Welcome to the New Year, which we hope will bring health, happiness and success to everybody in the larger CHR family of patients, colleagues and friends! In this newsletter we look forward to 2017 by looking backward at the year 2016.

Completely new IVF unit and laboratory facilities

For CHR, the year 2016 was truly a remarkable one. Almost on schedule but also over budget, CHR’s new IVF Unit was fully inaugurated in December (see photos: recovery area with reclining chairs and privacy curtains on the left and operating room on the right), offering more clinical space for procedures and recovery of patients, larger laboratories with updated state-of-the art equipment, for the first time a separate research laboratory and greatly expanded office space for our, in recent years, very rapidly growing staff of biologists/embryologists. The staff, indeed, did an amazing job in managing the transition period, where over approximately two weeks, both laboratories old and new were functioning in parallel, so that eggs and embryos did not have to be transported between floors.

Entrance into the new IVF Unit in the new building addition is now on the ground floor, directly off the Center’s also remodeled main waiting area.

A few words about CHR’s “magical” embryology laboratory

Likely unmatched by any other IVF center in NYC, CHR’s laboratory division now consists of 3 PhD-level biologists, 1 MD-embryologist/biologist and 1 MS-level embryologist/biologist. This, indeed, represents a highly unusual aggregation of senior staffing for any embryology laboratory but, certainly, for an IVF program of CHR’s size. Most embryology laboratories at best employ only one doctoral-level scientist, usually the director of the laboratory. Since at CHR Norbert Gleicher, MD, has been serving as IVF Laboratory Director since the lab’s inception (he is one of the longest-serving IVF laboratory directors in the nation), the aggregation of senior biologists is even more remarkable.

A 4th PhD-level biologist, who also earned an MS-degree in statistics, in addition serves as Director of the center’s Biostatistics Division, which not only is charged with outcome assessments in CHR’s clinical Continuous Quality Improvement Program (CQIP) but also supports all of the center’s clinical and basic science-related research activities. Having a medical statistician in-house, who also is trained as a PhD-level biologist, is, of course, a great advantage when complex biological connections need to be parsed out statistically.

Though this unusual accumulation of senior staff members in the laboratory of an IVF center, of course, represent a very significant investment, it to a large degree explains the rather “magical” performance of CHR’s embryology laboratory in what, unquestionably, represents the most difficult patient population of any IVF center in the U.S. and, likely, the world.

The year 2016, once again, confirmed the “magical” quality of CHR’s embryology laboratory, which so often makes CHR a center “of last resort.”

Continue reading on page 2
Above noted Biostatistics Division provided the table above, which demonstrates in simple to understand numbers how CHR’s patient population has been growing older and older over the last 5 years, already in 2012 having been the oldest of any IVF center in the nation (the 2016 data are not yet final). IVF patient populations in most U.S. IVF centers have been aging since older women for over a decade have represented the most quickly growing age group having children while younger women increasingly delay child birth. But no IVF center in the U.S. (and, likely elsewhere) still treats patients of as advanced age with use of their own eggs as CHR.

The pie chart demonstrates how over the last few years, even within CHR’s relatively old patient population, the group of women above age 42 has been growing, representing roughly 60% of all IVF patients in 2016.

As the table also demonstrates, age is not the only adverse prognosis factor in CHR’s patient population: Abnormally high follicle stimulating hormone (FSH) levels are further rising, and abnormally low anti-Müllerian hormone (AMH) levels are further declining. In other words, not only are CHR’s patients getting older every year but even younger patients present with very low functional ovarian reserve (LFOR), as demonstrated by rising FSH and declining AMH levels.

Yet, despite all of this, CHR’s IVF cycle outcomes have remained surprisingly excellent. As presented on CHR’s website and in multiple peer-reviewed publications (please contact us for reprints), as a clear testament to the high quality and “magic” of the center’s clinicians and above noted embryology laboratory staff, CHR’s IVF cycle outcomes generally significantly outperform potential outcomes quoted in the literature for such poor prognosis patients.

Almost all of these patients seek treatment at CHR only after they failed (often many times) at other IVF centers (often, indeed, at several different centers). We, here at CHR, therefore, always wonder why our patients do not seek earlier treatment at CHR? We, undoubtedly, would be even more successful, had we been given the opportunity to intervene earlier in our patients’ infertility journey.

The word really matters in older women or younger women with LFOR. Producing “magical” results in women who have had failed IVF cycles elsewhere, CHR could do even better, if given a chance to intervene earlier and at younger ages. At older ages, even a few months can make quite a difference in outcomes!

Over the last decade, CHR has achieved worldwide recognition as a “center of last resort.” For all the same reasons, patients would, however, also be well advised to view CHR as a “center of first choice.” Especially women in their mid- to late-30s would do much better if correctly diagnosed and treated at that age rather than after they crossed over into the 40s.

### Table: 2016 January to September Age Distribution of CHR Patients Undergoing IVF with Their Own Eggs

<table>
<thead>
<tr>
<th>Year</th>
<th>Age (years)</th>
<th>FSH (mIU/mL)</th>
<th>AMH (ng/nL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>39.6/-5.6</td>
<td>16.5/-19.0</td>
<td>1.3/-1.9</td>
</tr>
<tr>
<td>2013</td>
<td>39.6/-5.5</td>
<td>18.7/-22.7</td>
<td>1.4/-1.9</td>
</tr>
<tr>
<td>2014</td>
<td>40.4/-5.7</td>
<td>20.5/-26.3</td>
<td>1.4/-1.9</td>
</tr>
<tr>
<td>2015</td>
<td>39.6/-5.5</td>
<td>20.3/-24.5</td>
<td>1.2/-1.7</td>
</tr>
<tr>
<td>2016</td>
<td>41.4/-6.0</td>
<td>19.2/-19.2</td>
<td>1.1/-1.6</td>
</tr>
</tbody>
</table>

Data presented as mean +/- STD

See our 2015 pregnancy rates: [http://kaywa.me/T9kCG](http://kaywa.me/T9kCG)
With 24 PubMed-listed peer-reviewed publication, the year 2016 was also a record year for investigators at CHR. The influence of CHR’s research was, however, even bigger than numbers can demonstrate. CHR was instrumental in the reassessment of preimplantation genetic screening (PGS) in association with IVF that is underway worldwide.

Were it not for CHR’s initiative to transfer selected, allegedly chromosomally “abnormal” embryos, supported by some New York colleagues, and being able to demonstrate fully expected normal births following such transfers, the world would view PGS still as a reliable test, capable of assessing whether an embryo is chromosomally normal or not and, therefore, transferrable or not.

Reporting the first 5 healthy births in the world following such transfers at the Annual Meeting of the ASRM in 2015, CHR’s Medical Director and Chief Scientist, Norbert Gleicher, MD’s presentation attracted worldwide attention, from colleagues and media, alike. Shortly thereafter, Italian colleagues from Rome reported similar experiences, and other centers around the world started transferring aneuploid embryos, as well, since it had become increasingly evident that, likely, a large proportion of human embryos contained in their trophectoderm abnormal cell lines (i.e., were mosaic). The trophectoderm is, however, from where embryo biopsies are taken in PGS from blastocyst stage embryos. As also has become increasingly clear over the last year, these abnormal cell lines, likely more often than not, clinically are, however, irrelevant because they do not really correctly reflect on the embryo’s chromosomal make up (i.e., whether it is aneuploid). Consequently, we see little sense in performing these biopsies.

Kushnir et al then published the reanalysis of a national PGS data set, which demonstrated not only no beneficial PGS effects on IVF outcomes, as proponents of PGS have been claiming for over a decade, but that the procedure actually reduced live birth chances (Kushnir et al., Fertil Steril 2016;106:75-79). This paper was followed by studies from prominent California (Murugappan et al., Hum Reprod 2016;31:1668-1674) and New York City (Kang et al., Fertil Steril 2016;106:597-602) IVF centers, reporting that PGS neither reduced miscarriage rates nor improved pregnancy rates in their respective patient populations.

Today, the whole world looks much more skeptically at PGS, and even the Preimplantation Genetic Diagnosis International Society (PGDIS), the society we here at CHR jokingly call the “PGS Support Union,” found itself forced in 2016 to completely revise how it recommends to its members to assess the chromosomal status of embryos. Part of this reassessment included the acknowledgment that many embryos, until recently described as “aneuploid” (i.e., chromosomally abnormal and, therefore, discarded), are really “mosaic” and, therefore, eligible for embryo transfer, and can result in perfectly normal offspring.

Based on additional reported cases and cases we were made privy to from colleagues around the world, we are now aware of ca. 30 healthy births after transfer of such allegedly “aneuploid” embryos. Concomitantly, the number of reported false-negative PGS is also rising, where patients received allegedly “normal” embryos after PGS but had miscarriages that demonstrated an aneuploid fetus. False-negative diagnoses are, however, rarer than false –positive diagnoses and, at least, do not lead to wasteful discarding of normal embryos.

Another very important discovery at CHR involved the so-called hypo-androgenic polycystic ovary syndrome (PCOS), which represents a previously unknown presentation of PCOS, first described by CHR investigators. A first manuscript describing this new phenotype is in press at a prestigious medical journal, and a second manuscript, describing the ontogeny of this PCOS phenotype with advancing age, is currently under review.

We are convinced that, once published, the discovery of this new PCOS phenotype will, have considerable significance for infertility practice for two reasons: First, once aware of the clinical presentation, IVF centers will be surprised by how frequent this

Continue reading on page 4
phenotype is, especially in women with, otherwise unexplained, very poor IVF success rates. More importantly, IVF pregnancy chances in these women can be greatly improved by raising their androgen levels (male hormone levels) prior to IVF cycle start.

As 24 published peer reviewed communications very obviously suggest, CHR research in 2016 involved many other important subjects. CHR’s Assistant Scientist and Director of Fertility Preservation, Vitaly A. Kushner, MD’s work on national IVF cycle outcome assessments by the Center for Disease Control (CDC) and ASRM/SART has been a great impetus for the improvements introduced by ASRM/SART in how this registry, going forward, will report national IVF cycle outcomes at different centers. Hopefully, this work will also convince the CDC that their current evaluations of outcomes are artificially inflating IVF pregnancy rates in those fertility centers which excessively use embryo banking. In another study in submission, Kushnir et al, indeed, demonstrate that centers which excessively utilize embryo banking economically benefit from their greatly inflated pregnancy and live birth rates, while clearly misleading the public.

Research in mice on the utility of anti-Müllerian hormone (AMH) as a potential therapeutic agent, conducted in the laboratory of Visiting Assistant CHR Scientist Aritro Sen, PhD, from University of Rochester School of Medicine and Dentistry in Rochester, N.Y., together with two clinical studies conducted at CHR, all published in 3 papers during 2016, not only initiated 3 patent applications but may also lead to the clinical investigation of AMH as a medication in female infertility and, potentially, other medical conditions.

Collaborating institutions

In addition to above noted laboratory of Dr. Sen at University of Rochester School of Medicine and Dentistry, as readers of the VOICE, of course, know, CHR has also close collaborative relationships with a number of U.S. and overseas-based institutions. Perhaps the closest collaboration exists with the laboratory of Prof. Ali H. Brivanlou, PhD, at Rockefeller University here in NYC, where a number of very interesting projects are underway.

His laboratory in 2016 published a remarkable paper in Nature (Deglincerti et al., Self-organization of the in-vitro attached human embryo. Nature 2016;533:251-4), describing in an in vitro implantation model in minute detail how human embryos develop after implantation up to day-14. He and his group of investigators not only deserve congratulations for publishing this remarkable work but this paper was also chosen by readers of Nature as “The Breakthrough Paper of the Year 2016.” We sincerely congratulate!

Longstanding collaboration with the Medical University of Vienna in Vienna, Austria, recently also led to the appointment of CHR’s Medical Director and Chief Scientist, Norbert Gleicher, MD, as Professor (adj.) at that school. Other collaborations involve the Sheba Medical Center in Tel Hashomer, Israel, part of the Sackler Faculty of the Medical School of Tel-Aviv University and the Salk Institute for Biological Studies, where the laboratory of Prof. Juan Carlos Izpisua Belmonte is doing groundbreaking work in reproductive biology, stem cell sciences and regenerative medicine. His laboratory produced at least 3 “blockbuster” papers in Cell, Nature and Science, the last one earning him a lengthy write up (with photograph) by Nicolas Wade in The New York Times on December 16, 2016.

In collaborating with this laboratory, attempting to cure mitochondrial diseases in early stage embryos, CHR is still looking for women who know that they are carriers of mitochondrial diseases. If you are such a patient or if you know of such patients, please call Dr. Gleicher at 212-994-4400 for a free consultation.

Contact us to learn more about the study: http://kaywa.me/43Mdn

The Salk investigators are on the forefront of genetic editing, which has significant potential in eliminating genetic diseases and help infertile women conceive. CHR is looking forward to a long and fruitful collaborative effort between the two institutions, and hope you will consider participation in the study.

Mitochondria Study

DO YOU CARRY A MITOCHONDRIAL DISEASE OR KNOW SOMEBODY WHO DOES?

If you do, please call us at 212-994-4400 for a free consultation in person, by phone or via Skype. CHR is searching for a way to prevent inheritance of these awful diseases in collaboration with colleagues at the famous Salk Institute for Biological Studies in La Jolla, CA. You may be able to help!

Contact us to learn more about the study: http://kaywa.me/43Mdn

Read the NYTimes article: http://kaywa.me/ZO9Ex
Postgraduate education at CHR

Three purposes have been the foundation of CHR’s existence since its inception: clinical care, research and education. We have so far discussed the first two. The educational component can only be discussed within the context of The Foundation for Reproductive Medicine (FRM), a not-for-profit research foundation, which actively supports research at CHR and many of its postgraduate educational activities. So, FRM co-sponsors with CHR the monthly GrandRounds, where prominent speakers from all over the world are invited, in front of up to approximately 100 obstetrician/gynecologists, reproductive endocrinologists and biologists and other colleagues, to present their most recent research data. Above noted Nature “Breakthrough Paper of the Year 2016” from Prof. Brivanlou’s laboratory at Rockefeller University, indeed, saw its first public presentation at a CHR GrandRounds event on March 15, 2016, only days before its publication and wide exposure to media.

In November of 2016, FRM and CHR also got together to sponsor for the first time an international Conference on Translational Reproductive Biology and Clinical Reproductive Endocrinology in NYC, which was a huge success and, therefore, in 2017 will become an annual event. The 2017 dates will be November 16-19, and the Conference will, once again, take place at the Grand Hyatt Hotel on 42nd Street at Grand Central Station.

The Foundation for Reproductive Medicine (FRM)

This is also an opportunity to extend CHR’s appreciation to the FRM for all the support given to CHR in its research and postgraduate educational activities during 2016. The past year was not only a record year for the FRM in terms of sponsored activities but also in terms of outside donations received from patients, industry sponsors and other donors. In addition, a single donation of almost $60,000, also represented the single largest donation ever received by the foundation.

CHR, of course, always encourages donations to the FRM, which are tax deductible in accordance with the law. We also encourage participation in the activities of the foundation, whether by attending events the foundation sponsors or by considering joining the FRM’s Board of Directors. If you are interested in potentially joining the Board of the FRM, please contact Dr. Gleicher, who serves as the FRM’s President, by calling 212-994-4400.

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.

Egg cells develop within a community of cells that nourish them for several months as they prepare for the big event—ovulation. In this picture, scientists at the CHR have isolated one of these “communities” known as an ovarian follicle. Using special microscopes, we can detect the presence of chromosomes, seen here as the dark spots belonging to the egg cell itself (center on background of yellow showing the limits of the egg) or the cells surrounding the egg cell which are much smaller in size and have their “spots” (chromosomes) located on red circles, the nuclei for each of the follicle cells.

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Concerns over the effects of the new administration on reproductive research and practice

At the end of December British media reported that the Human Fertilisation and Embryology Authority (HEFA), the UK’s fertility regulator (approximately equal to the FDA in the U.S. in that position) announced that it would accept applications from UK-based IVF centers wanting to offer in these pages repeatedly discussed “three parents” pregnancies to mothers who are carriers for so-called mitochondrial genetic diseases. This decision was reached since HEFA concluded that appropriate safety studies had been completed.

This decision stands in quite radical contrast to what investigators and IVF centers face here in the U.S., where the FDA, as also previously discussed here, based on a recently passed Congressional resolution is not even permitted to review applications from IVF centers.

Serious concerns are spreading in the science community about further restrictions on reproductive research that may be mandated by the conservative Republican majority in Congress. Others, on the other hand, point out the non-ideological “common sense” approach President Elect Donald Trump has been espousing in other areas of political controversy.

We here at CHR very much hope that such “common sense” will, prevail, and will allow U.S. scientists not only to pull even with British colleagues in this area of research but also with Japanese, Chinese and colleagues in many other countries where government restrictions on reproductive research are far less restrictive than currently in the U.S. If we want to make reproductive research in the U.S. “great again,” then the FDA has to be encouraged by government, rather than discouraged, to engage with basic scientists and the clinical IVF community because the same techniques our British colleagues now are permitted to utilize in preventing generational transmission of mitochondrial diseases from mothers to offspring, can, likely, also be extremely useful in improving pregnancy chances of older women with use of their own eggs.

And as we noted elsewhere in this issue of the VOICE, older women above age 40 are now in the U.S. the by far quickest growing age group having children. As women now on average live postmenopausal longer than their total life expectation was at the beginning of the 19th century, they, of course, will want to continue to have children. And this trend will only accelerate!

We practically never used to see patients above age 50 here at CHR. In just the last two years, women over 50, wanting to have children, have become the norm. Hopefully, helping older women to have children will not turn into yet another political fight between left and right but will find both united in helping women to have the children they want and deserve.

Woman gives birth, whose ovary was frozen since childhood

We in these pages also have repeatedly written about the ability to “preserve fertility” for children and young women who undergo chemo- or radiation therapy that, otherwise, will wipe out their ovaries (Dr. Kushnir explains the procedure in a series of videos on our website--see below). Again from the U.K., media reported recently on a woman who gave birth after one of her ovaries was surgically removed and cryopreserved when she was only 9 years old, and was scheduled to undergo chemotherapy and a bone marrow transplant because of an inherited blood disease, called thalassemia.

Continue reading on page 7
She now at age 24 delivered a healthy boy after a few small pieces of that ovary had been surgically transplanted back into her pelvis. Those ovarian tissue pieces ‘took,” and started to develop growing follicles. She underwent IVF and conceived.

These ovarian tissue reimplantations have become quite successful, and a good number of young women have been able to become mothers all over the world after such reimplantations following, otherwise devastating chemo and/or radiation therapies. But most were older than this patient at the time their ovaries were removed. This pre-menarcheal case is, likely, the youngest female ever to succeed, and is a testimony to the fact that **one should never hesitate to freeze ovarian (or testicular) tissue when women (or men) face the stark choice of receiving medical treatments to survive that will cost them their ovarian (testicular) function.**

On a side-note, CHR is one of only few IVF centers fully licensed to cryopreserve and maintain ovarian tissue, and the center’s *Fertility Preservation Center*, headed by Vitaly A Kushner, MD, provides a comprehensive range of fertility preservation treatments, including ovarian tissue freezing, to patients with cancer and other life-threatening conditions.

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**The CHR**

*Fighting for every egg and embryo!*

**Staying Connected**

New informational material on treatments or news coverage on fertility breakthroughs, the best way to stay up to date on CHR’s activities is via our social media channels. Follow us, and never miss important news!

**Visit CHR on Facebook:**
https://www.facebook.com/thechr

**Follow CHR:**
http://twitter.com/infertilityNY

**Check out our video resources:**
https://www.youtube.com/user/CenterForHumanReprod

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