No new administration in recent history has raised as much concern among U.S. scientists as the ascendance of the Trump administration. And while climate sciences do get most media attention, reproductive sciences, likely, have some of the best reasons to be concerned.

Major universities have proactively started to review their funding support in various research areas but especially in politically controversial areas, like climate and reproductive sciences, and are developing contingency plans, should the federal government restrict current funding or even curtail future funding. Considering the control the Republican Party holds over both houses and the presidency, the party’s reinvigorated “pro-life” platform is, of course, of special concern for clinicians and investigators in reproductive medicine and reproductive biology, since both areas potentially involve the use of human embryos, for the longest time an antithesis of the right-to-life movement.

As one of the leading clinical and research centers in reproductive medicine, the position of the federal government on what research can be performed and what clinical treatments can be applied to patients in the U.S. greatly matters to CHR. Though CHR, by intent, never pursued federal funding sources, CHR closely collaborates with several major institutions, which are receiving substantial federal grant resources in support of their research.

We, therefore, decided to dedicate the lead article of this month’s VOICE to the current political concerns of the reproductive science community. As the principal beneficiaries of state-of-the-arts research and quick clinical applications of new discoveries in reproductive medicine, our patients are, after all, our best “ambassadors” to the community.

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How much government intervention in reproductive biology and reproductive medicine is too much?

In contrast to natural conception, where egg and sperm meet in the body of the female (in vivo) in vitro fertilization (IVF) involves the creation of human embryos from eggs and sperm outside of the female body in the laboratory (in vitro). The concept that a human being could be created in such a fashion even among many reproductive scientists and clinicians as recently as in the mid-1970s was still considered blasphemous. An alleged first in vitro fertilization in a laboratory at Columbia University in the mid 1970s was, indeed, destroyed by the Chairman of the Department of Obstetrics and Gynecology, himself a reproductive endocrinologist.

By July 1978, the first IVF baby was born in the UK, a feat that only 32 years later in 2010 was awarded with a Nobel Prize in Medicine and Physiology. While at the birth of the Brown baby media reports were still full with fears about Frankenstein-like monsters that would be born as the consequence of IVF, the procedure proved itself to be extremely safe, and by the time the Nobel was awarded almost 5 million children were born worldwide following IVF. Today in developed countries ca. 1-2% of annual births are IVF babies. In the U.S. ca. 61,000 (1.5%) of 3.9 million births were IVF babies in 2012. In Israel, the country
with the by far largest utilization of IVF in the world, over 4% of children are born every year following IVF.

Absent government support

The U.S. till today has by far the best clinical pregnancy and live birth rates of any country in the world, as the figure below demonstrates. What is most remarkable about the success of IVF in the U.S., however, is the fact that this medical procedure evolved and succeeded without government support. From early IVF days on, Congress, under Democratic and Republican administrations alike, kept a moratorium which strictly prohibited federal funds from being used for any research in support of IVF. In recent years, this moratorium slightly weakened as selected non-human experimentation and very selected, mostly epidemiological, human IVF-related research was funded but, in principle, the remarkable evolution of IVF in this country was achieved without federal funding support, and was primarily financed by the private clinical IVF market.

In addition, a multibillion dollar support industry has grown up around the IVF procedure, with thousands of companies offering supplies, medications, instrumentations and logistical support and, finally, well-paying employment to large numbers of people.

Learning from IVF experience

Here at CHR, we believe that IVF in many aspects can serve as a model for market-driven medicine. Like most other “industries,” competition led to survival of the “fittest” centers, whether based on outcomes, costs or other qualities, patients valued. Therefore, the IVF industry today involves a large variety of offerings, from small to big programs, from “bread and butter” IVF centers that serve the average fertility patient to highly specialized centers, like CHR, which patients, unfortunately, often choose too late in the process, after having failed repeatedly, and missing valuable time.

But in contrast to what has been happening with Obamacare, patients have a large variety of choices, geographically, based on acceptance of third party insurers, cost of services or any other parameter that may affect a patient’s choice of provider. And with choice usually comes satisfaction about service quality because the patient, of course, at any point also can exercise the choice of changing her provider.

Patients, in principle, face either non-emergent or emergent medical care. The clear majority of medical encounters, including fertility services, involve non-emergent care. In such circumstances, patients can easily exercise choices since non-emergent care allows for careful selection of providers, based on all above noted preferences (and many more). Though quality of medical care is very difficult to judge for lay people, due to information on the Internet it is nowadays much easier to judge the quality of an individual provider or an IVF center than in the past. In emergency situations, choice is, of course, limited because in most instances the quicker a patient gets into the closest emergency room the better.

The figure shows live birth dates in select developed countries after fresh ART cycle using patients’ own eggs. U.S. has the highest live birth rates among developed countries. Figure modified from Kushnir VA et al, Reprod Biol Endocrinol 2017.
Setting the record straight

In a rather exquisitely written editorial in the last 2016 issue of Reproductive Biomedicine Online, (2016;33:657-8) Martin H. Johnson, one of the journal’s editors “attempted” (and succeeded) in “setting the record straight” after what he called “some shoddy scientific journalism.” It all centered around the case, recently addressed in these pages, in which a New York City-based fertility specialist, John Zhang, MD, PhD, treated embryos of a Middle Eastern woman, who already had lost children to a mitochondrial disease she carried and passed onto her offspring, with a technique called meiotic metaphase II spindle cell transfer (for further detail, please refer to this VOICE’s lead article).

Based on media reports, a child was born in a New York City hospital, and early tests suggested (though it may take years to find out for sure) that the treatment was successful in preventing transmission of this genetic disease from mother to son. Johnson notes that this case was not reported as an article in a medical journal but only as an abstract submitted to last October’s American Society for Reproductive Medicine (ASRM) and published in Fertility & Sterility as such (Zhang et al 2016;106:e375-e376), and with typical British understatement also suggested that, in this case, it represented “unfortunate form” since the same authors, over a decade earlier, also reported only in abstract form (with no full-length paper follow up for 13 years until recently) on a case, that time in China, a similar technique, called pronuclear transfer (please again refer to this issue’s lead article for further detail) had been used. The unfortunate adverse pregnancy outcome in this latter case was only in 2016 fully reported by the authors in the same journal (Zhang et al., Reprod Biomed Online 2016; 33:529-533).

As Johnson, however, also notes those two cases had very different purposes: while the recent case, as noted above had the purpose of replacing the mothers genetically abnormal mitochondria, the 13-year-old case in China involved simple infertility treatment under the then vogue assumption that by exchanging “older” cytoplasm (containing older mitochondria) in eggs of older women with cytoplasm (and mitochondria) of young egg donors, eggs from “older” women would improve in their pregnancy potential. In those days, older women, thus, were believed to suffer from “ooplasmic deficiency,” which could lead to poor embryo development and implantation failure.

The techniques applied in those days (andquickly stopped by the FDA at the time) involved a much simpler and less invasive treatment, so called “ooplasmic injection” or “cytoplasmic exchange,” when only minute amounts of cytoplasm from a donor oocyte were injected into the cytoplasm of a fertility patient since in those days nobody was yet even dreaming about the possibility of performing pronuclear or spindle cell transfers, which give the recipient the donor’s almost complete cytoplasm, containing almost all of the donor’s mitochondria.

The FDA stopped these experiments, mostly conducted by investigators in New York City (NYU) and New Jersey (St. Barnabas Hospital), without citing specific reasons. But by declaring under their statutory power that such experimental treatments required an Investigational New Drug (IND) Application. This is the same kind of FDA approval process as is required for bringing a new Pharma drug to market and, therefore, makes it for financial reasons impossible for fertility centers to pursue such research since the costs end up running into the hundreds of millions of dollars per IND. The FDA in this way stopped fertility research in its tracks before it even could be started. And these same rules are still in place, still preventing fertility centers, like CHR, from responsibly exploring improvements in current IVF practices.

Johnson concludes in his editorial that a case can be made now that the current approval of use of pronuclear and spindle cell transfers for the prevention of transmission of mitochondrial diseases from mothers to offspring by UK regulatory authorities should now be extended to approval of these procedures for treating female infertility. For the Trump administration to pull even with the UK, it, therefore, appears time to allow the FDA to license appropriately qualified IVF centers to pursue pronuclear and spindle cell transfer for both indications, female infertility (mostly due to older age) and in preventing mitochondrial inheritance from mothers.
During the first week of January some, mostly European, media organizations like the Daily Mail, reported on a study that allegedly claimed that “using two embryos for IVF may cut chances of having a baby by 25%.” Investigators from Nottingham, UK, at least a presented by media outlets, claimed that “if one of two transferred embryos was of poor quality, it dramatically cut the odds of falling pregnant.” The investigators further commented to the media that, the uterus rejects the poor-quality embryo potentially together with the good-quality sibling embryo. The research leader then also suggested that “the current feeling is that a good-quality embryo will be recognized by the body and captured for implantation. But a poor-quality embryo should be rejected by the body.”

Where all of this knowledge supposedly comes from remains, however, unexplained since, as we determined after a careful literature search under the name of the alleged research leader, no such study has, at least so far, been published anywhere. Even more remarkably, however, this research leader further suggested that the research suggested that, putting a poorer quality embryo back with a better quality embryo, is likely to negatively affect the chances of the better quality embryo.

This very much sounds like “fake news” to us because if there is one area of data on a subject in reference with IVF that appears undisputable, then it is the observation that a two-embryo-transfer (2ET) will establish more clinical pregnancies and better live birth rates than an elective single-embryo transfer (eSET).

It is, indeed, remarkable to what degrees some colleagues are willing to sacrifice their scientific integrity to continue pushing for the concept of eSET. So whatever the media are reporting, a 2-ET will always result in significantly better clinical pregnancy and live birth rates than an eSET. In order to pull even in cumulative outcome chances, an eSET always needs a second frozen-thawed embryo cycle.

One more point: Retrospective studies (and this was performed allegedly for IVF cycles between 2009 and 2013) are, in principle, uncontrolled. That means that there usually are reasons why certain patients received eSETs and others 2-ETs. The most obvious explanation, of course, is that better prognosis patients received eSET, while poorer prognosis patients received 2-ETS. What a surprise then when 2-ETs did worse. Yes, not only politics suffer from “fake news!”

**IN FOCUS**

This feature presents microscopic images from CHR’s laboratories, edited by our Director of the Division of Laboratories and Senior Scientist, David F. Albertini, PhD.

This picture shows a small slice of ovary and each of the circles represents a special structure known as the ovarian follicle. Experiments ongoing at the CHR are aimed at understanding what changes in human egg cells as we age. For some of our research, we have to use animals -like mice as shown here-in order to study the changes in DNA that are believed to take place as the ovary ages. In this case, the red in this picture shows the DNA in two egg cells that has been damaged due to exposure to certain chemicals that are used to treat cancer. Each of the egg cells is encircled by the blue staining granulosa cells that make up an ovarian follicle. Research at CHR is aimed at offering fertility preservation to our patients by discovering exactly how radiation or chemotherapy may alter the egg DNA and most importantly, to determine how we can best protect it from damage due to aging or other causes.
The urgency of the situation here, quite obviously outweighs the benefits of choice. The dynamic of emergent and non-emergent medical services, thus, differ significantly. The economic evolution of IVF, however, can serve well as an example how non-emergent medical care could be structured in the post-Obamacare era.

Supporting medical progress

As another piece of evidence that the political establishment in this country has been discriminating against IVF, it is the only medical procedure, which under Congressional mandate must be reported to the Centers for Disease Control and Prevention (CDC). For that reason, almost all IVF centers in the U.S., CHR included) report every IVF cycle electronically to the CDC, and many centers (CHR included) also report voluntarily to the Society for Assisted Reproductive Technology (SART).

We, however, do not complain about this reporting mandate because it, in a way, allows for the monitoring of progress (or lack thereof) in the national IVF arena. Through this reporting we, for example know that until ca. 10 years ago, live birth rates after IVF increased year by year. Over the last decade that progress, however, slowed considerably, especially among older women. Through this reporting we also have learned that the IVF population in the U.S. is aging very rapidly, a theme we have repeatedly addressed in these pages before.

Older and older women are trying to conceive, as women above age 40 have over the last decade been the most rapidly growing age group having children, while younger age groups have been shrinking. So far, most IVF centers have addressed these facts almost exclusively only by strongly advancing the utilization of donor eggs. Donor egg cycles, therefore, have become the most rapidly growing IVF cycle category in the U.S.

We, here at CHR, have been quite frustrated about these developments. While we consider egg donation a wonderful last resort for women who have no other way to conceive (with use of their own eggs), to a degree, we perceive every donor egg cycle as a failure of our treatment efforts. After all, we have never met a woman who did not want to conceive with use of her own eggs rather than donor eggs. CHR, therefore, over the last 15 years developed unique expertise in treating older women and/or younger women with prematurely aging ovaries.

We now, however, are getting increasingly frustrated because new technologies are becoming available, which have the potential of helping older women conceive, while permitting transmission of all of their nuclear genome (nDNA) to their offspring; yet, because of restrictions by the federal government (specifically by the FDA), we are not permitted to pursue these treatments even in investigational protocols with full informed consent from participating patients, who, we know, would line up for such studies.

Nuclear transfer for older women

Based on work with animal models, CHR’s laboratory does have the manual expertise to perfume so-called nuclear and/or spindle transfers, previously discussed in these pages. These techniques with great likelihood will offer the next major advance in the IVF field, promising especially in older women additional pregnancy potential.

The principle is the same in both techniques: Animal data suggest that what ages in an egg with advancing female age is mostly the cytoplasm, and not the nucleus, which contains almost all the mother’s nDNA. This observation gave rise to the concept that combining an older woman’s nucleus with a younger woman’s cytoplasm should “rejuvenate” an egg and, therefore, improve pregnancy chances.

Nuclear and or spindle cell transfers do exactly that by removing the nDNA from a young woman’s donor egg and replacing it with the older patient’s nucleus (i.e., the patient’s nDNA). We have extensively reported on these techniques in these pages before, when we discussed the treatment of so-called mitochondrial genetic diseases, caused by abnormal genetic mutations in mitochondrial DNA (mDNA). In contrast to the FDA in the U.S., regulatory authorities in the UK issued permissions to British colleagues to use these techniques under experimental informed consents in attempts to prevent inheritance of such diseases into the next generation.
mDNA represents only approximately 1% of an egg’s total DNA and is located, as the name suggests, in small cytoplasmic tubules, called mitochondria. Mutations in mDNA, even though fortunately rare, can cause several severe, mostly fatal inherited diseases. Since mDNA is in mitochondria, and mitochondria are in the cytoplasm, replacing the cytoplasm in eggs of mothers who carry such a mutation is believed to have the potential of interrupting the transmission of these diseases from mothers to offspring (mitochondrial diseases are only transmitted by mothers). The price, however, is that the resulting offspring, besides DNA from mother and father, will also have ca. 1% of mDNA from the egg donor. The child will, therefore, have three genetic parents!

We just recently reported in these pages that a New York colleague performed spindle cell transfers on the eggs of a mother carrier for such a mitochondrial disease in Mexico because in the U.S. the FDA has refused to even consider giving permission for such treatment. The birth of a hopefully unaffected child in New York City made headlines all around the world (see also related article on “setting the record straight.”)

The January 26, 2017 issue of NATURE now reported that a first baby girl was born via pronuclear transfer (here, nDNA is obtained from a maternal pronucleus and inserted into the enucleated oocyte of a young donor) out of all places in Ukraine, where the indication for the procedure was not a maternal carrier state for a mitochondrial disease but, simply, to treat female infertility. Rumor has it that several additional pregnancies are underway.

Sadly, we, here in the U.S., under current FDA policy, are not permitted to use these techniques for either indication. As noted before, our British colleagues are permitted to use the techniques but only in attempts to prevent mitochondrial diseases. Even though female infertility due to advanced female age is a much more prevalent medical problem than inheritance of mitochondrial diseases, even the British authorities approved the technique only for the much rarer medical problem, once again demonstrating that medical and ethical research communities, still, discriminate against everything and everybody attempting to advance fertility treatments.

The principal argument for all of this caution is that all of these forms of nDNA transfer result in so-called “three parent” babies because resulting offspring have nDNA from both parents but, in addition, ca. 1% mDNA from the young donor who provided the cytoplasm. Assuming absence of complications from such triple genetic parent contributions (as studies with non-human primates and other experiments have suggested), it is difficult to understand why older infertile women should be deprived of the chance to contribute (with their partner) ca. 99% of the child’s genome when the only clinical alternative treatment often is egg donation, which deprives the mother of any genetic motherhood.

What we hope will happen

So, let’s be optimistic for a moment, and assume that President Trump is, indeed, the logical business man, who in all aspects wants “to make America great again.” If that were to be the case, then how can he and his administration accept the fact that older infertile U.S. women may have to travel to Mexico, the Ukraine and, maybe, the UK, to get treatments U.S. scientists and physicians are not allowed to offer.

We, of course, do not argue in favor of unregulated introduction of experimental treatments into IVF, for which, with current knowledge and experience, significant negative consequences cannot yet be ruled out. We, however do propose that the U.S. should not be prevented from maintaining its leadership in the field by prohibiting responsible research in attempts to advance the field.

Over almost 40 years, the field of IVF has through self-control responsibly advanced scientific knowledge as well as clinical care for millions of women who could not conceive and experience motherhood. This historical experience should be enough to demonstrate that this field is responsible and capable of exereting appropriate self-control in advancing science. Reproductive medicine does not need the government to determine what we can or cannot do in advancing our patients chances of safely conceiving. Imagine where IVF would be today, had IVF centers in the early days of IVF been dependent on FDA approvals before being allowed to start operating. Deregulation of government agencies is a major point in the Trump administration’s political program. President Trump, himself, has gone on record promising the radical reorganization of the FDA.

We seriously hope that this reorganization will not only contiune reading on page 7
be restricted to benefiting Big Pharma and medical device companies by simplifying the drug and device approval processes but will also help smaller players, like fertility centers, which are anxious to safely drive the practice of IVF forward. It is years now that, at instruction of Congress and without opposition by the prior Obama administration, the FDA has made it impossible for the IVF community to responsibly investigate promising new advances that especially may benefit older women. It is time for government to once again set free the ingenuity of the IVF field in this country. Nobody will benefit more from that than the public.

Here is a real opportunity for President Trump to “make America great again” in an area of not only great medical significance but, as we repeatedly before noted in these pages, also in an area of great societal importance, as having children at older ages is becoming of increasing societal importance in most countries of the developed world, suffering from dwindling birth rates.

Did you know that Norbert Gleicher, MD, CHR’s Medical Director and Chief Scientist, has a new stainless steel hip? He was back at his desk exactly one week following surgery, and started seeing patients on the 10th day after surgery. In the second half of this months he already will be off to India for a week of lectures in Udaipur, Rajasthan and New Delhi.

And did you know that CHR’s Senior Embryologist and Assistant Scientist, Emanuela Lazzaroni-Tealdi, MS, is again pregnant through IVF? And, yes, she again performed her own ICSI, and is expecting the baby’s arrival in late spring.

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CHR News

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