Center for Human Reproduction
Clinical Care - Research - Education
CHR VOICE
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CHR Achieves Superior IVF Pregnancy Rates for 2009

We are very pleased to report our Center's 2009 IVF outcome data. They, once again, were excellent, especially in view of the demographic changes that have been taking place at our Center over the last few years (for details, see ***CHR Voice***, Fall 2009).

In discussing IVF pregnancy rates in the pages of the ***Voice***, we have always made the point that these outcomes, are always influenced by how the patient population is selected: The more difficult the patient population is to treat, the lower will expected pregnancy rates be. The only IVF outcome that is hardly ever subject to patient selection is that of egg donation cycles, because egg donors, almost uniformly, are young and selected for normal ovarian function. We, therefore, consider IVF pregnancy rates in egg donation cycles to be the most reliable and most comparable IVF outcome between IVF centers.

Considering this fact, we are especially proud to report that, following many years of clinical pregnancy rates over 60%, **we in 2009 established a new outcome record of 66.7% clinical pregnancy rate from transfer of no more than 2 embryos**.

Considering that practically almost all egg donor cycles result in more than two embryos, this means that most patients end up with additional cryopreserved embryos, which, of course, represent additional pregnancy chances. So-called **cumulative pregnancy chances** include chances from these frozen embryos. Depending on the number of frozen embryos, patients, therefore, experience rates from the high 80's to the low 90's in egg donation cycles. **We would argue that such pregnancy chances are, likely, in the very top of world-wide rates.** These have been there now for over five years, - and are getting even better!

Below listed tables summarize clinical pregnancy rates in the various IVF categories. Live Birth Rates are, of course, not yet available and will be reported via CDC/ASRM-SART reporting in early 2011 (CDC just published 2008 data).

Below noted clinical pregnancy rates should, however, also be considered in view of CHR's unusually low miscarriage rates, which, like our unusually good pregnancy rates in women with poor prognosis, we attribute to DHEA supplementation (for more detail, see below). We strongly encourage you to read the foot notes, which explain relevant issues.

[1] Fresh IVF Cycles[1]

Patient Age (years)	Clinical Pregnancy Rate (%)[2]
<30	42.9
30-35	39.5
36-37	24.0
38-39	21.2
40	14.3
41	24.1
42	13.0
43	11.1
>44 (up to 49+)	3.8

[1]Here presented IVF pregnancy numbers would be considered excellent in any IVF program. What makes them, however, remarkable, almost astonishing, is the patient population in which they were achieved. CHR does not serve the traditional patient population of most IVF centers. As we reported in detail in the Fall 2009 ***CHR Voice***, the center's patient population has not only dramatically aged since 2006 (from mean ca. 36.0 to 39.5 years), but concomitantly our patients' ovarian reserve (OR) has dramatically deteriorated, most extremely in women ages 31-35 years, where mean AMH levels plunged between 2008 and 2009 from almost 6.0 to almost 2.0 ng/mL.

In practical terms, this means that our Center's youngest patients, up to age 35 years, are not the "usual" young patients with normal OR but to a great degree suffer from diminished ovarian reserve (DOR). Indeed, a large majority of these younger patients suffer from premature ovarian aging (POA) and come to our center after having failed IVF cycles elsewhere and, not infrequently, being advised to go into egg donation. Considering this very adversely selected patient population, the here reported combined pregnancy rate of 40.0% in women up to, and including, age 35 years is nothing but astounding!

The same considerations, of course, also apply to our patients above age 35 years, where OR parameters since 2006 have deteriorated to similar degrees, especially above age 40. Once

again, we do not deal with average 40 and 41 year olds (average pregnancy rate for these two years 20.9%) or average 42 and 43 year olds (average pregnancy rate for these two years 12.2%). Most of these older women do not only suffer from advanced age but, on top of it, also have been prematurely aging their ovaries and, therefore, demonstrate even less OR than they should, based on their already advanced age. Indeed, in this age group, almost two-thirds reach us for first consultation after having been told that they no longer have a reasonable chance with use of their own eggs and their only remaining option is egg donation. The here reported clinical pregnancy rates in these patients speak for themselves!

The most interesting group may, however, actually be here reported patients above age 44 (up to almost 50 years) because these are patients who are refused treatment at practically all other IVF programs. Not surprisingly, their pregnancy rates are low (3.8%), but considering the age of these women and their OR status, quite miraculous. A pregnancy chance that low is, of course, not offered lightly. Patients with such low pregnancy chances receive very detailed informed consent before entering treatment. Very often this involves women who just "want to try once" with use of their own eggs before proceeding to egg donation. In our opinion, they deserve this chance to know that they "at least tried," and 3.8% will win the lottery in addition.

[2]Per retrieval.

[2] Donor-Recipient (Egg Donation) Cycles

Clinical Pregnancy Rate	66.7%

As already noted in the introduction above, with two-thirds of patients achieving clinical pregnancy after fresh transfer of maximum of two embryos, this pregnancy rate is the best objective evidence for the superior quality of CHR's embryology laboratory and overall IVF performance.

[3] Eco-IVF Cycles[1]

Clinical Pregnancy Rate	14.5%

[1]Eco-IVF cycles use, as the name indicates, low-intensity, low-dose medication, and therefore are low-cost. The rate is per embryo transfer.

[4] Frozen-Thawed Cycles (FETs)

Clinical Pregnancy Rate	16.1%

Considering the high percentage of patients with DOR, CHR does comparatively few FETs. Moreover, embryo quality of cryopreserved embryos is often not the best, given the Center's challenging patient population.

These exceptional numbers, of course, once again raise the question: why does CHR succeed where so many others don't? The answer to such a question is never simple: We believe that our remarkable outcomes are not attributable to simply one factor. As is usually the case, they represent the current status of a long journey, which started approximately seven years ago, when CHR recognized that DOR represented something like the "last frontier" in infertility, and a conscious decision was made to develop expertise in this area by concentrating clinical research as well as clinical care on this problem.

Like surgeons who get better when they do more surgeries, CHR got better in dealing with DOR, whether physiologic due to a woman's age, or premature due to POA. A big step forward was made with the discovery of DHEA as adjuvant treatment in women with DOR, for which CHR was awarded a U.S. patent in 2009.

DHEA is now used world-wide and, likely, thousands of children are amongst us as a consequence of the original recognition that DHEA improves egg and embryo quality and pregnancy chances in DOR patients. It, however, now appears that DHEA may have the additional benefits of reducing aneuploidy (chromosomal abnormalities) and miscarriages, which adds a significant additional dimension to its clinical use.

Indeed, as we outlined in December 2009 ***UPDATE*** and fall 2009 ***CHR Voice***, we now believe that DHEA may represent only a first amongst, hopefully, many more medications, which have the ability to revert the ovarian environment, in which eggs mature, towards younger age. By doing so, the quality of the egg maturation process is improved, less aneuploidy occurs, ultimately leading to more pregnancies and fewer miscarriages, since both of these end points, of course, depend on euploid (normal) chromosome complements.

If we are correct in our assumptions, then exciting times appear ahead of us because then we can anticipate the development of a whole new family of fertility-enhancing drugs, which will allow women, especially older women with DOR, to conceive, thus expanding their reproductive life span.

It would, however, be a mistake to attribute all of above noted IVF outcomes only to our discovery of DHEA. First of all, DHEA alone offers only marginal improvement in fertility chances. Where DHEA becomes a highly effective adjuvant is within a comprehensive infertility approach, including IVF. Within such a context it is very easy to negate positive DHEA effects by stimulating ovaries incorrectly during the IVF cycle or by taking otherwise inappropriate treatment steps.

As noted earlier, here reported outcomes for 2009 are the current stage of a long journey, where physicians, coordinators and embryologists fight for every egg, every embryo and, of course, every pregnancy. It is the little steps, one by one, which in the end add up to constantly improving outcomes. This is an ongoing process, which cannot be stopped even for a single moment. Though we do not yet have enough data for 2010, our 2009 results demonstrate that we have been doing well!

Possible Previously Unreported Form of PCOS?

Readers of the ***Voice*** may recall that, last year, we for the first time suspected that our work with the ***FMR1*** **gene** might allow us to define an *FMR1*-associated form of **polycystic ovarian syndrome (PCOS)**. This work has made significant progress since. Not only did we confirm that there is such a PCOS form but we also learned much about the likely pathophysiology behind the condition. While prepublication restrictions from medical journals do not allow us to reveal too many details, here are some principal points:

We, indeed, confirmed that the number of CGG triple nucleotides on the *FMR1* gene defines, under certain circumstances, a very specific ovarian presentation, characterized by PCOS-like features at young age [i.e. very large number of follicles and very high anti-Müllerian hormone (AMH)]. Likely because of this particular *FMR1* pattern, these young women rather quickly deplete their **ovarian reserve (OR)** and, therefore, from an ovarian PCOS pattern, convert to a **premature ovarian aging (POA)** pattern (with few follicles and low AMH).

That, by itself, is already a very exciting finding because this genetic association now allows us to predict this very peculiar ovarian aging pattern in young women.

Much more exciting is, however, a very surprising finding. Readers of these pages will be aware of the fact that **autoimmunity**, usually considered separate from *FMR1*-induced POA, is the second principal cause of POA. To our surprise, we now found an extremely strong statistical association between above described *FMR1*-associated PCOS pattern and autoimmunity. While association should never be taken for causation, this association was so strong that the likelihood that this *FMR1*-associated PCOS pattern is autoimmune-mediated is considerable.

CHR's Medical Director, **Dr. Gleicher**, and his co-investigators already speculated about the likelihood of an autoimmune-induced form of PCOS (*Gleicher et al., Autoimmune Rev 2007; 7:42-45*) a number of years ago, but failed to confirm their hypothesis in various later attempts. Now, rather unsuspected, they have stumbled on confirmatory evidence that such an autoimmune-induced form of PCOS, likely, indeed, exists.

These new findings at CHR correlate well with previously published reports by other investigators about stimulatory autoantibodies that can affect endocrine organs, and also correlate well with reports of increased risk towards autoimmunity in association with certain X-chromosome defects, close to the *FMR1* site. Perhaps most importantly, however, these data may help explain why so many women with infertility show autoimmune abnormalities and, possibly, even why women have approximately seven times the prevalence of autoimmune diseases than men.

Clinically, these findings may also have considerable significance because they may point the way towards new diagnostic and treatment approaches for selected forms of PCOS. Just as medical diagnosis and clinical practice differentiate between thyroid autoimmunity and thyroid function or adrenal autoimmunity and adrenal function, we now may have to start differentiating between ovarian autoimmunity and ovarian function.

A first clinical application of above described research findings has already been identified: Women with the *FMR1*-associated PCOS pattern do very poorly in IVF managed conventionally, but respond very well to supplementation with **dehydroepiandrosterone (DHEA)**. Who would have guessed this, since PCOS is usually considered a high androgen condition? Exciting times seem ahead for understanding and treatment of ovarian pathophysiology!

All of this work, of course, fits well into CHR's continuous obsession with **diminished ovarian reserve (DOR)**, and reflects on how investigators at CHR, step by step, learn more about what can in different patients lead to DOR. It is then just a short step from the laboratory to clinical application; and finding new treatments for our patients is, of course, the ultimate purpose of all research at CHR.

Planned Collaboration with University of Toronto

CHR has recently completed a collaboration agreement with investigators at the *University of Toronto*, Toronto, Canada, funded by the **Foundation for Reproductive Medicine (FRM)**, under which the Toronto investigators will use a mouse model, well established in their laboratory, to investigate the effects of **DHEA** on aging ovaries. This project is expected to yield results within approximately one year and, hopefully, will foster information on how DHEA affects older ovaries. Stay tuned for the outcome of this exciting research collaboration!

29 YEARS LEADING INFERTILITY CARE

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Letter from a Patient

Hello Phyllis,

We wanted to send this note, even though it is very early on in our pregnancy, to you and Dr. Gleicher. We really believe that the DHEA prescribed by Dr. Gleicher was the cause of our spontaneous pregnancy!

We are taking this good news a day at a time and understand that miscarriage is still possible. Nonetheless, we are thrilled to know that we naturally got pregnant, especially after all the doctors we saw told us it would be impossible to get pregnant naturally, or even with IVF. We were constantly counseled to consider egg donation due to my diagnosis of POS at age 35.

As your website indicates, your center is considered a "last resort" for cases like mine. We strongly believe that the DHEA improved my egg quality. A year ago, we had undergone an IVF cycle where 2 eggs were removed, but no fertilization occurred. We then tried various other fertility treatments that included different hormone shots, but only 1-2 eggs would be produced so we didn't remove them. Instead, we did HCG shots to time a possible conception, but still no results.

I have been off birth control for exactly 2 years and this is the first time I have gotten a positive pregnancy result. This is amazing. I am glad I checked out your website and the news story on CBS. Again, many thanks for your research care, info and hope!

– J & G

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.