettles, PhD, MD and destroyed the experiment after he learned that Shettles had fertilized for clinical purposes an egg of a patient (named Del-Zio) with her husband's sperm. This created major controversy and headlines, especially since the Del-Zios filed a lawsuit against Columbia Presbyterian Hospital, and were awarded damages.
TRANSLATIONAL REPRODUCTIVE BIOLOGY AND CLINICAL REPRODUCTIVE ENDOCRINOLOGY

Conference Theme: Paradigm changes you may not hear about elsewhere!
Organized by The Foundation for Reproductive Medicine

NOVEMBER 17-20, 2016 • NEW YORK, NY, USA

The Grand Hyatt Hotel • 109 East 42nd Street, New York, NY 10017

Think Differently!

IF YOU THIS YEAR DID NOT HAVE THE OPPORTUNITY TO ATTEND THE ANNUAL ASRM MEETING IN SALT LAKE CITY, UTAH, GET YOUR ANNUAL UPDATE IN NEW YORK CITY.

Pre-Conference Workshops:

| In vitro follicle/oocyte maturation age: From primordial stages | A new paradigm in clinical IVF: Age-specific stimulation and embryology | An in vitro implantation model: Peeking into the “black box” of implantation | The biological basis for the demise of preimplantation genetic screening (PGS) |

Sessions:

| The future of fertility care | Paradigm change I: Expanding infertility treatments from the gonadotropin-sensitive to earlier stages of follicular maturation | Paradigm change II: Early diagnosis of premature ovarian senescence, offering women more and better reproductive options | Paradigm change III: Reconsidering embryo selection | Paradigm Change IV: Individualization of infertility care | Skeptical of current clinical practice? Here are some answers! |

Breaking News Lecture on Friday, November 18, 2016

Building the mouse and human embryo: cell fate and plasticity
Magdalena Zernicka Goetz, PhD, FMedSci | Professor of Mammalian Development and Stem Cell Biology, Department of Physiology, Development & Neuroscience | University of Cambridge

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Primary Care Network (PCN) and the Foundation for Reproductive Medicine. Primary Care Network is accredited by the ACCME to provide continuing medical education for physicians. Primary Care Network designates this live activity for a maximum of 23.25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

For program and registration, visit the official conference website:
http://frm.cme-congresses.com/

Foundation for Reproductive Medicine
Attendee Inquiries: FRM@cme-congresses.com
Sponsorship & Exhibitor Inquiries: ttan@foundationforreprodmed.com
This study once more establishes an etiological association between low functional ovarian reserve (LFOR), as assessed by anti-Müllerian hormone (AMH), and autoimmunity, in this case presence of anti-phospholipid antibodies (APAs). These observations, therefore, once again point toward an autoimmune etiology leading at least in a portion of infertile women to LFOR.

Practically for the clinician these findings suggest that if APAs are seen in an infertile women, LFOR has to be suspected and vice versa: If LFOR is diagnosed, the clinician should suspect presence of autoimmunity, and especially of APAs, which for decades have been associated with increased miscarriage risk.

As the tile indicates, this “letter to the editor” addressed a comprehensive review published in the journal by Spanish investigator, which well-reviewed the current state-of-the-arts of managing refractory endometrium to treatment. In this review the authors repeated referred to a series of papers published by CHR investigators, utilizing granulocyte colony-stimulating factor (G-CSF) to induce proliferation of thin endometrium in, otherwise, treatment-resistant patients.

Clinically, this means that CHR’s decision not to convert the IVF laboratory to this automated technology, at least considering the high quality of CHR’s embryology, was the correct one. These findings, however, do not mean that IVF laboratories with poorer embryology or with uneven embryology may not benefit from such instrumentation.

We last month in the VOICE noted that the initial enthusiasm for these instruments worldwide has abated since not a single study has been able to describe specific morphological markers of cultured embryos observed via time-lapse imaging that were predictive of IVF outcome and, therefore, could be used for so-called embryo selection.
In a way, this was a correcting letter because the authors of this overall excellent review article misrepresented the results of a prospectively randomized study CHR had reported in the literature. Clinically, the letter concluded that there is good evidence that G-CSG perfusion of the endometrium within 48 hours allows proliferation of the endometrium to at least 7.0 mm thickness.

This manuscript, we are convinced, will become a widely cited landmark article in the demise of PGS as a widely utilized test in association with IVF. CHR investigators in this article report for the first time in the medical literature remarkable inconsistencies in PGS diagnoses between multiple embryo biopsies of same embryos as well as between repeat embryo biopsies done in different (supposedly high quality) national PGS reference laboratories. The authors conclude that these findings with great likelihood can only be explained by much more mosaicism in the trophectoderm (from where biopsies are taken at blastocyst stage of embryos) than has so far been appreciated.

In a second part of the study, the authors report on so-far 5 healthy children delivered after transfer of allegedly chromosomally abnormal embryos, which IVF center traditionally have discarded. From these results they conclude that above cited frequent mosaicism in biopsies of trophectoderm, likely, frequently results in false-positive diagnoses and the unnecessary discarding of large numbers of perfectly healthy embryos.

Since this manuscript was submitted for publication, the Preimplantation Genetic Diagnosis International Society (PGDIS) actually confirmed these interpretations of here reported results, and dramatically changed how PGS biopsy results should be reported, as we presented in detail in the September VOICE. The in this manuscript reported findings, therefore, clearly already greatly affected how PGS is practiced worldwide.
In those days the concept of IVF was still unknown to the public, though a number of scientists had started to experiment, with the ultimate goal of helping women to conceive who were unable to do so with the fertility treatments available at the time. Shettles’ deed of fertilizing a human egg in an attempt to create in vitro a human embryos was, therefore, even by the Chairman of the Ob/Gyn (at that time himself a prominent fertility specialist) perceived as an ethically unacceptable step, warranting the violent destruction of the experiment.

Not surprisingly, therefore, even most liberal media sided with the Chairman, deploring the potential risks of human IVF, convinced that any such process would lead to the production of human “monsters.” Though probably one of the most talented investigators in the field at the time (he already in 1951 repeated the original fertilization experiments of John Rock and Miriam Menkin), Shettles had to leave Columbia and, while continuing to work experimentally on cloning experiments, never ever lived up to his scientific potential. He died in 2003.

Louise Brown, the first IVF baby in the world, was born on July 25, 1978 at Oldham General Hospital, Oldham, UK. Now the married Mrs. Roberts, and herself a mother, she is reported to have revealed how her mother received post-bags full of hate mail, including menacing notes, blood-spattered letters, a broken glass test tube and plastic fetuses because the concept of having a child via IVF was perceived as “the devil’s work” by so many in the general public.

Robert G. Edwards, PhD, who as biologist, together with Dr. Patrick Steptoe as the clinical Ob/Gyn, was responsible for the world’s first IVF birth, of course was finally in 2010, 32 years after Louise Brown’s birth, awarded the Nobel Prize for Physiology and Medicine. Steptoe missed the award because of death, and by the time it was awarded, Edwards was unable to appreciate the tribute because of dementia. It is reasonable to assume that, had their achievement been in a less “controversial” area of medicine, Steptoe and Edwards would have received the Prize much earlier.

Though millions of healthy offspring have been born worldwide, and IVF births in some countries now represent up to 5% of annual births, the scepter that fertility treatments and/or related research may end up creating in one way or the other human “monsters,” has remained with us. In 2002/2003, CHR investigators, for example, conducted experiments with embryos donated by patients for research, in which they transplanted individual cells (blastomeres) from one embryo to another to investigate whether these transplanted cells were able to integrate themselves and start dividing within the recipient embryo, thus creating a so-called chimera. The purpose of the experiments was to learn whether it might be possible to transplant at early embryo stages healthy cells into an abnormal embryo, which was missing an essential gene product that could be delivered via such cell transplants.

Before the study was published (Gleicher and Tang. Blastomere transplantation in human embryos may be a treatment for single gene diseases. Fertil Steril 2004;81:977-981), CHR’s Medical Director and Chief Scientist, Norbert Gleicher, MD, presented the material at the Annual Meeting of the European Society for Human Reproduction and Embryology (ESHRE), where it was selected as one of four finalists for the Prize Paper of the congress. Invited by ESHRE with the other finalists to be present at a press conference, Dr. Gleicher explained the study to the international press, which resulted in worldwide condemnation of the experimental set up of the study, repeatedly described by some media as “Frankenstein science,” even though there was never an intent of transferring these embryos. In response to the media outcry, though previously selected by the society’s own selection committee of scientists as a finalist, ESHRE withdrew the paper from further consideration.

Since then, the establishment of human chimeras for research purposes has become somewhat routine,
though experimental use of donated human embryos is, of course, still conducted with great respect for these embryos. Considerable effort has, indeed, gone in recent years into establishment of human-animal embryos (i.e., embryos made up of human as well as animal cell lines) because of the great biomedical potential such embryos represent. Insoo Hyun, PhD, Associate Professor of Bioethics and Philosophy in the Department of Bioethics, and Director of the Case Western Reserve University School of Medicine Stem Cell Ethics Center, recently made the point in NATURE that “illusory fears must not stifle chimaera research.” He also concluded that “human moral status is not assured by our genetic composition or the arrangement of our cells” (Hyun I. Illusory fears must not stifle chimaera research. Nature 2016;537:281).

Aside of discussions about establishment of human/animal chimera, crossing the germline has become the dominant topic among professional handwringers in the reproductive ethics arena. The VOICE has discussed this topic extensively in recent months and years because CHR has been attempting in collaboration with investigators at prominent academic institutions to pursue groundbreaking research in this area, which not only has considerable potential of advancing infertility treatments especially in older women, but also, potentially, could cure inherited single gene diseases in human embryos.

Unfortunately, over the last few years of the Obama administration, conduct of all such research has become impossible, as, like other federal agencies, the Food and Drug Administration (FDA) overreached, and declared itself the responsible supervisory government agency for all such research. By doing so, the Federal Government squarely inserted itself into the clinical practice and research in reproductive medicine. This represents unprecedented interference by government into the evolution of medicine, which government, traditionally, avoided by accepting professional self-controls.

Invasion of government regulations

Since it would have to undergo the same processes a pharmaceutical company has to undergo when planning on bringing to market a new drug, above-noted FDA declaration, alone, for all practical purposes made research involving potential manipulations of the germline unavoidable for academic institutions and private fertility centers, like CHR. The costs of any such research would be simply prohibitive, requiring millions, if not hundreds of millions of dollars.

Congress, a few months ago, made matters even worse, when attaching to another law a legal mandate for the FDA to abstain from responding to all such applications even if such research were to be submitted. In other words, even if an organization is willing to, and capable of, spending the money, such research is in the U.S. now for all practical purposes prohibited, even though government does not even have the decency to say so!

We reported in these pages that CHR over a year ago hired a prominent Washington law firm specializing in FDA relationships in attempts to set up a meeting with FDA officials to, simply, discuss options to pursue such research. Even before Congress forbade the FDA to address the issue at all, the FDA already refused any such face-to-face meeting. We, therefore, concluded that this unprecedented invasion of government into medical research and clinical practice would have at least three significant negative consequences: (i) Forcing U.S. investigators to pursue their research outside the U.S., (ii) loss in research leadership in a major medical area; and (iii) loss of control of the quality of such research since somewhere in the world this research would be done anyway. As the next section will demonstrate, recent developments proved us prophetic.

Importance of mitochondria research

In this context it is interesting that we actually always believed that many of our European colleagues were hamstrung in clinical reproductive practice and research in comparison to us here in the U.S. Many, indeed, still are exposed to restrictions that don’t seem to make sense to us. For example, why our colleagues in the UK and many other European countries are not allowed to pay egg donors a decent fee for their efforts is difficult to understand. As we recently noted in these pages, the precedent of a court case, clarifying that egg donors have a right to charge market rates for their eggs, required IVF centers in the U.S. to move into exactly the opposite direction.
Yet, though our European colleagues face many restrictions to clinical practice and research that we do not have to deal with in the U.S., paradoxically, in one research arena UK colleagues, already a year ago, were given permission by their national oversight body for all IVF-related procedures (and ratified by Parliament) to pursue experimental investigations of mitochondrial replacement.

We in these pages previously discussed in considerable detail mitochondria, small intracellular organelles within the cytoplasm of cells, which are essential in the energy supply of cells. Only so much here: In reproductive medicine, mitochondria in oocytes (eggs) have a number of very important roles. First, because the mature egg is the largest cell in the female body, the egg requires large numbers of healthy mitochondria for normal function. Second, it appears that with advancing female age, mitochondrial function in eggs declines, thereby negatively affecting egg quality.

This observation led to the concept of “cytoplasmic exchange,” which originally meant removal of small amounts of cytoplasm (with mitochondria) from egg of older women and replacing it with a small amount of cytoplasm (with its own mitochondria) from a young egg donor. The “older” egg, thus, received a mitochondrial “booster” with “younger” mitochondria. Since animal data suggested that such treatment might improve egg quality, a number of investigators under the leadership of James Griffo, MD, in New York City and Jacques Cohen, PhD, in New Jersey, over a decade ago attempted the procedure in human IVF of older women but were “shut down” by the FDA before definite outcomes could be recorded.

The reason for the FDA’s decision was concern that this procedure, if successful and resulting in offspring, would create so-called “three-parent offspring.” The reason is that mitochondria contain their own small amount of genetic material (mtDNA), which is distinct from nuclear DNA (nDNA), where a large majority of all human genes are located. By transferring mitochondria from a young donor into an older egg, this egg would, therefore, have mtDNA from two women. Once fertilized, the resulting embryo would have genetic material from the father and two genetic mothers, though the egg donor-derived portion, of course, would be relatively small. Because offspring exclusively inherit all mtDNA from the mother (the egg provides the cytoplasm for the embryo), all future generations would, therefore, inherit mtDNA from two different women. Three-parent IVF, therefore, crosses the germline and falls under regulatory control of the FDA.

The concept of cytoplasmic exchange has since been greatly improved and expanded. Especially the laboratory of Shoukhrat Mitalipov, PhD, at the Center for Embryonic Cell and Gene Therapy at the Oregon Health and Science University in Portland, Oregon, deserves much credit since these investigators greatly improved the process with two distinct approaches, called nuclear and/or spindle transfer.

All of a donor’s cytoplasm (and, therefore, all of her mitochondria) are in both of these procedures retained, while the donor’s egg’s nucleus (nDNA) is removed and replaced with a nucleus of a patient’s older egg (or, indeed, a nucleus from a patient’s somatic cell). This way, the newly combined egg has the infertile woman’s nDNA and almost exclusively cytoplasm (and mitochondria) from the young egg donor. Fertilizing this egg with sperm, once again a three-parent embryo is produced with one father and two genetic mothers, most DNA still coming from the patient but significantly more mtDNA coming this time from the egg donor than the birth mother.

Mitalipov’s group demonstrated in non-human primates that both of these techniques could give rise to normal offspring. It, therefore, appeared extremely likely that both of these techniques would also work

Continue reading on page 8
in the human experience. His (and others’, including CHR’s) attempts to receive permission from the FDA to start careful experimentation with human embryos, however, never even received proper consideration from the agency.

Both of these techniques deserve carefully designed human trials, and not only in older infertile women. Though we here at CHR do not necessarily agree with this argument, some colleagues in the research community have argued that these techniques’ first application should not be in older infertility but in patients with so-called mitochondrial diseases.

Those are, fortunately, quite rare, and are inherited exclusively from mothers, where mutations in mtDNA and/or nDNA with mitochondrial functions cause significant disease in offspring. By replacing mutated mitochondria with normal mitochondria from an egg donor, inheritance of such mitochondrial diseases can, possibly, be prevented. It is this clinical application of above described mitochondrial exchange techniques that UK regulators allowed to start exploring over a year ago. This is also how, as media widely reported on September 27, 2016, a first baby was born after utilization of a “new 3 parent technique.” Though this case was clinically managed by U.S.-based physicians and geneticists (and the child was delivered in New York City), the IVF cycle treatment had to be given in Mexico because under current U.S. laws, they were forbidden to do so in this country.

There was a time the whole world came to the U.S. with biggest and most complicated medical problems. And, while that may still be happening to significant degrees (approximately a third of CHR’s patients, for example, come from outside the U.S.), it clearly happens less frequently than in the past. Above noted case is only one example why government inertia (in this case through politically mandated inactivity of the FDA), at least within reproductive medicine, threatens the scientific leadership of the U.S. As Gina Kolata quoted Dr. Griffo in The New York Times on September 28, 2016, “this (birth) could (already) have happened in 2002 (had the FDA not shut down our work).”

Here is some details: The Jordanian mother in this case was a known carrier of one of the most frequent mitochondrial diseases, the so-called Leigh syndrome. She, indeed, had given birth before to two affected children who both had succumbed at young ages to the disease. For not very clear religious reasons, as the media reported, the couple objected to above described nuclear transfer technique but agreed to spindle cell transfer, a technique John Zhang, MD, PhD, the principal physician involved in the case, has been exploring for some time in association with colleagues in China. As described above, resulting eggs with nDNA from the mother but mtDNA mostly from a healthy egg donor, were then fertilized with the father’s sperm, obtaining through the same process five embryos. Those underwent preimplantation genetic screening (PGS) but only one was declared euploid (chromosomally normal 46XY) and transferred into the uterus. It implanted and resulted in above referenced recent birth, rightly making headlines all over the world. Dr. Zhang and his team deserve congratulations,

There was a time the whole world came to the U.S. with biggest and most complicated medical problems. And, while that may still be happening to significant degrees (approximately a third of CHR’s patients, for example, come from outside the U.S.), it clearly happens less frequently than in the past. Above noted case is only one example why government inertia (in this case through politically mandated inactivity of the FDA), at least within reproductive medicine, threatens the scientific leadership of the U.S. As Gina Kolata quoted Dr. Griffo in The New York Times on September 28, 2016, “this (birth) could (already) have happened in 2002 (had the FDA not shut down our work).”

Here is some details: The Jordanian mother in this case was a known carrier of one of the most frequent mitochondrial diseases, the so-called Leigh syndrome. She, indeed, had given birth before to two affected children who both had succumbed at young ages to the disease. For not very clear religious reasons, as the media reported, the couple objected to above described nuclear transfer technique but agreed to spindle cell transfer, a technique John Zhang, MD, PhD, the principal physician involved in the case, has been exploring for some time in association with colleagues in China. As described above, resulting eggs with nDNA from the mother but mtDNA mostly from a healthy egg donor, were then fertilized with the father’s sperm, obtaining through the same process five embryos. Those underwent preimplantation genetic screening (PGS) but only one was declared euploid (chromosomally normal 46XY) and transferred into the uterus. It implanted and resulted in above referenced recent birth, rightly making headlines all over the world. Dr. Zhang and his team deserve congratulations,

In an interview with a scientist from the University of Edinburgh in Scotland, the question of whether or not the human ovary has the ability to regenerate "eggs" has resurfaced once again in a recent article in the British newspaper Guardian.

Evelyn Telfer, PhD, and her team reported last summer that patients treated for cancer with a certain combination of chemotherapeutic agents, believed to damage a women's ovarian reserve of follicles and, therefore, believed to contribute to early menopause in women after chemotherapy, may actually see after chemotherapy experience a short rebound effect in follicle numbers. The investigators interpreted this finding as evidence that ovaries could "make" new follicles and eggs.

Such a finding, however, raises many more questions than it answers, noted David F. Albertini, PhD, CHR’s Director of Laboratories and Senior Scientist, when quoted in the same Guardian article. Interestingly, Drs. Telfer and Albertini are scheduled to square off on this subject in a luncheon conference at the upcoming FMR Conference on Translational Reproductive Biology and Clinical Reproductive Endocrinology, scheduled for November 17-20 in New York City (for details, see page 2).
and we to significant degrees sympathize with the sentiments that “to save lives is the ethical thing to do,” which he expressed when asked by reporters whether going to Mexico because neither nuclear nor spindle cell transfers had in the U.S. been approved by the FDA was the appropriate thing to do.

Beyond the FDA’s at least partial responsibility for U.S. scientists being forced to leave the country to advance reproductive medicine, this case, however, does raise a number of serious clinical, scientific and ethical questions. They are addressed in the next section.

Concerns and precautions

As noted before, we strongly sympathize with Zhang and co-investigators in their efforts, and congratulate them on their achievements in this case. It is also important to note that they acted responsibly by transferring only a male embryo because, as also noted before, mitochondrial diseases can be transmitted into next generations only by females. Even assuming the worst case scenario that this male, after all, turns out to be affected by his mother’s mitochondrial mutation, he would not be able to pass it on to future generations; an affected female could and, likely, would.

We earlier made the point that one of our three major concerns about the FDA’s unresponsiveness to investigators in reproductive medicine has been that, by driving relevant research activities and clinical efforts into places outside of the U.S., risk oversight is lost to a degree, since investigations, by definition, would be moving into countries without government rules and oversight for such highly sensitive human research activities. This was, indeed, well demonstrated by above described case in Mexico, a country with no such rules and no oversight.

Countries with appropriate oversight follow widely accepted norms of human research, which include the prior review and authorization of human research by appropriate Institutional Review Boards (IRBs). From so far published data it is unclear whether treatments in here reported case were, indeed, preapproved by an IRB. We can, however, with certainty, state that CHR’s IRB would not have approved transfer of so-established human embryos into a uterus without prior preliminary studies to confirm the likely ability of these techniques to, indeed, eliminate the abnormal mutation causing the mitochondrial disease. Only such preliminary work can establish that the likelihood of a diseased offspring after transfer of an embryo into the uterus of the patient has been minimized.

Considering potentially still unknown complications in offspring after nuclear or spindle transfer procedures, we, indeed, are convinced that any supervisory national agency and any responsible IRB would have demanded such preliminary studies in order to maximally predetermine the known risks of the procedures to potential offspring before allowing transfer of so-obtained embryos into a uterus. Risk can, indeed, be rather comprehensively assessed in advance by testing so-produced embryos, and stem cell lines established from such embryos over multiple generations.

Stem cell testing over multiple generations of divisions is of great importance because the laboratory of Dieter Egli, PhD, one of the world leading experts in this area (currently in the Department of Pediatrics at Columbia University School of Medicine and the New York Stem Cell Foundation), recently reported evidence that over
multiple generations of cell divisions so-derived stem cells steadily increase the amount of original (abnormal) mtDNA, while demonstrating in parallel decreasing amounts of healthy, from the egg donor derived, mtDNA, a process called “genetic drift” (Yamada et al., Genetic drift can compromise mitochondrial replacement by nuclear transfer in human oocytes, Cell Stem Cell 18:749-754). These findings raise concern that even seemingly normal newborns with very low loads of maternal mtDNA, over time, may express increasing levels and, ultimately, may develop the mitochondrial disease.

British investigators of these procedures, indeed, performed such investigations as appropriate first steps, once they received authorization to conduct their research on pronuclear transplantation (Hyslop et al., Toward clinical application of pronuclear transfer to prevent mitochondrial DNA diseases. Nature 2016;534:363-366). Not surprisingly, they discovered that certain changes in their techniques improved outcomes, including mtDNA carryover (how much abnormal mtDNA is carried over from the mother), which likely represents one of the principal risk factors of the procedure. Even though the clinical expression of mitochondrial diseases usually does not linearly relate to mutation load of a given patient, the lower that load in principle will be the risk of transmission of disease into offspring. Like Dieter Egli’s laboratory, these investigators, in addition, also reported a degree of genetic drift in their stem cell cultures, though to lesser degrees.

Combined, these two publications raise serious questions about whether a newborn’s maternal mtDNA load is really predictive of future risk for this infant. It will likely take years of follow up of these children to obtain an answer.

A just published abstract of the Mexican case, which will be presented at the upcoming Annual ASRM Meeting in Salt Lake City later this month, reported that the average rate of maternal mtDNA in the embryo that underwent PGS represented only 5.10 ± 1.11% with the heteroplasmy level for the mutated gene being 5.73%. Transmitted maternal mtDNA levels obtained from various tissues of the newborn were less than 1.60 ± 9.92%, and the by now three months old newborn is developing normally.

These transmission levels are, indeed, very low and, therefore, hopefully promising for that little boy to live a disease-unaffected life. We, however, just recently also became aware of another newborn at a university in China, conceived using the same technique, as in the Mexican case (Dr. Zhang was involved in this case as well). In that case, the genetic drift, increasing the maternally transmitted mutated mtDNA load during pregnancy, alone, allegedly by time of birth reached as much as 40.0%. Such a rate, of course, would suggest a very high risk for this newborn to develop the maternally transmitted disease.

Conclusions

We, therefore, at CHR enthusiastically welcome the principle concept of pursuing here discussed techniques of cytoplasmic transfer in reproductive medicine, whether in attempts to prevent mitochondrial diseases or to improve IVF outcomes in infertile older women. CHR, however, does not believe that such clinical treatments should be utilized without prior studies that establish their relative safety. It, therefore, appears time for the FDA to step in and authorize such studies under appropriate guidelines.

The community of reproductive scientists in the U.S., however, also faces the responsibility of defining for its own members who are licensed professionals in this country, whether it is ethically, professionally and legally acceptable for them to circumvent local laws by moving their patients for selective, in this country prohibited treatments elsewhere, where appropriate ethical, professional and legal frameworks for such clinical activities do not exist.

Coincidentally, and apparently preceding above discussed Mexican case, Jacques Cohen, PhD, and Henry E. Malter, PhD, reached similar conclusions in a very detailed Editorial on the subject in the most recent issue of Reproductive BioMedicine Online (2016;33:433-435), when discussing a with 13 years delay appearing publication in the same issue of the journal of an earlier attempt of nuclear transfer in China (also involving Dr. Zhang) that allegedly led to a triplet pregnancy and ultimate demise of all three offspring (Zhang et al., Pregnancy derived from human zygote pronuclear transfer in a patient who had arrested embryos after IVF. Reprod Biomed Online 2016;33:529-533).

Such FDA authorization and the issuing of guidelines also appears timely for use of gene editing techniques,
Comments: Continued from Page 10

like CRISPR-Cas9. Once again, CHR, in collaboration with colleagues at the Salk Institute in La Jolla, CA, has been attempting to conduct preliminary trials on donated embryos without, of course, transferring so-treated embryos until with reasonable certainty safety of such treatment has been established. But, once again, the Congress-mandated paralysis of the decision making process at the FDA has stopped all such considerations in their tracks.

Considering above cited clinical utilization of cytoplasmic transfer methods outside of the U.S., we, therefore, would not be surprised should there be soon a public announcement that CRISPR-Cas9 has been used to eliminate abnormal mutations in a newborn. Our collaborators from the Salk Institute reported in 2015 that this gene editing technique worked well in a mouse model for mitochondrial diseases (Reddy et al., Selective elimination of mitochondrial mutations in the germline by genome editing. Cell 2015;16:459-469). It should also work equally well on diseases caused by mutations of nDNA. CRISPR-Cas9, indeed, has the very significant advantage over above discussed treatment methods involving cytoplasmic exchanges that it does not require a third-party genetic parent. But that is a topic for a future article!

Addendum: Since this article went to press, Science announced in its September 30, 2016 issue that the Swedish investigator Fredrik Lama, PhD, of the Karolinska Institute in Stockholm, Sweden, was given approval to edit human embryo DNA using CRISPR/Cas9.

-Fighting for every egg and embryo!