THE CHR VOICE
CLINICAL CARE · RESEARCH · EDUCATION
27 Years Leading in Infertility Care
Spring 2008

Unexpectedly high life birth rates in older women

Two related findings deserve special notice: In a first analysis, Dr. Barad of CHR, demonstrated that, in parallel with the introduction of DHEA supplementation into CHR's treatment protocols, the overall program's life birth rates in older women have steadily improved. In 2006, we for the first time used DHEA systematically in, still carefully selected women (resulting in only 43% of women receiving DHEA) and achieved a quite stunning clinical pregnancy rate of 23.5% per transfer. In double- and triple- checking our 2006 pregnancy data in preparation for the annual CDC submission, we noted that our pregnancy rate had been even higher than we previously had assumed and reported. Our true clinical pregnancy rate in women above age 40 was 26.4%. Our originally quoted data had been lower because our embryology staff had been unaware of a few, mostly out of town, pregnancies. Considering that these statistics included women up to age 47, they are nothing but remarkable. Since women of such advanced ages experience very high pregnancy loss rates, the question, however, remained, whether these exceedingly satisfactory pregnancy rates would also translate into equally exciting life birth rates.

We are now pleased to report that they do! Our life birth rate after IVF in women above age 40 was 20.8% per embryo transfer. In practical terms this means that only approximately 21.4% of women, who conceived ended their pregnancy with a miscarriage, less than half the number one would expect, considering the very advanced age of our patients. The average miscarriage rate in a normal, fertile population is approximately 15%. A clinical miscarriage rate of only 21.4% in our extremely adversely selected patient population has, therefore, to be considered extremely low and surprising.

This finding raises immediate additional questions, the first one being, why would older women, under treatment at CHR, have so much lower miscarriage rates than universally reported in the literature for women of this age? The answer is that we do not know for sure; it appears that slowly a picture is emerging that can explain these findings and makes perfect sense.

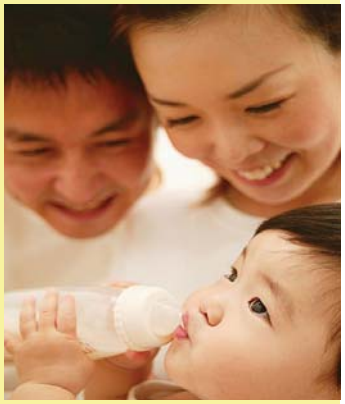
(for explanation, see below, "Does DHEA reduce aneuploidy?")

ANNOUNCEMENT

We are pleased to announce that fertility preservation pioneer KUTLUK OKTAY, MD, has joined CHR as of January 2008 in the position of Director of CHR's newly formed ***Fertility Preservation Instituute.*** Dr. Oktay's research interests in premature ovarian senescence due to chemo- and radiation therapies, and his widely recognized work in fertility preservation, including the first published ovarian transplant in the world literature, match very well with CHR's principal research activities on ovarian aging. Appointments with Dr. Oktay can be made by calling CHR at 212-994-4400.

Does DHEA reduce aneuploidy?

We previously reported that women after DHEA supplementation produce statistically significantly more chromosomally normal (*euploid*) embryos. We at that time, however, cautioned from reaching the conclusion that DHEA reduces chromosomal abnormalities (*aneuploidy*) and noted that our findings could be due to the fact that DHEA appears to increase egg and embryo numbers, which, of course, would also increase the number of euploid embryos.



At the same time we, however, also pointed out that DHEA, at least theoretically, also could have an affect on chromosomal abnormality rates (*ploidy*), since we believe that DHEA somehow affects the whole 4.5 months long follicular recruitment process and, therefore, also could affect ploidy.

As women age, the rate of aneuploidy in their embryos increases. As a consequence of more chromosomally abnormal embryos, their miscarriage rates go up with advancing age. This is exactly the reason why the expected number of miscarriages in our study group of women above age 40 (until age 47) would be expected around 45-50%. The fact that we see less than half the expected miscarriage rate strongly hints at a reduced aneuploidy rate in embryos of our patients. Together with our earlier data on more euploid embryos after DHEA treatment, all of this suggests that DHEA, indeed, may have a direct effect on ploidy and may reduce the risk for abnormal embryos. This then, of course, would also, at least partially, explain why we overall see so much better pregnancy rates with DHEA supplementation.

A **Desirable** *Fertility Outcome?*

Twins

"An infertile couple delivering a twin gestation has the immediate pleasure of two children."

Practically every fertility treatment increases the risk for multiple births. Depending on fertility treatment, multiples represent anywhere from approximately 5-35% of deliveries. The reason is quite simple: in 99% of natural cycles only one egg is released. The natural multiple prevalence is, therefore, only around one percent, with a large majority being twins.

Since fertility treatments turn single egg into multiple egg cycles, more than one egg is released, can get fertilized, and the consequence is then a multiple birth.

Increasingly successful infertility treatments have resulted in an epidemic of multiple births. Quite rightly, lay public and medical community have identified this as a major problem. Indeed, CHR's Medical Director, *Dr. Gleicher*, was in the vanguard of efforts to reduce multiple births, when he, in a study in the prestigious *New England Journal of Medicine* in the year 2000, found the risk for high order multiples (triplets or more) with intrauterine inseminations to be uncontrollable and suggested that patients be taken earlier into in vitro fertilization (IVF) *(Gleicher et al. N Engl J Med 2000;343:2-7).* Amongst all infertility treatments, IVF gives us the best control over an increased risk for multiples because we (that is patient and physician) decide how many embryos to transfer into the uterus. The more are transferred, the higher the multiple risk, though the age of the mother also plays a significant role.

As the utilization of IVF in infertility has increased over the last decade, so has our ability to control multiple risks. *CHR has always prided itself for achieving high clinical pregnancy rates, without exposing patients to risk for high order multiples.* Many patients bare witness to CHR's conservative embryo transfer policy, even if, at times, it has taken efforts and strong arguments to convince them of the wisdom of such an approach. *CHR's embryo transfer policy always was based on the acceptance of twins and the rejection of triplets or even higher order births.*

Everybody agrees that singletons represent the lowest risk pregnancy and that, with increasing order of pregnancy, the risk to babies and mothers increases. CHR always felt that the additional risk of twinning was minor enough to be more than made up by the benefits a twin pregnancy bestows on an infertile couple. Until recently, most of our colleagues agreed with us. More recently initially starting in Europe, but now also in the U.S., an increasing number of colleagues have started to argue that twins represent an unfavorable outcome of infertility treatment, to be practically avoided at all cost. *We strongly disagree!*

Our disagreement with many of our colleagues is based on hard statistical facts, and here is a short summary: The sudden antipathy towards twin delivery stems from the fact that perinatal (the offsprings') and maternal risks in a twin pregnancy are somewhat higher than in a singleton delivery. But so are the benefits, and this is usually forgotten!

Risk/benefit calculations form the basis for all decision making in medicine, since nothing in medicine is completely risk free. Patients and physicians, once risks and possible benefits of a medical intervention are known, then make a decision. What level of risk a person is willing to take to achieve a certain benefit, of course, varies between individuals. In other words, patients have an absolute right to take more or less risk, based on their own attitudes towards risk and how important a specific benefit may appear to them.

Physicians, who advise patients on risk/benefit, are more limited in what they may recommend. Since medical risks are numerically quantifiable, it is relatively easy to compare risks of alternative treatments, as long as benefits remain constant. A physician's advise is then bound by what such a comparison suggests because if outcomes are the same, good medical care requires that the procedure with lower risk be chosen.

In applying all of this to twinning after infertility care, opponents of twin pregnancies have correctly argued that twin pregnancies carry higher perinatal and maternal risks than singletons. What they, however, have forgotten is that the benefits from both are not the same. A singleton pregnancy results in the birth of only one child, while an infertile couple delivering a twin gestation has the immediate pleasure of two children.

In a mathematical sense this means that historical outcomes between singletons and twins can, and really should not be compared. If it is done anyhow, then the mathematics has to be corrected. Since the woman with a singleton delivery will have to undergo another, second pregnancy and singleton delivery to achieve the same outcome as the twin delivery achieved, the risks of a singleton delivery have to be multiplied by two before they can be compared. When this is done, – surprise – surprise -, twin deliveries no longer carry excessive risks for infants or mothers.

Dr. Gleicher presented this argument for the first time in November 2007 at the World Congress for IVF in Montreal, Canada. A more detailed presentation and mathematical analysis of published data was submitted for publication. The obvious conclusion is: *Twins are a very desirable outcome for most infertile couples undergoing fertility treatments.* The profession has apparently begun to listen because Dr. Gleicher recently received two requests for review articles on the subject from European specialty journals.

CHR to begin new prospectively randomized study in 2008

Now that our European colleagues have run into the same recruitment problems in attempting to randomize older women to DHEA and placebo, as we experienced here in New York City, we have to find another way to test DHEA in a prospectively randomized study. Since prospectively randomized studies are considered the gold standard, DHEA will not find universal acceptance until such a study has been performed, and confirms the utility of DHEA supplementation.

We are pleased to report that our IRB recently approved such a study. Starting in early 2008, we will prospectively randomize *younger women (below age 38)* to DHEA and placebo if they (i) were diagnosed with so-called *unexplained infertility* (as you will recall, a diagnosis we do not really believe in here at CHR); (ii) were proven to have *open fallopian tubes*; and (iii) have a male partner with *normal semen*. Such qualified women will then undergo cost-free ovarian function testing at CHR. If their FSH or AMH levels are abnormal, suggesting that they may suffer from **premature ovarian aging (POA)**, we will offer them, once again free of charge, randomization to DHEA and placebo for up to 8 months. Since they will have no other obvious causes of infertility, there will be no further intervention and we will simply follow their spontaneous pregnancy rates, while either on DHEA or placebo.

The study will be formally registered in early January and advertisements, to recruit patients, will start running shortly thereafter. ***If you feel that you may qualify for this study, and are interested in participating, please call 212-994-4400 and tell our staff that you are calling for the "BELOW 38 DHEA STUDY."***

Abnormal autoimmune function and female infertility

More weight given to the link between the two

Our *FMR1* work demonstrates that POA has two principal causes: (i) a *genetic form*, characterized by increased triple CGG numbers (though often still within a generally considered normal range); and (ii) an *autoimmune form*, characterized by abnormal autoimmune laboratory tests, but usually normal triple CGG repeat numbers (below 31). A small number of women may have a combination of both abnormalities.

Both forms also differ in clinical presentation, with the genetic form of POA usually demonstrating much higher FSH, and lower AMH levels, which means that the genetic form seems to be associated with more severe ovarian dysfunction.

These findings have major potential significance: First, they demonstrate that ***abnormal autoimmune function, on its own, is associated with POA, and, therefore, female infertility.*** Since POA is frequently missed and/or misdiagnosed, it should not surprise that abnormal autoimmune function is so frequently found in women with infertility. The medical literature on the unusual prevalence of abnormal autoimmune function in infertile women has become extensive, though this association was first pointed out by *CHR's Medical Director, Dr. Gleicher*, almost 20 years ago *(Gleicher et al., Am J Obstet Gynecol 1989;160:1376-80)*. ***Abnormal autoimmune function, as a cause of female infertility, therefore, needs to be taken much more seriously by the profession than it currently is.***

Maybe this genotypical and phenotypical separation of POA into two distinct sub-types will allow us to develop specific treatments for either type of POA, which will improve our ability to successfully treat affected patients. Studies are underway at CHR to determine whether treatment responses differ between these two patient groups.

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27 YEARS LEADING INFERTILITY CARE

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We're on the Web!

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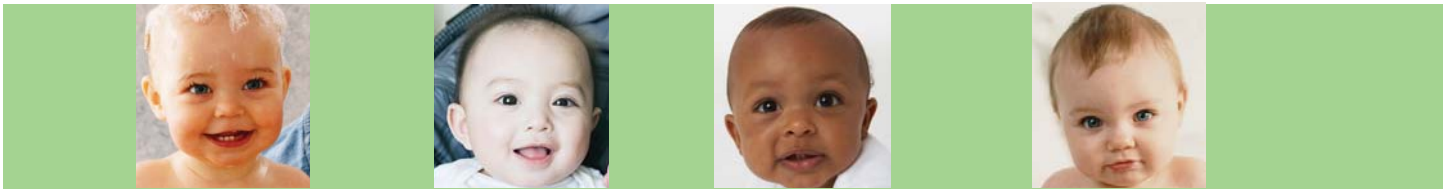

Some photos from Japan

International Ovarian Conference, November 2-3 2007, Hakone, Japan

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(1) Norbert Gleicher, MD, Medical Director, CHR.

(2) Prof. Bunpei Ishizuka, Chairman, International Ovarian Conference 2007, Hakone, Japan (left) and Norbert Gleicher, MD, Medical Director, CHR

(3) Prof. Hefeng Huang, MD, Associate Dean and Professor of Ob/Gyn, Zhejiang University School of Medicine, Hangzhou, China (left) and Norbert Gleicher, MD, Medical Director, CHR (right) at the Faculty Dinner.

If you'd like to share your experiences or success stories, please contact us by phone, fax or e-mail at:

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