Some general information on HGH
GH, considered a mitogen (making cells divide), is a stress hormone that raises blood sugar (glucose), free fatty acids and the family of so-called insulin-like growth factors (IGFs), which stimulate protein production. Many of the hormone’s functions are, however, still not known.

HGH and the IGFs closely interact. HGH stimulates the production of IGF-1, one of two IGFs (the other being IGF-2), a process often called the IGF “axis” or HGH/IGF-1 axis. Because this axis plays a role in cell proliferation and inhibits cell death (apoptosis), it has been associated with many normal physiologic processes, including follicle maturation in ovaries. At the same time, the axis is also involved in a number of pathological conditions, including certain cancers.

This dichotomy of function is one of the main reasons why HGH has become a controversial substance in the medical community and subject to frequent coverage in the lay press. Further controversy comes from its abuse by prominent athletes and by its use as a so-called “anti-aging” hormone by some physicians.

HGH use in female infertility
In attempts to improve ovarian responses to stimulation with gonadotropins, some fertility specialists have been supplementing HGH for years. The idea arose from the observation that IGF-1 is closely involved in early follicle growth. Peter R. Casson, MD, (currently head of the Reproductive Endocrinology at the University of Vermont), then with colleagues from Baylor University in Houston, Texas, was the first to suggest that DHEA supplementation may be effective in women with LFOR and suspected that DHEA exerted its effects via IGF-1.

We now know that most of DHEA’s effects are exerted through testosterone (to which most of DHEA is converted) and via the androgen receptors (AR) on granulosa cells, the cells surrounding the egg in every follicle (look for more on this topic in a future CHR VOICE). But because IGF-1 in various animal models has been demonstrated, just like DHEA, to be very important for follicle growth and maturation at early follicle growth stages, CHR has been considering its clinical use for quite some time.
Interesting news from Oregon

One of last year’s GrandRounds speakers at CHR, Shoukhrat Mitalipov, PhD, made national headlines not once but twice in the last month. In mid-March, the Food and Drug Administration (FDA) called a special meeting of experts to discuss his work. And just a few days later, he published yet another one of his “bombshell papers” in the highly prestigious journal Nature, for the first time succeeding in reprogramming the nucleus of oocytes with interphase cytoplasm of 2-cell mouse embryos.

This work is revolutionary because it further opens possibilities for regenerative medicine by potentially allowing production of embryonic stem cells and, if one wants to be daring, for a variety of fertility-related purposes.

Dr. Mitalipov’s work that gave the impetus to above noted FDA meeting is, however, revolutionary for another reason: it has amazing potential therapeutic implications in so-called mitochondrial diseases, a thankfully quite rare group of genetic diseases (ca. 1/4,000 newborns is affected), not inherited like most genetic diseases via nuclear DNA but through the special DNA found in mitochondria. And it also can, potentially, help older women to conceive!

In an article by Sabrina Tavernise in the New York Times on March 17, 2014, Dr. Mitalipov was quoted as calling himself a “mitochondriac” because of his lifelong obsession with mitochondria, the small structures floating in a cell’s cytoplasm, and considered the cell’s “batteries.” As women age, these “batteries” get weaker, which is widely considered a principal cause for why aging eggs do so much more poorly in reproduction.

Approximately 15 years ago, a group of scientists under the leadership of Jacques Cohen, PhD, now Editor-in-Chief of the medical journal Reproductive Medicine Online, therefore, experimented with adding “young” cytoplasm from young, healthy women, containing “young” mitochondria, to eggs from older women. Because this created 3 potential genetic parents for the embryo/baby, these experiments, meant to help older infertile women, caused considerable controversy and, before final results could be obtained to allow a judgment on the usefulness of the technique, the FDA stepped in, and closed down all such experimentation.

Dr. Mitalipov, on staff at the Oregon Health and Science University’s National Primate Research Center, already in 2008 reported the birth of healthy twin monkeys after successful replacement of mitochondria. Since then, he has done preliminary work in other animal models and with human eggs, which strongly suggest that the replacement of mitochondria may also be possible in human eggs.

The March FDA conference was meant to discuss this possibility – not in attempts to treat older women but, primarily, in trying to avoid mitochondrial genetic diseases. A similar body in the United Kingdom already last year tentatively approved human research to do so.

Though the conference was advertised to discuss “practical” and “technical” issues, and specifically was announced not to address ethical issues, the ethicists, as one could have expected, once again took over the discussion. Tavernise’s piece in the Times quotes one ethicist, attending the conference, as arguing “that mitochondrial replacement is completely unnecessary since women have other options to have healthy children.”

And what did he consider these alleged options to be: “Egg donation or having prenatal genetic diagnosis to find eggs with fewer mutations.”

Unless Tavernise misquoted him in her article, this ethicist quite obviously does not know what he is talking about because (i) which serious person would consider as a more ethical solution 50% of “foreign” DNA from an egg donor in comparison to a smidgen of mitochondrial genetic material from a donor; and (ii) “doing prenatal diagnosis to find eggs with fewer mutations?” Which biology class did this ethicist attend or actually, more likely, which classes did he skip?

People left the FDA conference somewhat discouraged since few believe that the FDA will in the near future allow human experiments to restart in the U.S. involving mitochondrial transfers. We strongly hope that those sentiments, expressed in the lay media, will turn out to be incorrect. Women at risk to deliver children with mitochondrial diseases and, yes, older women trying to have children are anxiously awaiting progress in this area of medicine. Dr. Mitalipov, if permitted, would likely offer such progress quickly and ethically.

And we are saying this not only because he is a friend of CHR or because his laboratory in Oregon is an important part of the research consortium we joined a few months ago with Rockefeller University. We are saying this because he has repeatedly proven to have a genius to do this work that nobody else in the world so far can match.
A number of published studies, reporting on the use of HGH as an adjuvant to gonadotropins in stimulating ovaries, however, produced conflicting results. Some claimed improved results after ovarian stimulations, while others reported no benefits. As a consequence, utilization of HGH remained the purview of only a small number of fertility centers, mostly in Australia and the U.S.

CHR decided to start a HGH protocol after a careful review of published data, which concluded that the likely explanation for discrepancies in reported outcomes by colleagues was the way reported studies supplemented HGH. Because most published studies reported on supplementation only during ovarian stimulation or for short periods before stimulation started, we concluded that these studies “missed” the most important target population of follicles for HGH, the small growing follicles. In analogy to DHEA, CHR, therefore, decided to institute a radically different HGH protocol, which targeted small growing follicles, the stages of follicle growth and maturation where IGF-1 appears most active.

Like with DHEA, this, of course, meant pre-supplementation with HGH for at least 6-8 weeks before the IVF cycle starts. Because of the very significant costs of HGH, this protocol also imposed considerable additional costs for patients who chose to utilize HGH. To minimize those costs, CHR researched available products and their respective costs, and settled on a very reasonably priced product (in comparison to others in the market place) of excellent quality, offered by one pharmacy, which we now recommend to our patients.

**How CHR got interested in HGH**

As regular readers of these pages likely know, the aging ovary has been CHR’s main research focus over the last decade. Especially in the last five years, our interest has increasingly concentrated on the *early stages of follicle maturation*, weeks to months removed from when these very small growing follicles reach the so-called gonadotropin-sensitive stages and become responsive to standard fertility drugs.

Our interest in these very early stages of follicle maturation – immediately after follicles are recruited out of the resting stages in which they populate the ovary likely from birth (called *primordial follicles*) – stems from a number of DHEA-related observations we made over the years and reported in the medical literature:

i. At such early stages, it appears we can still affect the quality of eggs in follicles, while at much later stages of follicle maturation the damage has already taken its toll and, likely, no longer is reversible.

ii. We learned this from DHEA supplementation which, as we know from animal work, is effective at these early follicle stages but not later in the follicle maturation process.

iii. Animal data also suggest that androgens and IGF-1 at these early follicle stages, indeed, appear to have similar effects on growing follicles.

iv. Finally, we concluded from our DHEA work that the current dogma that eggs “age” while sitting at primitive stages in primordial follicles as women age, likely, is incorrect. Instead, our DHEA work suggested that it is the ovarian environment, in which follicles mature, that ages. And unlike eggs that have, hypothetically, already been damaged by advancing female age, ovarian environments can still be “repaired” by reconstituting them with, for example, androgens (DHEA).
In practical terms, these observations and conclusions suggested to us that DHEA represented only a first drug, capable of supplementing the ovarian environment in which follicles (and their eggs) mature. The evolving hypothesis was that one could expect many other drugs to follow, which would help in “rejuvenating” the ovarian environment to its “younger” microenvironment, which is better able to support normal follicle growth and maturation. HGH appeared to be the perfect second candidate!

**How CHR now offers HGH use**

Like with DHEA, unable to interest the pharmaceutical industry in supporting the center’s research with HGH, CHR decided to do it on its own, once again counting on some patients to voluntarily participate.

Earlier this year, CHR decided to offer selected patients supplementation with HGH in parallel to the center’s standard DHEA protocol. How CHR offers this protocol is, however, very important to understand. To qualify for HGH supplementation, patients have to:

i. suffer from severe LFOR;

ii. have failed standard treatment protocols at CHR, including DHEA supplementation;

iii. give written consent to HGH supplementation that states this treatment represents “off-label” use of this medication for a yet unapproved indication by the FDA and is “experimental” (i.e., its clinical efficacy has not been established);

iv. confirm that they understand risks associated with HGH use; and

v. confirm in writing that they are aware of medication costs and that insurance companies are unlikely to cover this expense.

**What we already know**

As is so often the case when these kinds of clinical investigations start, one of the first HGH patients at CHR, a young woman from Boston, conceived spontaneously while on DHEA and HGH, waiting to go into a first IVF cycle on the new protocol.

She had previously been advised by local centers in Boston that her only chance of pregnancy was via egg donation. She then transferred her care to CHR, where she was started on the center’s standard DHEA protocol for severe LFOR. In a first IVF cycle she produced 3 excellent embryos, but the number declined in a second cycle to only 1. Considering the decline in egg and embryo numbers, she at that point raised, herself, the option of adding HGH (and actually convinced her insurance company to cover the expense).

Because spontaneous pregnancies during the pretreatment phase in highly unfavorable patients, while waiting to go into IVF cycles, was also one of the first observations made when CHR initiated investigations into DHEA supplementation, CHR considers this experience encouraging. It, however, is anecdotal and, therefore, has to be considered with great caution.

The facts are that, as noted above, at this point nobody knows whether HGH, as supplemented by CHR’s new protocol in women with the most severe forms of LFOR, will improve outcomes. From everything we know from animal experiences, it will; but many beautiful hypotheses based on animal work have failed to be confirmed in clinical practice in humans.

**A clinical trial**

We, therefore, in the foreseeable future will reserve such treatment only for patients who have either completely failed to respond to ovarian stimulation while on DHEA supplementation or have demonstrated declining oocyte/embryo yields on such protocols.

Our Institutional Review Board (IRB) in its upcoming April meeting will be presented with a request for approval of a prospectively randomized open label crossover trial of HGH. In this trial patients with extremely low FOR will be randomized to either DHEA + HGH in IVF cycles or to only DHEA. Patients who do not conceive on only DHEA will then in the subsequent cycle be given DHEA + HGH and vice versa. Pending approval from the center’s IRB, we hope to initiate this trial no later than June of this year.

We, of course, will report on our experience with HGH in these pages, as new data are developed.

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CHR Guest Blogger

Sara from LAUGHING AT THE I-WORD

For the past few months, CHR guest blogger Sara has been sharing stories of her infertility journey, discussing everything from coming to terms with your infertility to providing and receiving emotional support to loved ones. Recently, she’s begun to tell the story of her first experience with IVF, from stimulation to retrieval. Sara’s story is one every infertility patient can relate to:

“The HCG shot was unlike any of the other injections I had administered so far. As one of the clinical coordinators told me, it was my turn to be Cinderella. No, I didn’t get all dressed up in a gown and sparkly tiara; but I did have to wait until about midnight (give or take 30 minutes) to receive the HCG shot.”

To read Sara’s full post about preparing for her first IVF retrieval and to see what else she’s written about her infertility journey, log on to centerforhumanreprod.com/blog.
A recent publication in the prestigious *Proceedings of the National Academy of Sciences, U.S.A.* – written by CHR collaborators and co-authored by CHR’s own Drs. Lee, Barad and Gleicher – also received considerable media attention in March (Sen et al. *Proc Natl Acad Sci USA* 2014;25:111:3008-3013).

This research conducted in the laboratory of Aritro Sen, PhD, and his mentor Stephen R. Hammes, MD, PhD, at Rochester University School of Medicine and Dentistry adds important additional information to our understanding of how androgens (male hormones) affect ovaries.

Dr. Sen, is, of course, well known to readers of these pages because he has for two years been a Visiting Assistant Scientist at CHR, closely collaborating with CHR investigators on a number of projects. He and Dr. Hammes also, a number of years ago, published the crucially important paper that demonstrated how essential male hormones are in the mouse for normal follicle growth and maturation. It was their work that gave CHR investigators the experimental underpinning for their DHEA work with infertile women.

In this newest paper from these investigators, they demonstrated that androgens in the mouse attenuate atresia (i.e., destruction) of follicles and defined the mechanism by which this is achieved. They, in addition, demonstrated that androgens, in contrast, augment FSH-mediated follicle growth and development and defined how a molecule, called paxillin, modulates both processes. Finally, they demonstrated, again in support of DHEA supplementation, how low dosages of exogenous androgens enhance gonadotropin-induced ovulation in mice. *ScienceDaily* reported extensively on this paper in an article posted on March 4, 2014, which was widely picked up by multiple newspapers.

**Dr. Gleicher talks “mini-IVF” and a CHR baby makes the Times!**

Dr. Gleicher discussed the real costs of low-intensity IVF in a recent *Wall Street Journal* article about the growing popularity of this alternative treatment. Citing CHR research, Dr. Gleicher explained that, while it may be marketed as a cheaper alternative to regular IVF, the lower success rate of so called “mini-IVF” may lead to more repeat cycles, ultimately matching or even exceeding the costs of tradition IVF. Dr. Gleicher told the *Journal* that low-intensity IVF “reduced pregnancy chances without demonstrating cost advantages.”

And we were thrilled to see a CHR family featured in the *New York Times*!

Former CHR patients Krystal and Claudia recently emailed our clinical coordinator, Maria, to let her know that “a CHR baby made the New York Times!” The couple was featured in an article on tax laws for same-sex couples, which included a video with their beautiful son, Malaya!

To read the full *Wall Street Journal* article on low-intensity IVF, visit: http://online.wsj.com/news/articles/SB100014240527023045554004579423553575221452

To read the full article and watch the video of this CHR family, visit: www.nytimes.com/2014/02/25/your-money/for-same-sex-marrieds-a-tax-season-to-look-back.html

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CHR in the Media

**Androgens research makes headlines**

CHR currently offers the following positions:

- **Medical Statistician**, Minimum MS degree, PhD preferred
- **Clinical IVF Coordinator**, RN or equivalent, prior fertility experience a plus
- **Post-Doc PhD Scientist**, Currently actively involved in molecular level research in genetics, reproductive physiology and/or immunology; Tissue culture and small animal IVF experience preferred
- **Medical Assistant**, Prior experience in private office setting, ability to multitask required

If you, or someone you know, would like to apply, contact Jolanta Tapper at jtapper@thechr.com

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A letter from a patient

Dear Dorota,

I want to thank you and all of the coordinators for always taking care of me at CHR. Your support & Dr. Barad’s guidance has helped me bring into this world a beautiful baby girl who was born on December 10, 2013. She was 6lbs 1oz 19 1/2 inches long. We couldn’t be more happy & we feel so complete. Be well & thank you for the great care at CHR.

Love,
LM

- The CHR
  “Fighting for every egg and embryo!”