It is hard to believe but May is the month when CHR’s construction is, finally, scheduled for completion. After over two years of ongoing headache, and after over four years since construction planning started, we, finally, see the end of all the efforts, which at times were truly herculean, considering that the construction crews had to work around seven days a week activities of a medical center.

CHR’s patients have already experienced important completions, like the move of the IVF Unit from the 4th floor down to the ground floor of the new building addition. Likely less visible have been many other changes, like the greatly expanded laboratory and office space for the laboratory staff on the second floor of the new building addition or the brand-new nursing station in the totally renovated basement space, which previously could only be used for storage.

Laboratory and nursing staffs have significantly grown in numbers since CHR moved into our current building in 2001, and both deserve the additional space the new construction has given them.

Another person, well deserving of more space, is Vitaly Kushnir, MD, Director of CHR’s Fertility Preservation program, whose office has been by far the smallest among physician consultation spaces. A few weeks ago, he also, finally, moved into a new and larger office, just down the hall in what used to be the center’s nursing station and conference room. His old office, after a makeover, is becoming a “guest room” for the almost constant stream of visitors at CHR from all over the world, who, up to now, did not even have a place to put their computers down. Finally, the partial extension of that floor into the former courtyard, now houses a small conference room for small meetings.

The problem with "add-ons" to IVF treatments, usually at additional expense offered to patients with claims of improving chances of live births. Examples discussed in their manuscript were use of “embryo glue” and other adherence compounds, sperm DNA fragmentation, time-lapse imaging, preimplantation genetic screening (PGS), mitochondrial DNA load measurements and routine use of assisted hatching. In reviewing their clinical use, the authors concluded that there presently really is no valid evidence in the literature for safety and/or efficacy of any of these treatments and/or tests and, therefore, for their routine use in association with in vitro fertilization (IVF).

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For steady readers of these pages, this may not be news because we, here at CHR, have made this point for years, including in detailed reviews of the utility of time lapse imaging and PGS. However, the fact that *Human Reproduction* finally published a manuscript, making this point loud and clear, represents progress because that could never happen under the current editors of *Fertility & Sterility*, the official organ of the American Society for Reproductive Medicine (ASRM), who over years now have demonstrated pronounced biases in favor of accepting manuscripts that favor “add-ons,” while discriminating against articles critical of those practices (see also *The hijacking of...*).

Interestingly, the subject of “add-ons” has been attracting much more attention in the U.K. than the U.S. Yet, “add-ons,” like PGS, are still much more popular in the U.S. than the U.K. or in the rest of Europe.

It all started in November of 2016, when the British Broadcasting Corporation (BBC) in a Panorama Documentary on the subject concluded that many “add-ons,” advertised on fertility clinic websites in the U.K. were not backed up by solid evidence. On a side note, CHR’s Medical Director and Chief Scientist, Norbert Gleicher, MD, was extensively interviewed by BBC producers before that broadcast.

In March of this year, again in the U.K., *The Progress Educational Trust* organized at the Royal College of Obstetricians and Gynecologists a public debate under the heading, “Fertility Treatment Add-Ons: Do They Add Up?”, in which leading clinical and laboratory experts, the Human Fertilisation and Embryology Authority (HEFA), and the British Fertility Society (BFS) participated. As one would expect, opinions differed, with, as in the U.S., the strongest support for “add-ons” usually coming from parties with considerable financial interests in those procedures/tests, like PGS laboratory owners (and their agents) and corporate IVF interests, as represented by the Founder and President of CARE Fertility, Simon Fishel, PhD, the U.K.’s largest corporate provider of IVF services. Fishel, one of the original scientific pioneers in IVF, has been a strong promoter of time lapse imaging and PGS for years.

Sally Cheshire, the chair of the HEFA, noted that her organization did not regulate drugs or procedures associated with IVF. She, however, announced a new website that will include reliable information on “add-ons” for the public. Others were more outspoken, and Antony Blackburn Starza in a commentary on this public meeting on the website BioNews (http://www.bionews.org.uk/page-asp?obj_id=814093, accessed 4/9/17) noted that, “any consent solution without (vigorous further) debate may, therefore, be at risk of operating as a mere procedural justification for what might, at times, remain unethical practice.”

What, indeed, makes these “add-ons” a truly moral issue is that, subconsciously or consciously, their utilization is, often, no longer guided by honest attempts to improve IVF outcomes but by financial necessity, as revenues generated through “add-ons” are becoming an economic lifeline for IVF centers. With third-party reimbursements for IVF over the last decade actually declining in the U.S., many IVF centers derive 30-40% of their IVF cycle revenue now from “add-ons” like PGS since those, usually, are not covered by third party insurers and, therefore, represent significant additional cycle revenue for IVF centers. How far some IVF centers are taking this is best demonstrated by some centers now simply refusing to perform IVF cycles, unless patients consent to the addition of PGS to their cycles.

Similarly, diagnostic laboratories that perform “add-on” tests to IVF are, of course, highly motivated to promote use of their laboratory services. This is nothing new, and was seen decades ago, when specialty laboratories aggressively promoted certain families of blood tests, like immunological testing in association with IVF, and more recently in the aggressive promotion of genetic screening tests. The growth of the laboratory industry surrounding PGS has, however, reached unprecedented proportions, best evidenced by the sale in 2016 of the leading U.S.- and U.K.-based PGS laboratories to Cooper Surgical for hundreds of millions of U.S. dollars.

Why “add-ons,” however, have become a real ethical and practical clinical problem was recently best demonstrated when CHR investigators looked at IVF practices all around the world and noticed (previously unreported) that almost everywhere, including in the U.S., 2014 live birth rates after IVF were lower than in 2004. Up to 2004, in contrast, live birth rates had steadily increased almost everywhere.
Collaborators and CHR scientists won Presidential Poster Competition at 2017 ENDO Annual Meeting

We are pleased to report that a poster, summarizing some of the collaborative work between CHR investigators and Arirto Sen, PhD, from the Division of Endocrinology & Metabolism of the Department of Medicine at the University of Rochester School of Medicine and Dentistry, Rochester, N.Y. (he also is an Assistant Visiting Scientist at CHR), won the Presidential Poster Competition at The Endocrine Society Annual Meeting in Orlando, Florida, on April 1, 2017, the most important annual meeting in the medical endocrinology field.

CHR and the Division of Endocrinology & Metabolism in Rochester have maintained a collaboration agreement for over four years, which initially was based on a common interest in the physiological importance of androgens in the maturation process of ovarian follicles. With Dr. Sen maintaining a leading mouse laboratory that investigated effects of androgen supplementation on follicle maturation, and CHR investigating the same subject in infertile women, the collaboration proved very fruitful. It allowed constant exchange of information between clinical practice and an excellent animal model, thereby gaining invaluable information and understanding about how androgen supplementation improves outcomes in treatment of women with low functional ovarian reserve.

Approximately three years ago, CHR investigators developed interest in the concept of using anti-Müllerian hormone (AMH) as a potential therapeutic agent in ovarian stimulation. The hypothetical clinical concepts for use of AMH could not be tested in clinical practice because an AMH product cleared for even experimental human use, currently, does not exist anywhere in the world. Building on the longstanding collaboration with Dr. Sen’s laboratory, CHR investigators, therefore, proposed appropriate mouse investigations in Dr. Sen’s laboratory.

Those were initiated, and resulted in a combined, still pending U.S. patent application between the University of Rochester and CHR (2 separate AMH patent applications are independently pending for CHR), and a combined publications [Hayes et al., Intra cellular mechanism of anti-Müllerian hormone (AMH) in regulation of follicular development. Mol Cell Endocrinol 2016;14:26]. This work was further expanded in the poster presentation that was selected as winner of the Presidential Poster Competition this year [SAT 072: Hayes et al., Regulation of anti-Müllerian hormone (AMH) expression during follicular development].

We congratulate Dr. Sen and his laboratory team as well as CHR’s investigators, who have been pushing this subject forward in our combined research efforts, especially Vitaly A. Kushnir, MD, Director of CHR’s Fertility Preservation Program, on this accomplishment, and hope to, soon, be able to convince the pharma industry to start testing a pharmacological grade AMH product in clinical practice. In the poster reported laboratory results in the mouse model offer further evidence that the clinical use of a pharmacological AMH product, likely, could help infertile patients in a variety of ways. Such a product, in addition, also could have potential applications in treatments of a variety of malignant tumors.
After a very successful 2016 meeting, we are very pleased to announce the dates for 2017: November 16-19. The 2017 Conference promises to be even bigger and better than the 2016 Conference, which received glowing reviews from over 250 participants from nearly 50 countries. With 6 pre-conference workshops and main conference program showcasing the thought leaders of the field, the Conference offers a unique opportunity to visit New York City in the very popular pre-Christmas season to interact with colleagues, gain new ideas that will change clinical practice patterns and develop new research concepts. We look forward to welcoming you in New York City in November.

Workshops: Thursday, November 16

Maximizing access to fertility services | Individualization of ovarian stimulation protocols | Changing and enhancing genomes in human IVF | Maximizing IVF outcomes for poor prognosis patients | Social, medical and economic realities of egg donation | The FMR1 gene in female infertility

Conference Day 1: Friday, November 17

Welcome and announcement of the Young Investigator Award | The "Breaking News" Lecture | The future of assisted reproduction 1 | Successful reproduction is tolerance dependent | Debate: Preimplantation genetic screening (PGS) in association with IVF | Paradigm Change I: Polycystic ovary syndrome (PCOS), a multi-etiological epigenetic syndrome? | The future of assisted reproduction 2

Conference Day 2: Saturday, November 18

Quintessential questions in assisted reproduction | Paradigm Change II: Preventing rather than treating female infertility and other new concepts | Debate: How important is the implantation window? | Paradigm Change III: Avoiding in IVF practice "fashions of the moment" | Paradigm Change IV: Reading the medical literature with appropriate skepticism

Conference Day 3: Sunday, November 19

Ovarian physiology | Quick updates on the "most interesting presentations at the 2017 ESHRE and ASRM meetings"

For program and registration, visit the conference website: http://bit.ly/2qlChqO

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CHR-OPINION

The “hijacking” of our medical specialty journal Fertility & Sterility

A big part of the current poisonous political atmosphere in the U.S. is the responsibility of media companies, which have abandoned evenhandedness in coverage of political events. That media take sides in political discourses is nothing new, but identification of a media outlet with a political party or opinion used to be restricted to editorial pages or editorial comments on television, clearly identified as such. Coverage of news was, still, expected to be non-partisan.

This clear distinction between objective reporting of news and political editorial opinions has in recent years almost completely disappeared from newspapers, television and especially in news coverage on the Internet. The reason is not only that political biases have invaded news coverage but, even more importantly, that media outlets selectively cover news that fit their political bend, while ignoring news that contradicts their philosophy. The result of these developments has been record-low trust by the public in the news media and the recent popularity of the term “fake news.”

Readers may wonder why we, suddenly, here are addressing “fake news,” and what all of that may have to do with what the VOICE usually covers? The answer is that it is finally time to speak up about Fertility & Sterility, the official organ of the American Society for Reproductive Medicine (ASRM), which has been “hijacked” by an editorial leadership that has abandoned all objectivity in selection of materials for publication, and very obviously favors a small group of closely connected insiders with often shared commercial interests.

The May 2017 issue of the journal, finally, made it impossible to remain quiet: It not only reflected a new peak in how unabashed senior editors of the journal (for years) have been promoting their own interests in preferentially allowing business partners, spouses and otherwise associated parties to publish in the journal, but also how, without embarrassment (on more than one occasion), editors declared a study from their own institution as the journal’s “seminal contribution” of the month. Most serious editors of medical journals, possibly except for opinion pieces (i.e., editorial opinions), do not even allow submissions from their own departments. There are enough other publication opportunities available for serious scientists to publish in, if one wishes to avoid even the appearance of favoritism.

This is, however, not even the most deplorable aspect of the current editorial management of Fertility & Sterility. Much more dangerous is the “fake news” the journal spews by aggressively promoting by evidence unsupported practices, but rejecting (often even without outside review) even well supported manuscripts with opposing data and/or opinions.

It does not help that as principal owner and administrative leader of what claims to be the world’s largest IVF corporation, with centers all over the world (now also including the U.S.), a senior editor simply cannot avoid commercial conflicts of interest. Those conflicts are further aggravated when the journal preferably publishes the editor’s employees’ and business partners’ manuscripts, and offers articles that favor commercial interests in which the editor and/or his company hold ownership, while rejecting (often without outside review) manuscripts hostile to those interests. That the leadership of ASRM would even tolerate appearance of such conflicts of interest is astonishing. That it allowed appearance to progress to current levels of obvious certainty, finally reaching a crescendo with the May issue of Fertility & Sterility, is inexcusable!

Among a whole series of citable examples, two such conflicts of interest deserve special attention: The first involves time-lapse imaging, which several years ago entered the IVF field with much pomposity and a very aggressive marketing effort by two commercial companies. Above noted editor’s company held ownership interests in both. To this day, Fertility & Sterility published the only prospectively randomized study claiming IVF outcome benefits from time-lapse imaging. Noteworthy, the editor’s own IVF company performed the study, and no other study has been able to confirm IVF outcome benefits from time-lapse imaging ever since. Critical studies of time-lapse imaging, even when submitted by highly reputable academic embryologists, were, however,

Continue reading on page 6
Hijacking: Continued from Page 5

rejected, and, as we repeatedly were told, without outside review. Also suggesting no benefits for IVF outcomes, a prospectively randomized study from CHR experienced the same fate.

As both companies peddling these goods were sold off, and marketing dollars got sparser, little has been heard about time-lapse imaging anymore (see also “add-ons”). Yet, IVF centers in the meantime have spent millions of dollars on these expensive toys.

The most important and clearly most consequential procedure Fertility & Sterility has been promoting in radically biased ways, however, is preimplantation genetic screening (PGS). Dedicating in the May 2017 issue not fewer than nine articles to the subject, including six invited opinion pieces in the monthly Views and Reviews section, not one came from an individual critical of the reliability and/or clinical value of PGS, even though the recommended utilization of PGS has undergone truly revolutionary changes over the last few months, as even the most ardent proponents of PGS no longer were able to maintain the hypothesis that PGS could reliably differentiate between clearly euploid and aneuploid embryos, and really improve clinical pregnancy and live birth rates.

Contrast that with the May 2017 issue of Focus on Reproduction, the official monthly magazine of the European Society for Human Reproduction and Embryology (ESHRE), which presented not only a very balanced review on the currently very widely discussed differences of opinion about PGS, fairly referencing proponents and opponents, but also an equally balanced article on “add-on” treatments to IVF, including PGS and time-lapse imaging, which, in contrast to the U.S., in the U.K. have become very controversial (for details see this month’s lead article on “add-ons”).

The difference between the positions staked out by ESHRE and ASRM is, therefore not only striking but highly consequential because, with the official organ of the ASRM taking such a one-sided view on PGS, the society basically endorses the utilization of PGS. Since PGS is ineffective in improving IVF outcomes and, at least in women with low functional ovarian reserve, likely, reduces live birth chances because of disposal of potentially normal embryos (false positive PGS), we consider it incomprehensible that the ASRM leadership tolerates the current editorial policy at Fertility & Sterility.

Remarkably, not one published article among all the PGS papers in the May 2017 issue of the journal explained the sudden switch in recommended PGS reporting, recently announced by the Preimplantation Genetic Diagnosis International Society (PGDIS). After IVF centers were advised for years by PGS laboratory reports to discard “aneuploid” embryos, suddenly, that recommendation now is to do so only to embryos with trophectoderm biopsies that are over 80% mosaic-aneuploid. One wonders how many infertile women over all those years disposed of their last pregnancy chances by discarding embryos at the advice of PGS laboratories that, now, are considered transferrable.

Instead of a “mea-culpa” from the PGS laboratory community for all the damage that has been done to infertile women over more than a decade (not even addressing the unwarranted costs they were committed to), as some of the papers in the May 2017 issue of Fertility & Sterility demonstrate, we are once again being exposed to a well-thought-out marketing campaign by laboratory interests. Like, suddenly, PGS 2.0 was born, after PGS 1.0 was finally disclosed as ineffective, so now, that even proponents of PGS 2.0 must again acknowledge that the procedure does not improve pregnancy and live birth rates, the marketing machine goes again into overdrive: Readers will notice that in many of the PGS articles in the May issue of the journal the term PGS is no longer used; suddenly we are back to calling the procedure by a completely different name, “PGD-A” (preimplantation genetic diagnosis for aneuploidy), as if that could hide that the procedure is not only ineffective but often harmful to our patients. And, since claims of improved IVF outcomes are no longer sustainable, PGS/PGD-A, suddenly, has found yet other alleged new indication, as at least one of the papers (again from the senior editor’s own department) claims, shortened time to conception and lower miscarriage rates.

We don’t have the space here to explain why even these newly suggested indications are unsupported by data, but just to mention one obvious point: randomizations are to occur after patient exclusions and not vice-versa, even (or, maybe, especially) if they are done in the editor’s company.

What a shame that ASRM leadership is allowing our journal, Fertility & Sterility, to be “hijacked” for such unsavory purposes!
First birth following spindle cell transfer: How not to do it!

Zhang et al finally reported in a medical journal (Live birth derived from oocyte spindle transfer to prevent mitochondrial disease. Reprod Biomed Online 2017;34:25-32) details about the first case of a birth after spindle cell transfer to prevent transmission of a deadly mitochondrial genetic disease from mother to offspring which, when first reported in September of 2016, attracted worldwide media attention. We also cautiously applauded the efforts of John Zhang, MD, and his collaborators in these pages in hopes that this case would help in convincing the Food and Drug Administration (FDA) to loosen the legal strings that currently prohibit spindle cell transfers and other nuclear transfer methods from being clinically applied in the U.S.

Unfortunately, exactly the opposite has happened: with more public information about the case, it became increasingly apparent that experimental treatments that cross the germline, indeed, do require close regulatory supervision, since how Zhang et al approached this case, likely, not only was unethical but, possibly, even broke U.S. regulations and Mexican laws.

This is not our opinion but represents the sum of three publications, an in-house piece in Nature (Baby’s DNA mix revealed, 2017;544:17-18); an editorial written by the editors of Reproductive Biomedicine Online (Alikani et al., First birth following spindle transfer for mitochondrial replacement therapy: hope and trepidation. 2017; 34:333-368), the journal where the article by Zhang et al was published; and a Commentary by Dr. César Palacios-González, a research associate at the Centre of Medical Law and Ethics, Dickson Poon School of Law, King’s College, London, U.K., in BioNews on April 24, 2017 (http://www.bionews.org.uk/page.asp?obj_id=824168, accessed 5/2/17).

The Nature piece questions the uncertainty surrounding the newborn boy’s long-term health as well as the scientific value of the experiment (and an experiment it was!). Here is a short recapitulation: Zhang et al removed the nucleus from the egg of a healthy egg donor and replaced it with the nucleus

Letter from a Patient

CHR was the answer to our prayers.

Before contacting CHR, we had been trying to conceive for 5 years, saw 3 different fertility doctors and underwent 5 unsuccessful IUI cycles. We attempted a round of IVF which was cancelled due to low response. The doctor said any subsequent cycles would likely be unsuccessful and suggested I consider using a donor egg, saying that I was showing signs of early menopause.

After hearing that we decided to look for a second opinion and contacted CHR, who said due to my age (35) and AMH levels that I could have a great chance of success. So my husband and I flew out (we live in Chicago) for 2 rounds of IVF at CHR. I got a significantly better response with the protocol chosen by Dr. Barad and we got pregnant on our 2nd round of IVF, using my OWN eggs! Our beautiful miracle baby boy was born this April!!!

My husband and I were beyond impressed with the knowledge and expertise held by the doctors at CHR. We loved knowing they were on the front lines of research in reproductive endocrinology and each decision was backed by empirical research. We had no doubt we were getting the best care. We fell in love with Dr Barad and our nurse, Dorota. Both are such caring and compassionate people and were incredible blessings to us. We hold the utmost respect for the doctors at CHR and are so grateful to have found them!

- M. W. from Illinois
of an egg from a woman who was a carrier for the deadly mitochondrial genetic disease called Leigh syndrome. Consequently, the newly constructed egg had almost only cytoplasm from the healthy egg donor but the nucleus of the future birth mother.

The reason for all of this was that Leigh syndrome is inherited through a gene that does not, as most genes, sit in the nucleus (nDNA) but is one of only 37 genes located in small tubules in the cytoplasm, called mitochondria DNA (mDNA). The hope of such a procedure is that by creating a new egg cell out of the donor’s healthy cytoplasm and the mother’s nucleus, and fertilizing this new egg with sperm from the woman’s husband, the resultant embryos would have all the mother’s and father’s nDNA but almost exclusively only the egg donor’s (normal) mDNA (this process is, therefore, sometimes also called “three-parent IVF”). The mother’s abnormal mDNA would, hopefully, not be transmitted to the offspring.

Unfortunately, this kind of cytoplasmic transfer never is perfect. There is always a little maternal cytoplasm that remains attached to the maternal nucleus and, therefore, a little maternal mDNA, which contains the abnormal gene. And that, as the Nature article correctly notes, can have long-term negative repercussions for the health of the newborn child.

It is unknown how much maternal mDNA in the offspring is safe, and at what levels disease risks start but mouse studies have demonstrated that mitochondrial mixtures can cause neurological disorders and metabolic problems. Moreover, other studies demonstrated that maternal mutated mDNA amounts increase with subsequent cell divisions proportionally to the donor’s normal mDNA declining, a process called genetic drift. Consequently, even apparently successfully treated offspring with relatively low levels of abnormal maternal mDNA at birth, may in later years, still, become symptomatic for the genetic disease, once abnormal maternal mDNA levels reach a certain threshold. What that threshold is, greatly varies between individuals; a reason why children must be carefully monitored over time.

The wellbeing of the child and, of course, our ability to learn important information from such an experimental treatment, therefore, depends on the long-term follow up of this child but, as the publication, the editors’ commentary and the Nature article revealed, the family refuses any such follow up. Zhang et al during the informed consent process apparently never raised this point with patient or family.

The informed consent process in this case has, rightly, received considerable criticism. A legal scholar is quoted in the Nature piece, making the point that because the boy could not give informed consent himself, “duties for physicians to protect the best interests of the future child were even bigger,” and, yet, the publication by Zhang et al in the materials and methods section only noted the parents received “cautious counselling for mitochondrial replacement therapy.” This is, of course, completely inadequate informed consent for practically any human research but, especially, for a potentially highly consequential experimental treatment, as was given in this case.

One of the world’s leading experts on nuclear transfers, Dietrich Egli, PhD, from Columbia University in New York City, also a Visiting Assistant Scientist at CHR and a research collaborator with CHR scientists, is extensively quoted in the Nature article. He concluded: “It looks like a rush to use this as a treatment and telling patients that this is the treatment during a time when we still know very little about what the outcomes are.”

Since the editors of Reproductive Biomedicine Online, quite obviously, for ethical reasons faced a quandary whether to publish this paper or not, their four pages-long editorial should not surprise. It is very apparent from their editorial that they carefully considered whether to publish this case report or not, ultimately balancing, as already the title of their editorial suggests, hope and trepidations. While criticizing an obviously unsatisfactory informed consent process, and expressing concerns about the ultimate fate of the boy, they also acknowledge the achievements of Zhang et al in carrying through with the experiment.

We, however, disagree with their conclusions when they in their commentary are glossing over one of the most important facets of the case: the legal framework. We find it, indeed, puzzling that journal editors would even give the impression in their commentary that Zhang’s (failed) attempts to discuss a pre-IND application with the FDA could be viewed as a possible excuse for performing a procedure over which in the U.S. the FDA had clear statutory control. What the agency’s position was on the subject, has been widely known by the research community. That the FDA refused to meet with Zhang et al to discuss a pre-IND for a clinical nuclear transfer procedure (as the editorial also correctly noted, the FDA under Congressional mandate was prohibited “from consideration” of this matter), therefore, was not surprising.
Besides Zhang et al., several other qualified investigators and centers, including CHR as we reported in these pages, were also refused meetings with the FDA. CHR (and others) was not even trying to get permission for experiments involving embryo transfers into patients; we just wanted to perform basic stem cell studies to determine normality of embryos produced via nuclear transfer techniques. Yet, to our knowledge no other in the U.S. licensed physician or laboratory scientist proceeded with nuclear transfer experiments and, certainly, not with embryo transfers into patients.

The editorial also failed to fully appreciate other legal circumstances surrounding the case: They are best addressed by the commentary of Palacios González who made two important points: While initial reports suggested that the mitochondrial spindle transfer and embryo transfer took place in Mexico, after publication of the paper (and confirmed by the editorial) it now appears established that only the embryo transfer took place in the city of Guadalajara, Mexico, in an “affiliated clinic” to Zhang’s New York IVF center.

By performing the spindle transfer, using donor eggs in New York City, Zhang et al., therefore, clearly, disregarded current FDA rules, which prohibit any experimentation that crosses the human germline even if no embryo transfer takes place. Considering that to use donor gametes and/or embryos, practically every IVF center in the U.S. is dependent on a tissue bank license from the FDA, such a breach could have serious consequences on licensing status of any FDA-licensed IVF center, should the FDA choose to pursue the case. Palacios González further claimed that the Zhang team also broke the Mexican Regulations of the General Health Law on Health Research. Whether Mexican authorities plan on pursuing the matter is unknown, though considering Zhang’s group’s announcement that they were planning 20 more such transfers, that is apparently not anticipated.

Finally, the editorial claims that “the authors received approval” (for all procedures in the case) from the Internal Review Board (IRB) of the Mexican clinic where the embryo transfer was performed. That, of course, sounds like complete hogwash: We are unaware of any IVF clinic in Mexico or the U.S. (except for CHR) that has its own IRB. Moreover, even assuming the IVF clinic in Guadalajara, indeed, has an IRB, such an IRB would be ineligible to approve a highly experimental procedure performed in New York City. The spindle cell transfer in this case, therefore, clearly was not preapproved by an IRB.

These now for the first-time public facts present a very different and disturbing scenario from the one reported by media outlets in September of 2016 after the New York City birth resulting from this experimental embryo transfer. This new scenario raises serious ethical and legal questions and, even for investigators who very much favor research opportunities and progress toward potential clinical utilization of nuclear transfer methodologies, poses the question whether this was the right way of pursuing this goal?

We really do not think so!

**Spindle transfer: Continued from Page 8**

FDA refusal to meet: http://kaywa.me/ZCR7a

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.

During the process of egg retrieval, many of the cells that line the ovarian follicle are harvested and used for research. These cells, known as granulosa cells, can be cultured in plastic dishes outside the body where they will continue to divide and eventually become progesterone secreting lutein cells. In this month’s image, we take a close look at the inner workings of a colony granulosa cells that have been labeled with colored dyes to make certain elements of their internal structure apparent. In yellow, the DNA-containing nucleus of each cell can be seen and in pink, the delicate fibers of the cytoskeleton are observed coursing throughout the interior of human granulosa cells.
Egg freezing and social change

Social egg freezing is in the U.S. rapidly increasing in popularity and, indeed, has become something of an “industry.” We here today do not want to be repetitive in our condemnation of some of these trends toward commercialization of social egg freezing but want to address some of the social changes that feed these new developments.

Women who underwent social egg freezing (including some from CHR) in the U.S. and Israel have been submitted in two papers for publications and, therefore, cannot be revealed here in detail. We will concentrate on her presentation at Cambridge, as reviewed by Rickman.

Women who chose to freeze their eggs in a majority were urban, affluent, highly educated professionals and in their late 30s. Likely the most challenging finding of her study was the observation that they were not what Facebook’s Sheryl Sandberg described as “lean in, want it all” women but women who strongly desired a family but, simply, never met the right partner. In other words, the problem was dearth of eligible men since, currently, the U.S. four female college graduates compete for only three male college graduates. Men, intimidated by women of higher status, prefer “to marry down,” by sociologists called the “emasculaton thesis.” The declining pool of male candidates then ends up “playing the field,” without ever choosing a permanent partner (“Peter

Noteworthy in the medical literature

It is always a special pleasure when an opportunity arises to mention favorably a New York City colleague. Such an opportunity presented itself with the recent publication of a study by Kara Goldman, MD, Assistant Professor in the Reproductive Endocrinology and Infertility Division of the Department of Obstetrics and Gynecology at New York University (NYU), who with colleagues in the very prestigious journal Proceedings of the National Academy of Sciences (PNAS) recently published a very interesting study, potentially pointing to a pharmacological solution how the loss of ovarian function from chemotherapies can be prevented (Goldman et al., mTORC1/2 inhibition preserves ovarian function and fertility during genotoxic chemotherapy (2017;114:3186-3191).

Though this study was conducted in a mouse model (and men are not mice), it strongly suggests that blockage of the so-called kinase mammalian/mechanistic target of rapamycin, (called mTOR) with already existing small molecule inhibitors preserves ovarian follicles during chemotherapy that, otherwise, would be destroyed. To demonstrate this effect, the investigators induced in a mouse model gonadotoxicity by administering cyclophosphamide, while inhibiting mTOR complex 1 with everolimus (RAD001) or mTOR complex 1/2 with the still experimental drug INK128. So treated animals preserved their ovarian reserve when treated with gonadotoxic drugs, as demonstrated by stable primordial follicles, anti-Müllerian hormone levels (AMH) and overall fertility.

These are extremely exiting findings because if such treatment can be confirmed as equally efficient in preserving ovarian function in young women undergoing chemotherapy, other methods of fertility preservation, like oocyte or even ovarian tissue cryopreservation would become unnecessary. Interestingly, Everolimus (Afinitor®, Novartis) is already widely used in cancer treatments (advanced renal and advanced HR+, HER2-Negative breast cancers) and as an immunosuppressant in prevention of organ rejection and, therefore, off-label could be tested very quickly. This study was considered of enough importance to be summarized by Science in its April 21, 2017 issue. We congratulate our NYU colleagues on this accomplishment.

An issue that received considerable attention in the media recently was the length human embryos can be cultured in vitro in the laboratory. Currently worldwide
CHR news: Continued from Page 1

staff meetings, patient education and staff lunches, from which one can exit onto a big new terrace, where everybody is planning on open air lunches when the weather allows.

The last two pieces to the puzzle that remain to be completed are the 4th floor, where the IVF unit used to be, and the main entrance into the center. The 4th floor will be the new administrative and education hub of CHR, with a new office for CHR’s COO, Ms. Jolanta Tapper and her staff, and a new large “living room” (i.e. conference room), which will have all the electronic gadgetry to present talks and hold conferences, even with colleagues on the other side of the globe. The very last step of the renovation will be the resurfacing of the entry area to the center, which after over 15 years of use and abuse from heavy traffic and deliveries deserves a complete makeover.

All of this should be completed no later than mid-June. Sometimes in June/July we then are planning an “Open House” for patients, colleagues and friends to proudly show off the fruits of over two years of suffering. We will let you know about the date, and consider yourself all invited!

Noteworthy: Continued from Page 10

respected limits mandate termination of human embryo cultures not later than 14 days after fertilization. Two in vitro implantation studies of human embryos published in 2016 by the laboratories of Ali Brivanlou, PhD (Rockefeller University, N.Y.) and Magdalena Zernicka-Goetz, PhD (Cambridge University, U.K.), at the time reviewed here, however, challenged these limits, as embryos, completely self-sufficient, appeared to develop up to day-14, and, likely, could have been grown much longer.

A recent paper in the journal eLife by George Church, PhD and co-workers at Harvard University ignited flames of controversy, when actually recommending an even more structured set of guidelines than are currently in place. The Wall Street Journal on March 22, 2017 dedicated almost a full page to the subject with Ali Brivanlou PhD representing the contrarian viewpoint. Brivanlou, of course, is also a Senior Visiting Scientist at CHR, and CHR investigators maintain a close collaboration with his Stem Cell and Molecular Embryology Laboratory at Rockefeller University.

Pan thesis”). All is further complicated by limitless choice due to online dating, creating perpetual dissatisfaction: the “soulmate thesis.”

Egg freezing offers women then a way to (supposedly) preserve rather than postpone their fertility, and is a necessity rather than a choice to avoid the stigma that often accompanies singledom and childlessness. Egg freezing, therefore, is not, as widely propagated by the egg-freezing “industry,” a statement of female empowerment but a private decision, often associated with as much sadness as hope.

These are important findings, and quite contradictory to the widely presumed profile of the young single woman who is considering freezing her eggs, demonstrating the psychological vulnerability of candidates for social egg freezing.

Professionals who advise them about the process of social fertility preservation via egg or, possibly, embryo freezing, therefore, must be fully transparent and brutally honest about what social fertility preservation can and cannot offer. Over-promising would only add further insult to injury!

Egg freezing: Continued from Page 10

IVF "add-ons": Continued from Page 2

Since CHR investigators who did this work submitted a manuscript for publication, we currently are not at liberty to disclose further details of their study. Only so much: In various regions of the world, the declines in live birth rates observed were closely associated with distinct new practice patterns, often including above listed “add-ons” to IVF. In other words, though associations are not always equal to causations, because these observations were made repeatedly in different regions of the world, the likelihood that introduction of certain “add-ons” to routine IVF in those 10 years contributed to observed declines in live birth rates from IVF worldwide is rather convincing.

Unvalidated “add-ons” to IVF, therefore, not only add to already unaffordable high IVF costs for many, and fail, as promised by their proponents, to improve IVF outcomes; but, in addition, often actually reduce live birth chances from IVF for patients.

As our European colleagues apparently are starting, it appears time to recognize the problem in the U.S., and stop this nonsense before it gets worse!

Egg freezing: Continued from Page 10

- The CHR
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