Center for Human Reproduction
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CHR VOICE
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Three Important Outcome Predictors, Developed at CHR in One Year!

What is my chances, doctor? This is one of the most critical questions that our patients ask us.

During 2010, CHR investigators published three papers, addressing this very crucial question and defined three new markers of pregnancy success with In Vitro Fertilization (IVF). A first paper appeared earlier in the year: It demonstrated that **women who improved their anti-Müllerian hormone (AMH) levels (i.e., improved their ovarian reserve) after DHEA supplementation had much better pregnancy chances than those who did not** (*Reprod Biomed Online. 2010;21:360-5*). This, of course, is a very important clinical marker, which now allows us to counsel women on DHEA supplementation much better.

Two other papers appeared in peer-reviewed journals shortly after each other at the very end of the year, in December. In a first, CHR investigators further expanded on the AMH story by demonstrating that, **independent of age, an AMH level of 1.05 ng/mL differentiates between lower and higher live births chances** (*Fertil Steril 2010;94:2824-7*).

This paper is of importance because it is only one amongst very few in the literature that look at live births as end point, instead of clinical pregnancies. This, of course, means that this end point also considers miscarriage risks. Since miscarriage risk is greatly dependent on age and ovarian reserve, here developed information, once again, allows for much better patient counseling. **This, in turn, gives patients better information to choose between treatments, using their own or donor eggs.**

Last but not the least, the third paper that appeared in 2010 reported on a remarkable genetic marker for predicting pregnancy successes of IVF. In a paper published in the prestigious *PLoS One*, CHR investigators demonstrated that **different sub-types (genotypes) of the so-called *FMR1* gene (fragile X mental retardation gene) are statistically associated with distinctly different chances to conceive with IVF** (*PLoS ONE 5(12):e15303*).

Three specific genotypes were investigated: Amongst those, the so-called *normal* genotype was associated with highest pregnancy rates and the so-called *heterozygous-normal/low* genotype with almost 50% lower chances and, therefore, the lowest pregnancy rate. A third genotype, *heterozygous-normal/high*, produced an intermediate pregnancy chance.

The genotype associated with the lowest pregnancy chance was also statistically associated with a specific form of a common ovarian condition called **polycystic ovaries**, and with evidence of abnormal function of the immune system, reflected in **autoimmunity**.

The authors, therefore, concluded that adverse effects of the *heterozygous-normal/low FMR1* genotype on IVF pregnancy chances may be mediated by autoimmunity.

The effect of autoimmunity on female fertility has been one of the most contentious issues in reproductive medicine. These findings revive this issue. Indeed, they, likely, offer an intriguing hint that autoimmunity, after all, can negatively affect pregnancy chance with IVF, and probably spontaneous conception chances as well. The findings also strongly suggest that **with an *FMR1* sub-genotype of het-norm/low, not only pregnancy chances are reduced but this reduction may be autoimmune in etiology, likely related to problems with implantation, rather than inferior egg/embryo quality.**

In addition, **this is the first evidence ever reported in the medical literature that one specific gene appears directly associated with IVF outcomes**. Since the *FMR1* gene and autoimmune sites are closely associated on the long arm of the X chromosome, these findings make considerable sense, and, likely, will translate into clinical applications in the future.

In 2011, we are excited to follow up on these findings, because if correct, these results may suggest a larger impact of the endometrium and implantation process on pregnancy success rates in IVF than has been estimated in the past. Failure to conceive due to implantation problems has been believed to be a rare event, affecting less than 15% of IVF failures. Considering these findings, however, this issue obviously needs to be reassessed. And trust us, CHR is already hard at work!

Nobel Prize in Medicine for IVF

2010 was a memorable year for the whole IVF community: a Nobel Prize in Medicine was awarded to **Robert** (Bob, as those of us who personally know him call him) **G. Edwards, PhD**, the father of In Vitro Fertilization.

CHR's Founder and Medical Director, **Norbert Gleicher, MD**, had the privilege of knowing Bob since the early days of IVF. In 1980, when Dr. Gleicher became Editor-in-Chief of the first medical journal dedicated to IVF, Bob joined in as one of the first Associate Editors. Bob, of course, went on to bigger and better things, being among the founders of *ESHRE*, and the first Editor-in-Chief of *ESHRE*'s official medical journal, *Human Reproduction*.

When in January of 2009 Dr. Gleicher was given the extraordinary honor of presenting the *Patrick Steptoe Memorial Lecture* before the *British Fertility Society* in Edinburgh, he noted how unfair it was that Bob had not been yet named a Nobel laureate.

Though the decision came rather belatedly, we are absolutely delighted that the Nobel Committee, in the end, found the courage to do the right thing. There had been 4 million IVF births world-wide by the time the Committee made the decision. Which Nobel Prize winner before Bob Edwards could ever make such a claim?

This Nobel Award is Bob's and Bob's alone, but in many ways, it is also an award in recognition of the ingenuity of the IVF process in general, and of the many scientists and practitioners who have advanced IVF from a highly controversial and experimental procedure to a mainstay of modern infertility treatment, and far beyond.

IVF today is no longer only a fertility treatment, applied in thousands of fertility centers around the world. It is also a widely available diagnostic tool to prevent genetic diseases, and will, undoubtedly, become increasingly important in areas of therapeutics, as more and more stem cell therapies will be developed.

CHR's first IVF program, one among the first half dozen in the U.S., and the first in the Midwest, was founded by Dr. Gleicher in 1981 in Chicago's Mount Sinai Hospital. The program's first pregnancy was reported in 1982. After almost 30 years, at the time of writing, more than 17,300 babies have been born through our IVF program.

New International Affiliate

Dr. Andrea Weghofer, MD, PhD, MBA, who has been our research collaborator for a long time, now has her own fertility practice in Vienna, Austria. Even better, she has joined us as our affiliate, serving German-speaking patients of CHR. We look forward to a fruitful collaboration!

DHEA Update: DHEA Reduces Embryo Aneuploidy

In the years since CHR introduced **DHEA** supplementation for **diminished ovarian reserve (DOR)**, its use has spread to fertility centers all over the world. A recent worldwide survey of IVF centers concluded that approximately one-third have introduced DHEA supplementation into their treatment regimens for women with DOR.

Investigators at CHR now report to have elucidated at least one of the mechanisms by which DHEA exerts beneficial effects on egg and embryo quality, thereby improving pregnancy chances and reducing miscarriage rates after IVF. The mechanism involves improvement of chromosomal integrity of embryos.

It is well known that as women age, the risk of chromosomal abnormalities in pregnancies and offspring increases. Most chromosomal abnormalities in embryos result in miscarriages, usually early in the pregnancy. Collaborating in 2009 with colleagues from Toronto, Canada, investigators from CHR reported unexpectedly low spontaneous miscarriage rates in pregnancies conceived on DHEA supplementation (*Reproductive Biology and Endocrinology 2009, 7:108*). They suspected that such low miscarriage rates had to be the consequence of lower aneuploidy (chromosomal abnormalities), but proof was lacking.

In a recently published study (*Reproductive Biology and Endocrinology 2010, 8:140*), investigators from CHR now, for the first time, confirmed through preimplantation genetic screening (PGS) that DHEA reduces chromosomal abnormalities (aneuploidy) in embryos. The greatest reduction in aneuploidy, by approximately 22%, was observed with 4-12 weeks of DHEA supplementation prior to IVF.

This is the first direct evidence that **DHEA beneficially affects egg and embryo quality by reducing chromosomal abnormalities**. It appears likely, however, that this is not the only way by which DHEA exerts its positive effects on older ovaries. Indeed, DHEA may only be a forerunner for a whole new family of infertility drugs, which, ultimately, may allow older women to conceive through well-designed infertility treatments.

This finding may have implications far beyond infertility, too, because **it suggests that beneficial effects of DHEA supplementation on embryos' chromosomal health could also be extended to normally fertile older women**. If further study confirms this hypothesis, DHEA supplementation, like taking folic acid to prevent neural tube defects, may become a part of routine prenatal care.

Inadequate Endometrium Study Well Under Way

As many of our readers will recall, our work with DHEA started more or less by accident when an older patient with severe DOR started self-supplementing with DHEA without our knowledge, and remarkably increased her oocyte (egg) yields in subsequent IVF cycles. Something a little bit similar happened recently, in regards to **chronically thin endometrium**.

The thin endometrium has remained an unresolved clinical problem since the inception of IVF. It has been known for a very long time that best pregnancy rates are achieved when the endometrium reaches a thickness of 9 mm on ultrasound measurement, but that 7 mm really represents the minimum thickness for reasonable pregnancy chances.

There are, of course, other parameters that count as well: For example, how the endometrium looks also matters. Ideally, it should present not only with appropriate thickness but also nicely layered. Innumerable studies have been reported in the literature, and almost as many suggestions have been made on what can be done in case the endometrium does not meet expectations.

Here is the scenario as it presents itself over and over again in association with IVF: With the IVF (or frozen-thawed) cycle coming closer and closer to the day of embryo transfer, the endometrium remains inadequate.

What to do?

No IVF center has a foolproof protocol. We usually start by giving or increasing estrogen support; if that does not work, a vasodilator is added. At CHR, we utilize a beta-blocker called Atenolol or, believe it or not, Viagra. When nothing works, however, the choices become stark: either the whole cycle is cancelled or the eggs are retrieved, but the resultant embryos are not transferred into the uterus. That means an **all-freeze cycle**, where all embryos are cryopreserved, because **it would be a total waste to transfer good embryos into an inadequate endometrium**.

In mid 2010, an out-of-state Chinese patient presented at CHR with above outlined scenario. Circumstances were even worse: in addition to very thin endometrium, she also demonstrated a fluid accumulation in her endometrial cavity. Shortly before her scheduled egg retrieval, **Dr. Gleicher**, CHR's Founder and Medical Director, had to present the options of cycle cancellation or all-freeze. Cycle cancellation was not an option for her, who did not want to restart from the beginning after spending most of the IVF costs. Being from out of state, she was not interested in an all-freeze cycle, either.

Dr. Gleicher offered her aspiration of the fluid from the endometrial cavity but warned her that it would likely re-accumulate (even though there were no hydrosalpinges present) and also commented that even if no re-accumulation occurred, the endometrium still would be too thin for transfer of embryos. The patient inquired whether there wasn't anything "experimental" that may have a beneficial impact on her endometrium.

Following the successful removal of the thick, mucous fluid, Dr. Gleicher decided to treat the patient off label (with appropriate informed consent) with an FDA-approved drug with well known systemic effects, which he thought, theoretically, may have a chance to beneficially affect the endometrium. [Due to an impending publication, we are unfortunately not in a position to reveal further details].

Two days later, the patient demonstrated a perfect endometrium; she had egg retrieval, had a routine embryo transfer (after preimplantation genetic diagnosis, PGD) and is now pregnant with twins.

Based on this experience, **Dr. Barad**, the Clinical Director of CHR's IVF Program, treated another patient with extremely poor endometrium in identical fashions and she, too, conceived after embryo transfer, although, unfortunately, her pregnancy turned out to be intramural and had to be terminated. A third patient improved her endometrium significantly but did not conceive.

The CHR's physicians communicated this experience to a colleague at another center in NYC who asked permission to apply this new CHR protocol to one of his patients with poor endometrium, and, lo and behold, his patient, who had failed innumerable IVF cycles, reached embryo transfer with an improved endometrium and conceived.

With all four patients receiving this treatment reaching embryo transfer and three of them conceiving, this, indeed, in magnitude of potential treatment success, even exceeds the remarkable experience of our first DHEA patient.

This experience, of course, completely changed our plans for the 2010. Considering the potential magnitude of its implications, it became immediately clear that this new treatment required immediate testing by prospectively randomized trial. With Institutional Review Board (IRB) approval, we started two trials in September.

At the time of this writing, patients are being actively enrolled into the two trials, and very soon we expect to reach the point where we can perform a mid-point analysis.

Stay tuned! **This very much promises to become another clinical "hit," from CHR Research.**

29 YEARS LEADING INFERTILITY CARE

The Center for Human Reproduction
Editorial Office
1015 Madison Avenue #504
New York, NY 10075

We're on the Web!
www.CenterForHumanReprod.com

Contact the Editor:
Yu Kizawa • ykizawa@thechr.com



Letter from a Patient

Dear Dr. Gleicher and CHR Team:

Before we came to Doctor Gleicher's Center for Human Reproduction in New York City, we tried to do IVF cycles with different clinics and doctors, but everything unsuccessfully. When we came to Dr. Gleicher (recommended by one of our friends), we did not have much of a hope left.

I'm not very good at writing letters or essays, but all I can say now is that we have a beautiful son, after so many years.

Doctors and staff of the clinic did everything they could to help us to get through the cycle. Nurses were there when we needed it (even to ask stupid questions) day or night. Once we called at 3 AM and she called us back in about 5 minutes. All I can say - with Dr. Gleicher there is always a hope, and he will do much more then humanly possible to get your dream to reality.

Thank you very much, DOCTOR!!!!

-N.L. and D. G.

Grandrounds

CHR has, following its charter, for over 20 years been an independent provider of complimentary continuing medical education to the OB/GYN community. As such, CHR has become widely known for its popular Grandrounds Lecture Series. Grandrounds are presented in clinically relevant fashion by leading authorities for practicing clinical providers.

Grandrounds in spring 2011 will resume on **Tuesday, February 8**, with a lecture by **Avner Hershlag, MD**, Professor of Obstetrics and Gynecology and Reproductive Medicine at the *Hofstra North Shore LIJ School of Medicine*. Dr. Hershlag will discuss all aspects of **egg donation**.

Following Dr. Hershlag, on **Tuesday, March 8**, will be a lecture by **Uri Elkayam, MD**, Professor of Medicine and Obstetrics and Gynecology at the *University of Southern California in Los Angeles*. Dr. Elkayam will discuss **diagnosis and prognosis of cardiac disease in pregnancy**.

Practicing physicians and clinical providers, please register at *www.CenterForHumanReprod.com/newyork_events.php.*