



Summer 2006

THE CHR VOICE

CLINICAL CARE • RESEARCH • EDUCATION

25 Years Leading in Infertility Care

ALL THE CHR-NEWS FIT TO PRINT

A FLOOD OF NEW PUBLICATIONS

A record number of our scientific papers have been accepted for publication in leading medical journals and will be appearing in print over the next six months approximately. One of the papers (**Gleicher N, Barad D. The relative myth of elective single embryo transfer; Human Reproduction**) has already been posted electronically on the journal's website and can be seen there. Because of prepublication confidentiality rules, we are not permitted to disclose further details beyond the fact

that the topics covered in these manuscripts include *unexplained infertility, ovarian aging, in vitro fertilization (IVF) outcomes in the United States and Europe, polycystic ovarian disease (PCO), IVF in general, preimplantation genetic diagnosis (PGD) and, of course, dehydroepiandrosterone (DHEA)*. Quite a number of additional manuscripts are either already submitted for publication or in preparation for submission. We, therefore, expect a record number of CHR manuscripts in print during 2006.

OUR TEACHING PROGRAM

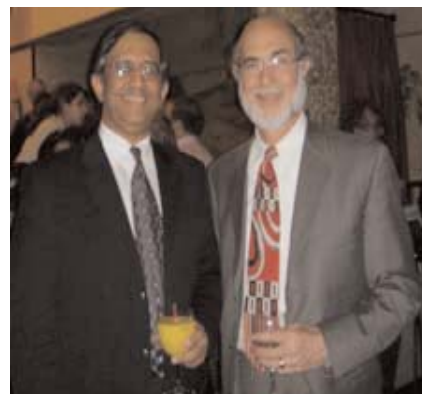
One of the reasons for this increase in our scientific productivity was our teaching program. CHR serves as a training base for residents and fellows from a number of teaching hospitals. Most of them rotate through CHR for brief elective, clinical periods of 4-6 weeks. Some choose a longer, intermittent rotation, which usually entails a year-long research affiliation and allows them to complete research projects and publications. Over the last year, we had two excellent physicians working with us.

Andrea Weghofer, M.D., Ph.D., from Vienna, Austria, spent considerable time at CHR during the last academic year as part of her research fellowship at the Department of Ob/Gyn at Yale University. **Hayama Brill, M.D.**, a senior Ob/Gyn resident at Lennox Hill Hospital in New York City, did the same as a step in preparing for a clinical fellowship in reproductive endocrinology and infertility. Both are now co-authors of a number of CHR publications.

CHR's 2006 GRANDROUNDS

Our monthly *Grandrounds* for the Ob/Gyn Community, started the New Year with a bang, when our first event of the year, in February at *Blaue Ganz*, Kurt Gutenbrunner's outstanding new restaurant in TriBeCa, was so oversubscribed that many members of the audience had to consume the restaurant's culinary delights standing up at the bar. The following Grandrounds was our *Annual Residents and Fellows Day*, starring Hayama Brill, M.D. and Andrea Weghofer, M.D., PhD. In April, Salim Daya, M.D. from Canada (*pictured below*), spoke to an over-booked audience at Tuscan Square Restaurant and Marketplace. In May our speaker, Mark D. Hornstein, M.D., of Harvard Medical School, presented on the topic "Trends in IVF Outcomes in the United States." The last CHR

Dr. Salim Daya (on the left) and Dr. David Barad, Medical and Research Director of MRI.



Grandrounds of the year will be held on June 6, 2006 at *Le Charlot* Restaurant with Professor Roy Homburg from Tel Aviv University, Israel, and VU University, Amsterdam, The Netherlands, as the speaker.

Guests, including Mrs. Dr. David Barad (second from left) at April Grandrounds held at Tuscan Square Restaurant and Marketplace.



AN UPDATE ON DHEA

Our DHEA experience is increasing and the more we know, the more convinced we have become of the benefits of DHEA supplementation in women with aged ovaries. What is even more rewarding, is the fact that colleagues around the world seem to have started using DHEA in accordance with our protocols. There almost doesn't pass a day when we are not contacted by e-mail by either patients, or their physician, for advice. Most rewarding are, of course, the many reports of success, which we worldwide are made privy to. Thank you for letting us know!

We, however, do *not* rely on such anecdotal evidence and, therefore, continue our very active research efforts in this area. Because it is practically impossible to conduct a prospectively, placebo controlled, randomized study on women with aging ovaries, we seek out other study designs, which allow us to judge the effectiveness of

DHEA. We previously reported the fact that in paired IVF cycles, comparing in the same patients, IVF outcomes pre- and post-DHEA supplementation, we confirmed that DHEA increases egg and embryo numbers, improves egg and embryo quality and improves pregnancy rates. This study is currently under revisions at a leading medical journal in our specialty and we expect its final acceptance for publication in the very near future.

We also previously reported on the remarkable cumulative pregnancy rates from DHEA supplementation, since many pregnancies occur *spontaneously* while women wait (on DHEA) to go into an IVF cycle. Because we now know that the efficacy of DHEA peaks only after at least four months use, we try to keep women for some time on DHEA *before* we take them into an IVF cycle. These data, too, are reported in above noted manuscript under revision.

What we, however, have not reported here before are the results of a

recent case control study. In this new study, we matched women with proven *diminished ovarian reserve*, who prior to the advent of DHEA treatment, were treated at CHR with otherwise identical IVF protocols, with women who, over the last two years, received pre-treatment with DHEA and, then, if not pregnant spontaneously, went into IVF cycles. In comparing over 80 DHEA patients with over 90 controls, we found that women, pretreated with DHEA, even though, based on ovarian function tests, showing much more compromised ovarian function, still conceived significantly quicker and at significantly higher rates. This was true for all age groups, including women over age 42 years.

In other words, *this study, once more, demonstrated the beneficial effects of DHEA on pregnancy chances!* We are currently in the process of writing the paper, describing this study. (*Much of this research at CHR was conducted by Hayama Brill, M.D.*)

Premature Ovarian Aging

The previously described study contained a considerable number of POA patients. We, therefore, are by now quite convinced that DHEA is highly effective in women with POA.

In a prior UPDATE we briefly mentioned a recent study in which we, somewhat (though not completely) to our surprise, found out that women with POA do *NOT*

show an increase in chromosomal abnormalities in their embryos, as one might have suspected in women with "older" ovaries. Indeed, their *aneuploidy* rate was absolutely identical to that of age matched controls and potentially explained a number of contradictory findings which have been confusing the relevant literature:

● On the one hand, everybody agrees that

women with POA have greatly decreased pregnancy chances and, therefore, can be found disproportionately in infertility programs.

● Yet, on the other hand, it has been widely reported that baseline ovarian function tests, and especially FSH levels, if abnormally high, had less negative predictive value in younger women than in older ones.

FROM THE CHR MAILBOX

"Dear Dr. Gleicher and Dr. Barad:

Tanner entered the world a little early (2 months) with much fanfare! He was born May 5, 2005. It was a very rocky pregnancy and at the end of a three week stay in the hospital, he was delivered via emergency c-section. At 4 pounds, 16 inches he was tiny but perfect. There were no complications other than



severe jaundice, but as you

5-year-old Tristan & 1-year-old Tanner

can see he overcame that. He is now 8 and a half months old and still tiny (16 pounds) but healthy and very happy. His older brother adores him and that makes life easier for us all. We call the boys "Gleicher babies," and we are very proud of it. Enclosed is also the picture of our first success-Tristan. He is now 5 years old. We wish you continued success with each patient that knocks on your door. They are little miracles and we are very lucky people.

-Deneen Zirotsky"
Pawling, New York

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Premature Ovarian Aging...

continued from page 2

● Somewhat expected, therefore, younger women, if stimulated based on their "ovarian age", rather than based on their birth day, will have surprisingly excellent pregnancy rates. In two studies conducted at CHR, we achieved clinical pregnancy rates of 32% and 43%, respectively, once we stimulated POA patients with a microdose agonist protocol, rather than with long agonist or an antagonist protocol. **Such rates are, of course outstanding, and approach those of women with normal ovarian reserve.**

Therefore, nobody should be talked into egg donation, just because FSH is mildly elevated!

This does not, however, appear to be the end of the story: When, in the above noted PGD study, we followed pregnancy outcomes, we noted a rather unexpected finding. Even though the data did not reach full statistical significance, women with POA, who conceive, may demonstrate an increased risk to miscarry. Maybe even more unusual, the risk for miscarriages appears especially high after a fetal heart has been detected; i.e. rather late in pregnancy.

These are potentially very important findings because they may hint at an underlying cause for the occurrence of POA. And here is why:

● Most pregnancy loss (approximately 85%) is genetic in nature. We, however, know from above described PGD study that POA patients do **not** show an increase in genetic/chro-

mosomal abnormalities. *Therefore, it appears unlikely that the observed likely increase in pregnancy loss in POA patients is genetic in nature.*

● The earlier pregnancy loss occurs, the more likely it is genetic in nature. The later pregnancy loss is seen, the more likely it is medical in nature (i.e. immunological, diabetes-caused, etc.). The increase in pregnancy loss, observed here, was primarily after fetal heart tones had been detected; i.e., **late**. This observation strongly suggests that **POA may be associated with a medical cause for pregnancy loss.**

● The most frequent medical cause for pregnancy loss is *abnormal (auto) immune function*. We have previously associated POA with adrenal enzyme defects and are currently in the midst of a study investigating the association of POA with such adrenal defects. Most *acquired* adrenal enzyme defects (in contrast to those from birth) are believed to be *(auto) immune* in nature. *Premature Ovarian Failure (POF)*, the end stage of POA, has been for decades associated with abnormal (auto) immune function towards ovary and thyroid gland. In summary, there appears to be increasing evidence that POA may be **an (auto) immune disease**. *(Much of this research at CHR was conducted by Andrea Weghofer, M.D., Ph.D.)*

Our findings are still very preliminary and larger case numbers may fail to confirm these preliminary

results. However, if we will be able to confirm an *(auto) immune etiology* for POA, we may be able to develop better methods for early

diagnosis of POA and treatments to stop, or, at least slow down the process leading to premature ovarian exhaustion.

THE MENOPAUSE RESEARCH INSTITUTE (MRI)

On April 3, 2006, CHR formally expanded its *MENOPAUSE* practice. Because menopause therapy used to be rather standardized, it traditionally occupied the realm of the general gynecologist. In recent years, especially as a consequence of the many studies conducted by the *Women's Health Initiative*, the treatment of menopause has, however, become much more complex and controversial. Consequently, with increasing frequency, patients and our colleagues in general gynecology, have been turning towards reproductive endocrinologists for subspecialty advice.

In order to create a more formal framework for our menopause practice, we, therefore, decided to establish the **Menopause Research Institute (MRI)** as a fully independent division of CHR. *Dr. David Barad* will be serving as MRI's Medical and Research Director. As one of the *Women Health Initiative's* principal investigators (you can find his name on quite a number of their published studies), he has demonstrated a long-standing interest in menopause research and is eminently qualified to head up our new effort clinically as well as in its investigational aspects.

For more detailed information on the rather unprecedented set up *MRI* will be offering, please visit *MRI's* new website www.menopausereserchinstitute.com, or email us at MRI@menopausemd.com or call us at 212-434 7055. The *Institute* will be housed at our CHR facility at 21 East 69th Street, in Manhattan.



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25 YEARS LEADING IN INFERTILITY CARE

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