



Center for Human Reproduction

Clinical Care - Research - Education

CHR VOICE

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Benefits and Perils of Infertility as a “Disease”

Earlier this year, two infertile Austrian couples won a decision in their favor in front of the *European Court of Human Rights*, which ruled that the country's ban on sperm and egg donation violated the right to respect family life, and that not allowing them the use of donor gametes (when others could use their own) was discriminatory.

As quoted in the May issue of *Focus on Reproduction*, **Luca Gianaroli, MD**, current *European Society of Human Reproduction and Embryology (ESHRE)* Chairman, feels it is too early to determine what this decision means for other European countries but believes that the ruling sets a precedent that restrictions on gamete donations are in violation of the *European Convention on Human Rights*.

This argument is similar to that of the *Human Rights Commission* in the State of Illinois, which, quite a number of years ago, based on a challenge by a CHR-Illinois patient, ruled that withholding infertility care, in contrast to other medical services which are offered, is discriminatory under the *Americans With Disability Act*. Under that ruling, State of Illinois was practically mandated to provide comprehensive infertility service coverages to all of its employees.

Infertility is increasingly defined as a “disease.” At a presentation in Rome, *ESHRE* for the first time presented a number of new definitions, which included infertility defined as a “disease,” rather than “diagnosis” or “condition.” The reason is clear: diseases fall under coverage by medical insurance; diagnoses and conditions may not!

The *ESHRE* representative, summarizing these new definitions, also noted that Europe does not have a legal framework like the *Americans With Disability Act*, which prohibits discrimination against basic life activities (including reproduction) and, therefore, had to resolve to define infertility as a disease.

Such a definition, however, of course raises quite a number of potential issues: Is infertility one disease or a compendium of many diseases? How can one consider male infertility within the same framework as, for example, tubal disease?

The biggest issue may, however, lie with the fact that diseases usually require treatments (unless, of course, known to be self-limited). In association with infertility (undoubtedly not a self-limited condition), presence of the “disease” does not necessarily indicate intent to conceive. Indeed, it is well known that a large percentage of infertile couples choose not to even pursue diagnosis. Amongst those that reach confirmatory diagnosis, many choose not to pursue treatments and amongst those who do, many voluntarily drop out of treatment for whatever reason.



Which percentage of truly infertile couples end up receiving fertility treatment is, therefore, rather poorly defined. Definition of infertility treatment needs is further complicated by the fact that, increasingly, single and gay women also seek out fertility treatments while widely recognized definitions of infertility require “regular exposure to semen” over a certain period.

Words and their definitions are of great importance! Whether infertility is a disease, for example, matters greatly when it comes to designating pharmaceutical agents as so-called “orphan drugs.” The *Food and Drug Administration (FDA)* has the power of such designation when the number of potential individuals affected by any given disease is below a certain cut off. The idea is that large pharma companies are not interested in developing drugs for small markets. Such “orphan drugs,” therefore, deserve the *FDA*'s help.

Probably no area in medicine would need such help as much as infertility. Yet, because infertility is seen by the *FDA* as a “disease,” and since approximately 7.4% of married couples are believed to have this “disease,” the *FDA* recently rejected an orphan drug application, which attempted to develop an innovative approach towards treatment of diminished ovarian reserve. The argument was that the infertility market was too large for an “orphan drug” designation, completely ignoring the fact that, in contrast to practically all serious diseases, only a small fraction of the patients of this “disease” ever seek out treatment.

Defining infertility as a “disease” is, therefore, not always beneficial to those who seek treatment!

Low-Intensity “Mini” IVF

Low-intensity EcoIVF in carefully selected patients can, indeed, be quite cost-effective. [...] However, the data is not applicable to patients with diminished ovarian reserve.

Regular readers of **VOICE** will know about CHR's relative lack of enthusiasm for so-called **low-intensity IVF**, also called “**mini**” IVF, **natural IVF**, etc. We have been offering such cycles at CHR under the name **EcoIVF**, emphasizing the primarily economic motives behind this type of IVF.

In contrast to many colleagues who have been utilizing these kinds of cycles for women of all ages and with all levels of ovarian reserve (OR), **we have restricted the use of EcoIVF only to women younger than 38 years, and require evidence of normal OR (normal FSH and AMH) before such a cycle is recommended.**

We now completed enough such EcoIVF cycles to compare outcomes with carefully matched controls who underwent regular IVF. Unsurprisingly, pregnancy rates differed to the disadvantage of EcoIVF. However, we were surprised by the cost-effectiveness analysis, which determined that **low-intensity EcoIVF in carefully selected patients can, indeed, be quite cost-effective.**

Our study was performed in young women with normal OR. Therefore, the data is not applicable to patients with diminished ovarian reserve (DOR). Logic, however, would suggest that it, likely, will be less effective in women with DOR, but a final answer will only come from a properly conducted study.

While the size of this study is small, these data are encouraging. However, we still believe that low-intensity IVF should NOT be offered indiscriminately, and should be offered only with appropriate consents, unless a properly conducted study confirms otherwise.

We caution against the utilization of low-intensity IVF cycles in women with DOR and strongly urge patients to familiarize themselves with published data on the subject before exposing themselves to such an “experimental” approach, whatever it is called.

New International Collaboration



CHR is pleased to announce that we are now in a collaborative affiliate agreement with Dr. Koji Aoki, a prominent Japanese expert in recurrent pregnancy loss (RPL). In the last three decades, Dr. Aoki treated more than 4,000 women with RPL. His Aoki Ladies Clinic is the first of its kind in Japan, focusing on RPL. Dr. Aoki will serve as CHR's Japanese representative in the treatment of RPL. For a complete list of our affiliates, please visit www.CenterForHumanReprod.com.



DHEA Update: Israeli Study Confirms CHR Finding with Small Randomized Trial

A study conducted by Adrian Shulman, MD, and coworkers of *Tel Aviv University* in Tel Aviv, Israel, confirmed our previously published research about the positive effects of the supplement **dehydroepiandrosterone (DHEA)** in improving fertility in women with diminished ovarian reserve. Dr. Shulman's study, which featured just 33 women, 17 on DHEA and 16 controls, confirmed that DHEA supplementation increases the likelihood of conception with in vitro fertilization (IVF) approximately threefold. This study, though relying on a small pool of study subjects, represents the first prospectively randomized study of DHEA in infertility.

Strangely, the July press release accompanying publication of the Israeli study left unmentioned CHR's almost 6-year trail of published studies in leading peer-reviewed medical journals, implying that the Israeli team acted upon rumors and instincts, instead of research already published in peer-reviewed journals. As readers of these pages are well aware, since 2004, we have published in medical literature a number of controlled studies of various designs demonstrating the benefits of DHEA in increasing fertility, which contributed to the increasing popularity of DHEA supplementation world-wide. CHR's prior studies are, indeed, fully referenced in the scientific paper by Shulman and associates published in *ALAYA*, the journal of *Israeli Fertility Association*, although it is mysteriously absent from the press release.

Over 2,000 women from all over the U.S. and the world so far received treatment with DHEA at CHR, because of diminished ovarian reserve due to either advanced female age or POA. This comparatively large experience contributes to CHR's world-wide reputation as a “**fertility center of last resort.**”

By successfully recruiting 33 women into a prospectively randomized study, of which 17 received DHEA, Dr. Shulman's group achieved a key research milestone that CHR, despite several attempts over six years, failed to realize - a feat that should be congratulated.

However, there is no end to medical research. To further refine our understanding of DHEA and fertility, **we are currently recruiting women with either POA or POF for two clinical trials to investigate the effects of DHEA supplementation on live birth rates.** Interested parties should check out www.infertilitytrials.com for details and application forms.

CHR Research Focuses on DHEA and *FMR1* Gene

We are pleased to report that the academic year 2009/10, in many ways, likely, will end up the most successful year in CHR's research history. With 2009 being a record year in number of published papers in peer reviewed journals (by last count 21), 2010 may not only match this number but, with considerable certainty, will exceed 2009 in importance.

Important breakthroughs have been made, especially in our understanding of ovarian aging, over the last few months: We no longer believe in the decades-old dogma that the eggs age as women age. Research at CHR suggests that eggs, in their most immature stages at which they are "stored" at, indeed, do not age. Independent of the female ages these eggs are recruited into **folliculogenesis**, they are, likely, just as "young" as they were when women were born with them. What appears to age, instead, is the ovarian environment in which follicles and eggs mature.

Because in **older women** (or women with **premature ovarian aging, POA**) this ovarian environment deteriorates, the follicle/egg maturation process takes place under subpar conditions, leading to more **chromosomal abnormalities (aneuploidy)**, among other possible negative effects on eggs. As a consequence, the resultant embryos also demonstrate more chromosomal abnormalities, leading to lower pregnancy chances, and more miscarriages.

We previously reported that **DHEA** (which declines with advancing age) is, likely, a first pharmacological agent able to "restore" the aged ovarian environment and, by doing so, reduces aneuploidy and miscarriage rates (*Gleicher et al., Reprod Biol Endocrinol 2009;7:108*). We deduced this from greatly reduced miscarriage rates after DHEA supplementation, but until recently, we lacked direct evidence for a reduction in aneuploidy.

We have now collected such convincing direct evidence. **We are now confident in stating that DHEA supplementation, indeed, appears to reduce embryo aneuploidy in women with diminished ovarian reserve.**

This significant observation suggests that by finding additional pharmacological agents which can positively affect the ovarian environment, we may be able to improve the follicle/egg maturation process even in very "old" ovaries. In practical terms, this then will translate into older

and older women, or young POA patients with "older" and "older" ovaries, still being able to conceive, possibly up to menopause at average age 51-52 years and/or quite high follicle stimulating hormone (FSH) and/or very low anti-Müllerian hormone (AMH).

As we previously reported in *VOICE*, **CHR has so far established over 30 clinical pregnancies in women with either completely undetectable AMH (< 0.1 ng/mL) or extremely low levels (≤ 0.4 ng/mL)**, while only one such woman who conceived has been reported in the scientific literature in the world. All of our pregnancies were, of course, established with **DHEA supplementation!** [See the last page for disclosure of possible conflict of interest.]

Clinical relevance of these findings may, however, go far beyond infertility: It is well known that aneuploidy increases with advancing female age, leading to increasing risks

of **chromosomally abnormal pregnancies** at older ages. This is the reason why **prenatal genetic diagnosis** is so often recommended to older mothers-to-be. If DHEA, indeed, reduces aneuploidy, the supplementation of women planning on pregnancy at older ages may reduce this risk. Like prenatal supplementation with **folic acid** to reduce risks for **neural tube defects**, **DHEA supplementation to reduce risks for chromosomal anomalies may become a routine component of prenatal care schedules.**

Another area of focus has been the way the ***FMR1* (fragile X) gene** appears to affect **ovarian reserve (OR)**. Particularly exciting is the definition of an **autoimmune-associated polycystic ovary (PCO) phenotype** in association with a specific *FMR1* genotype. An abstract that reports on this finding, as well as another on a related finding that *FMR1* genotypes significantly associate with **IVF pregnancy chances**, were accepted for presentation at the annual meeting of *ASRM*.

These data not only reaffirm the importance of CGG triple nucleotide repeat counts on the *FMR1* gene in infertility, but also now allow predicting IVF chances based on underlying genotype. But, probably most importantly, now that it is understood that IVF pregnancy expectations are different with different *FMR1* genotypes, we can get to work trying to find out how we can improve chances of those women with, a priori, lower chances.

Breaking News from CHR Research

An often intractable problem in infertility is the too-thin endometrium. Affected patients know how big of a problem this can become, when various remedies (increasing estradiol dosage, prescribing Viagra or other vasodilators) do not work, requiring cancellation of embryo transfers and cryopreservation of embryos.

CHR investigators now think they solved the problem for most affected patients by "washing" the endometrial cavity with a medication that is FDA-approved (for other indication).

As of this point, we are not yet at liberty to discuss further details, but in a small number of women with horrible endometria, this medication was remarkably effective, allowing embryo transfer in all. Further studies are underway. Stay tuned to another, very likely, treatment breakthrough from CHR-RESEARCH!



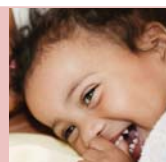
29 YEARS LEADING INFERTILITY CARE

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Letter from a Patient

"Letter from a "patient" is a misnomer this time around: the "patient" has not sought treatment at CHR because she spontaneously conceived at age 44 after self-supplementation with DHEA. Nonetheless, this exuberant mom-to-be wrote us to report on her DHEA experience.

Keep up the great work. I'm 44 years old and intended to see you before year's end. My first visit would have been in September. I've done enough research to like you guys. Years ago I thought that CHR had a gimmick, DHEA, to distinguish itself from other fertility clinics to attract patients. I found not enough info at the time to verify DHEA met up to CHR's claims.

In fact, one doctor posted that if anything, one should take pregnenolone so the body can determine which hormones it converts into. I got nervous and stopped taking DHEA which I'd taken for five weeks. I took pregnenolone for about 6 weeks and stopped as it seemed to make my cycle worse.

Anyway, on Feb 26 and March 25, 2010, CHR emailed me regarding spontaneous conception of a 46-year-old woman. Finally in early April, I reopened the bottle and started taking 50 mg DHEA per day. In early July 2010, I felt the cycle was excellent as the DHEA caused an abundance of cervical mucus. July 1, 2010 I conceived!

There's no doubt it is directly related to CHR's progressive insights. Because CHR, out of the fertility clinics within NYC, appeared to be the only one which promotes DHEA supplementation, it is the only one worth going to. Who knows, I still may be in to see you, though hopefully not. You and you alone in NYC are the best!!

–M. O. from New York City

Conflict Statement

Dr. Gleicher and Dr. Barad are listed as co-inventors on an already awarded and other pending patent applications which claim therapeutic benefits of DHEA in women with diminished ovarian reserve. Drs. Gleicher and Barad are also listed as co-inventors on a pending patent application, which claims diagnostic benefits from evaluating the *FMR1* gene in regards to ovarian reserve. Both doctors have received research support, speakers fees and travel funds from various pharmaceutical companies, none in any way related to the topics of this newsletter.