Welcome New Readers, and Introduction to CHR

We welcome our readers to the February issue of the CHR VOICE, which as of this month goes to an expanded mailing list of colleagues in general Obstetrics and Gynecology all over the U.S. We, therefore, especially welcome our new readers to this and future issues.

Many colleagues in general Obstetrics and Gynecology who practice in the larger New York City Tristate area have in past years asked to be placed on our mailing list for the same reason why CHR’s monthly GrandRound events in New York City (now co-sponsored by the Foundation for Reproductive Medicine) have been so popular: Reproductive endocrinology and infertility, though to a considerable degree still part of general practice, receive relative minor attention in institutional CME activities in comparison to other subspecialty areas, such as perinatology and gynecologic oncology. Since over half of CHR’s patients are located outside of the larger New York City Tristate area, we feel that it is time to reach out to colleagues beyond our primary geographic area.

As a fertility center that has evolved into a worldwide referral center of “last resort” for patients who have failed infertility treatments elsewhere, it is important to us that our colleagues fully understand why CHR is often able to succeed where other fertility centers do not, and often choose not even to try.

Because so many of CHR’s patients are long-distance patients, our medical staff is daily in touch with colleagues all over the U.S., Canada and overseas since these patients require considerable local management before they come to CHR for their IVF cycle treatments. Expanding our mailing list, we hope, will further help in this process.

By familiarizing our colleagues with how CHR’s fertility treatments differ in many aspects from those of other centers, we not only hope to serve an important educational purpose (postgraduate education is one of CHR’s three main purposes, together with clinical care and research), but also strive to save patients time in pursuit of fertility treatments. The time it takes from treatment start to pregnancy, and especially healthy delivery, is of great importance, especially as women nowadays start the process at more advanced ages. Age at treatment start is, therefore, of crucial importance: The younger the patient is when she initiates treatments, the more likely will the treatment succeed. As successful as CHR is in treating women who repeatedly have failed elsewhere, had these patients consulted with CHR’s physicians earlier, our treatment approaches would have been even more successful.

One issue of the VOICE, of course, cannot offer a comprehensive picture of CHR’s practice, but after reading just a few consecutive issues, differences will become very apparent. Much of these differences in practice are based on CHR’s in-house research efforts, which in quantity and quality are unique for a private fertility center, and are further augmented by close research collaboration with major academic institutions all over the U.S. and the world, including in the U.S. the Rockefeller University in New York City, Rochester University School of Medicine and Dentistry in Rochester, New York, and The Salk Institute in La Jolla, California, and overseas with multiple institutions in Europe and Israel. We in this issue will offer a few examples how recent CHR research not only has changed practice at CHR but, hopefully, also will affect fertility treatments elsewhere.

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Early Egg Retrieval in Women with LFOR

Regular readers of these pages will recall that CHR investigators earlier in 2015 published a paper in the prestigious Journal of Endocrinology (Wu et al., Aging-related premature luteinization of granulosa cells is avoided by early oocyte retrieval. 2015;326:167-180), in which they reported the discovery that in older women above age 43 (i.e. in women who usually demonstrate LFOR because of their advanced age) the intrafollicular environment matures quicker than in younger women, thus leading to so-called premature luteinization of the follicle and over-matured eggs. As a consequence of that finding, CHR’s physicians started retrieving eggs from older women’s follicles earlier by giving the ovulation-inducing hCG shot when the lead follicle reaches 16mm rather than at the usual 19-21mm. This simple management change in older women over age 43 more than doubled IVF pregnancy chances.

We can now report that the same group of CHR investigators completed a follow-up study in younger women with premature ovarian aging (POA) (i.e., in women with premature LFOR, characterized by prematurely elevated FSH and/or prematurely low AMH levels), and, lo and behold, found that their follicles demonstrated exactly the same molecular signature of premature luteinization found in older women above age 43. Even more remarkably, with early egg retrieval at ca. 16mm, the improvements in clinical pregnancy rates in younger women with POA were even more pronounced than in older patients.

Since a manuscript, describing these findings in POA patients, was just submitted for publication, we are not yet at liberty to go into further detail. Only so much: we predict that earlier egg retrieval in women with LFOR will become standard of care in IVF worldwide, once our colleagues recognize how favorably it affects their outcomes in women with LFOR.

Watch Dr. Barad explain early retrieval: http://kaywa.me/4btTq

2015 Publications

The year 2015 was another banner year for peer-reviewed scientific publications by CHR investigators. PubMed, the national registry of peer reviewed publications in biomedical sciences, recorded 21 publications that appeared in print during the calendar year. Additional publications were accepted but did not appear electronically or in print before the year’s end. Indeed, one of those appeared already in print in early January of 2015. In addition, approximately 10 additional manuscripts were submitted to various medical journals, and are still under review.

Above noted website lists all electronically or in print published scientific articles in the medical literature, and is freely accessible to the public. We encourage readers of the VOICE who are interested in viewing our center’s publications to either use this website by looking up published papers under the name of one of the authors, or to simply contact us at www.CenterForHumanReprod.com with a request to have specific reprints sent to them.

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!

The collaboration with the Salk group, headed by Prof. Juan Carlos Izpisua Belmonte, the Roger Guillemin Chair at the Salk’s Gene Expression Laboratory, was established early last year, but research project had to be temporarily put on hold for administrative reasons. 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, now that the study can finally proceed.

Contact us to learn more about the study: http://kaywa.me/43Mdn
Treating Very Poor Prognosis Patients

In the December 2015 issue of Fertility and Sterility, the official journal of the American Society for Reproductive Medicine (ASRM), CHR investigators published a study of very poor prognosis patients, which attracted wide attention because of how “unfavorable” the reported patient population was (Gleicher et al., Live-birth rates in very poor prognosis patients, who are defined as poor responders under the Bologna criteria, with non-elective single embryo, two-embryo, and three or more embryos transferred. Fertil Steril 2015;104:1435-1441). Indeed, likely never before, has an equally poor prognosis population been reported in the medical literature because most fertility centers simply refuse to treat such patients, and offer them as only option the use of donor eggs.

Investigated patients not only were quite old (mean ages 41-42 years) but had very low AMH levels (mean 0.3-0.5 ng/mL) and very high FSH (mean 11.7-16.2 mIU/mL) and, thus, had very low functional ovarian reserve (LFOR). As a consequence, they, not surprisingly, produced very few eggs and embryos. Indeed, out of 768 started IVF cycles, only 397 cycles produced at least 1 embryo for transfer. The study then looked at those patients who got all of the embryos they produced transferred, which included 381 cycles since 16 women, either for medical reasons or because they did not want to take the chance of a multiple pregnancy, had an elective single embryo transfer and extra embryos cryopreserved.

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<td>&lt; 35</td>
<td>33.3%</td>
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<td>35-37</td>
<td>15.4%</td>
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<tr>
<td>38-40</td>
<td>8.3%</td>
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<tr>
<td>41-42</td>
<td>6.4%</td>
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<td>≥43</td>
<td>0.0%</td>
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- denotes inadequate case numbers; Modified form Table 3 of the above-noted paper in Fertility and Sterility.

The study then further investigated the question—in our opinion a crucial one for national IVF practice—how those women did at various ages who had only 1, 2 or 3 (or more) embryos transferred.

Why is this such an important question to answer? Because the vast majority of patients in this study in a vast majority of IVF centers all over the world would be refused treatments with use of their own eggs under the argument that their pregnancy and live birth rates would be negligible. We hear frequently from our patients that they were quoted live birth rates of 1% or less before coming to CHR.

This study, however, demonstrated very different outcomes for at least some of these patients and, for the first time, defined what real outcome chances were at different ages.

Specifically, the study demonstrated that for those patients who reached embryo transfer (i.e., at least produced 1 embryo for transfer) live birth rates were surprisingly high.

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Dear Colleagues and Friends,

This Conference has the principal goal of offering an authoritative 2016 update for reproductive scientists and clinicians about important new translational developments in reproductive biology/physiology and clinically relevant patient care issues, while at the same time pointing out paradigm changes and imminent new potential developments of significance. By targeting clinicians as well as basic scientists as audience, this Conference will offer both groups a unique and intimate framework for interaction and exchange of ideas.

David F. Albertini, PhD | Ali H. Brivanlou, PhD, MD | Norbert Gleicher, MD | Zeev Shoham, MD

June 15, 2016 Abstract deadline for inclusion in the Journal of Assisted Reproduction and Genetics (JARG) and eligibility for Young Investigator Award of $5,000

Due to limited space and limited numbers of discounted hotel rooms available during the pre-Christmas season, we recommend early registration and hotel reservation.

Pre-Conference Workshops:

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

Sessions:

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

For the full Conference program, registration, and abstract submission, visit the official Conference website: http://frm.cme-congresses.com/
Why reported IVF outcomes in many published studies must be viewed with considerable caution

Just following headlines in lay media makes it obvious that what is published in the medical literature does not always make sense. Why, otherwise, can a moderate amount of coffee on one day be considered healthy and the next day be described in the media as bad for our health? Other examples for contradictory data abound, and not only in the lay press; they are also a constant feature of reporting in the medical literature. Patients, therefore, should not be surprised when receiving contradictory opinions from different fertility experts.

Since CHR does not always follow what many other centers may consider “common wisdom,” our physicians often face the question: why do other centers not do what CHR is doing? The answer is relatively simple: Medicine, after all, is not only a science but also an “art” and, in that, not always an easy one to practice because it is so multifactorial. Conclusions are not always straightforward: for example, just because there appears to be an association between A and B, it does not follow that A causes B.

Indeed, often such associations are misleading because they occur due to the so-called confounding factors. For example, the age of studied patients in infertility is very important: If two groups are compared, and they do not have similar ages, the younger group will do better in general. If such age differences are not considered in comparing outcomes, resulting outcome differences may be erroneously attributed to a new treatment, while in reality they simply reflect the age difference between the two groups, not the treatment.

Aside from using its extensive research program to constantly update clinical practice, CHR’s investigators also very closely follow the published literature. In contrast to many colleagues, they do not, however, automatically accept everything that is published but carefully evaluate how the study was conducted. Only too often, this kind of critical review of published papers (even in prestigious medical journals) reveals shortcomings, which, when taken into account, eliminate significant findings claimed by their authors.

Indeed, as steady readers of these pages already know, especially in recent years, we here at CHR consciously chose not incorporate into routine practice a number of IVF-associated practice patterns, which many other IVF centers keenly embraced. In these cases, our own data re-analyses (usually using the original data published in those papers) did not agree with the authors’ published conclusions. Examples include the excessive use of blastocyst stage embryo culture, preimplantation genetic screening (PGS) for chromosomal abnormalities of embryos, embryo banking, mild ovarian stimulation (often also called “mini IVF”) and the introduction of closed incubation systems with time lapse imaging for embryo culture and embryo selection.

In principle, we have reached the conclusion that the whole concept of “best embryo selection,” which lies at the basis of most of these procedures, is biologically and statistically flawed. It is biologically flawed because the transferrable embryo is at the last stage of a many-months-long egg maturation process, followed by a very short embryo maturation process of only a few days. It, therefore, appears naïve to assume that by “selecting” the so-called “best” embryos we can achieve significant improvements. Interventions have to happen much earlier, during egg maturation, since approximately 95% of embryo quality is determined by egg quality.

Statistically, the concept is flawed because practically all published studies claiming outcome advantages from these embryo selection methods used statistically questionable methods eliminating unfavorable patients from outcome assessments by reporting outcomes only for patients who reached embryo transfer. This, of course, left only relatively good prognosis patients included in any subsequent statistical analyses; thus, greatly exaggerating outcomes in comparison to what an unselected patient population would demonstrate.

For those readers who are interested in this subject, we suggest to be on the lookout for a paper in the Journal of Assisted Reproduction and Genetics (JARG), authored by Gleicher et al., which should be appearing electronically and in print in the near future, and in much more detail addresses the issue why many IVF outcome studies in the medical literature must be read with caution.
British scientists receive permission to genetically edit human embryos

We have repeatedly before in these pages addressed the controversy surrounding investigations of germline editing involving human embryos. After the typical initial response by some members of the scientific community who demanded a complete research moratorium, cooler heads have prevailed and, as recently noted in the VOICE, an international conference of biologists and ethicists recommended that carefully conducted research be allowed, as long as so treated embryos are not transferred into uteri with possibility of establishing pregnancy. The conference also suggested that such research be carefully followed, and that serial evaluations about the possibility of using these treatments clinically be made, once safety of such procedures has been established.

It, therefore, is only appropriate that the U.K’s Human Fertilisation and Embryology Authority (HFEA) now gave permission to the Francis Crick Institute in London, a recently established biomedical research institute, to pursue “genome editing” in human embryos with the goal of better understanding the development of human embryos during the first week of development. As recommended by the above-noted international conference of experts, transfer of so-treated embryo into uteri will not be permitted.

Like for any IVF-related research, federal funds cannot be used for “genome editing” experiments in the U.S., but, similarly to IVF, such research can be privately funded. And if the success of IVF in the U.S. over the last 30 years is any indication, such privately funded research can be extremely successful.

CHR is, indeed, committed to research in this area. We have previously announced collaboration with the Salk Institute in La Jolla, California, one of the leading biomedical research institution in the world. We are currently seeking women who are known to be carriers of mitochondrial genetic diseases, which they would pass on to their offspring with considerable likelihood. If you are a patient with a mitochondrial disease, have a relative who is, or if you are a physician who has such patients in the practice, CHR will be very pleased to offer you or your patient a free consultation with the center’s Medical Director and Chief Scientist, Norbert Gleicher, MD. Please just call us at 212-994-4400, and tell our staff that you wish to make a free in-person, telephone or Skype appointment with Dr. Gleicher to discuss your mitochondrial disease. Overseas patients are welcome, and research funds available for this project may also cover long-distance travel expenses.

Support your IVF cycles with FERTINATAL® DHEA.

Research shows that a healthy level of androgens in the ovaries is essential to the development of eggs*

FERTINATAL® provides androgen support with 25mg of DHEA (dehydroepiandrosterone), micronized to the same standards used in CHR's original published research
CHR investigators recently developed an additional prediction model, which has been submitted for publication. We, therefore, are not yet at liberty to report details beyond the fact that it will further improve prediction of whether patients, likely will produce transferrable embryos based on age-specific FSH and AMH levels.

Ultimately, however, only ovarian stimulation will allow final determination of availability of transferrable embryos. Most IVF cycle costs arise with egg retrieval, fertilization and embryo transfer. In this study 51.7% of women reached embryo transfer. Among those who did not, over half were cancelled before egg retrieval and, therefore, encountered limited cycle costs.

Simply trying to stimulate women with severe LFOR may, therefore, be a highly appropriate treatment approach, as long as patients understand that their live birth chances are obviously dependent on whether they are still able to produce transferrable embryos, and how many, which ultimately can only be determined in an IVF cycle. Concomitantly, patients, of course, also have to be advised that live birth chances with young donor eggs would be significantly higher.

- 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!