



The Truth Revealed

DOES PREIMPLANTATION GENETIC SCREENING (PGS) IMPROVE IVF OUTCOMES?

A huge controversy has now been brewing in our specialty for quite some time: Quietly, many in vitro fertilization (IVF) centers world-wide introduced over the last few years the use of genetic testing of embryos in attempts to improve pregnancy rates with IVF (primarily in Europe, given the acronym *preimplantation genetic screening*, PGS, to be differentiated from *preimplantation genetic diagnosis*, PGD, for the detection of genetic abnormalities in embryos).

The basic concept behind PGS appears attractive: Since many normal looking embryos are chromosomally abnormal, many transferred embryos will be chromosomally abnormal. Since such chromosomally abnormal embryos less likely implant, and if they implant, more likely miscarry, elimination of chromosomally abnormal embryos prior to transfer should improve pregnancy rates and diminish miscarriage rates.

Based on this hypothetical model, PGS was widely propagated as a successful tool to improve IVF outcomes. In the enthusiasm of introducing PGS, warning voices, including that of CHR's Medical Director, Norbert Gleicher, MD, were, however, widely ignored. What was ignored were clear warning signs that above outlined hypothetical model apparently did

not work, as predicted, in practice. Early studies were unable to show pregnancy benefits from PGS. More importantly, the model overlooked a highly important outcome predictor: the effect of embryo biopsy on the chance of the embryo to implant (i.e., to lead to pregnancy).



Common wisdom in the PGD/PGS community was that biopsying embryos did not affect their implantation chances. Should this opinion, however, be incorrect, then in order for PGS to improve IVF outcomes, it would first have to compensate for the decline in pregnancy chance due to the embryo biopsy and, only secondly, then achieve further outcome advantages for IVF. In other words, if embryo bi-

Continued on page 2...

Ovarian Function and Triple Repeats on the *FMR1* Gene

A New Correlation?

There still is quite a number of "holy grails" to be discovered in reproductive medicine; but it appears that investigators at CHR just have reduced the number by at least one, and here are some of the details: Approximately 10% of women are believed to age their ovaries prematurely. As CHR investigators recently reported (*Barad et al., Obstet Gynecol 2007; 109;1404-10*), amongst infertility patients in treatment the prevalence is even much higher and risk for premature ovarian aging (POA) among CHR patients approaches, especially at younger ages, 50 percent.

Many POA patients go for years undiagnosed and/or have, falsely, a diagnosis of so-called unexplained infertility attached. As Drs. Barad and colleagues in above quoted

study in the medical journal *Obstetrics & Gynecology* reported, the diagnosis of POA can be significantly improved if, in place of universal cut-off levels, age-specific follicle stimulating (FSH) values are used to assess ovarian function. However, even with age-specific FSH levels, an accurate assessment of ovarian function is still difficult. Moreover, the "holy grail"

"What young woman would not want to know whether or not she can expect a normal reproductive lifespan?"

of ovarian function assessment is not in the assessment of already infertile women; - it lies in the prediction of *future* infertility!

Which young woman, at ages 18 or 20, would not want to know whether she can expect a normal reproductive lifespan, or whether, as one amongst the approximately 10 percent of women with

premature ovarian senescence, she has to be concerned about early declines in ovarian function and, possibly, premature ovarian failure (POF), also called premature menopause?

Knowing that one is at risk is, potentially, a life-changing event. It allows for closer than usual monitoring of ovarian function, if needed adjustments in pregnancy timing plans, or even fertility preserving steps, such as egg freezing. *Unfortunately, however, nobody so far could predict, who may be at risk for POA and/or POF!*

As Dr. Gleicher recently reported at the Austrian Fertility Society Meeting in Innsbruck, Austria, recent research at CHR suggests that, at least for some women, the prediction of risk for POA (and POF) can, indeed, be made at young ages because their risk is linked to a gene, representing only

Continued on page 3...

Continued from page 1 "Does Preimplantation..."

opsy, indeed, reduced implantation chances, then the above outlined "simple" rational for PGS would have to be considered seriously flawed and PGS, under such circumstances, could, if at all, mathematically be expected to improve IVF outcomes only in carefully selected patients.

Arguing that, considering basic embryology experience, it was illogical to assume that embryo biopsy would not negatively affect embryos, Dr. Gleicher has voiced this point with colleagues now for over two

years. Indeed, based on his calculations, *CHR* changed the information in its informed consents accordingly, stressing that embryo biopsy can be expected to negatively affect the pregnancy chances per embryo. Consequently, even though, in contrast to most other IVF centers, *CHR* performs PGS in house, *CHR* physicians never recommended PGS to improve IVF outcomes. Indeed, much more often than

not, we recommended against PGS when patients came to us, often after having received PGS recommendations elsewhere.

Now a Dutch study, recently published in the prestigious *New England Journal of Medicine* (Mastenbroek et al. 2007; 357:9-17), reported the obvious to the surprise of many, - though not at *CHR*: Not only did PGS not improve IVF outcomes; it, indeed, reduced pregnancy chances in the patients studied!



Ob.Gyn. News reported in their August

1, 2007 edition how outraged some "experts" were about the poor quality of the Dutch study. What these experts, however, failed to note is that they (and others) recommended, and applied, PGS in clinical situations, where, aside of flawed theoretical considerations, no scientific evidence supported their practice.

This is not the first time, and certainly not the last time, that well meaning

CHR NEWS

Unprecedented number of accepted abstracts at annual ASRM Meeting!

Before going on summer break, we announced that we had submitted an unprecedented number of abstracts to this year's ASRM meeting, but we did not know how many amongst those would be accepted. In July we were notified that all, but 2, of our submissions had been accepted. This means that 9 CHR abstracts were featured at this year's ASRM meeting during October in Washington, DC. This is truly an unprecedented number and, probably, unmatched by even most of the largest academic medical centers in the country.

physicians apply medical technology in the belief of maximizing outcomes, only to discover later that this was not the case. When data in support of a hypothetical concept is lacking, it behooves physicians to consider their clinical approach as "experimental," and to present it as such to the public.

CHR is proud of having presented PGS as an experimental approach to our patients, and of having advised our patients (and everybody else who was willing to listen) about its use accordingly.

CHR Publications

The summer also saw an unusually large numbers of CHR papers published. Reprints are available if you contact us at editorial@thechr.com. Here is a brief summary:

1. Weghofer et al. Aneuploidy rates in embryos from women with prematurely declining ovarian function: a pilot study. *Fertil Steril* 2007;88:90-4
2. Weghofer et al. Lack of association between polycystic ovary syndrome and embryonic aneuploidy. *Fertil Steril* 2007 doi:10.1016/j.fertnstert.2006.12.018
3. Gleicher et al. Female infertility due to abnormal autoimmunity: frequently overlooked and greatly underappreciated. Part I. *Expert Rev Obstet Gynecol* 2007;2:453-64
4. Gleicher et al. Female infertility due to abnormal autoimmunity: frequently overlooked and greatly underappreciated. Part II. *Expert Rev Obstet Gynecol* 2007;2:465-75
5. Gleicher N and Barad D. Mild versus standard in vitro fertilization techniques. *Lancet* 2007;369:1855
6. Gleicher N. Postpartum depression, an autoimmune disease? *Autoimmune Rev* 2007;6:572-6
7. Gleicher et al. Functional autoantibodies, a new paradigm in autoimmunity? *Autoimmune Rev* 2007; doi:10.1016/j.autrev.2007.06.001
8. Gleicher et al. Differences in ovarian function parameters between Chinese and Caucasian oocyte donors: do they offer an explanation for lower IVF pregnancy rates in Chinese women? *Hum Reprod* 2007; doi:10.1093/HumReprod/dem289
9. Gleicher N and Barad D. The choice of gender: is elective gender selection, indeed, sexist? *Hum Reprod* 2007; doi:10.1093/humreprod/dem227



Continued from page 1 "A New Correlation?"...

a minute portion of the X-chromosome, - the so-called *fragile-X gene (FMRI)*. This gene has been known as a trouble maker for quite some time because it, in some women, has the tendency to expand. What this means is that under normal circumstances this gene contains up to 45 so-called triple CGG repeats. In some cases, however, these triple repeats expand and can exceed 200. At over 200, a so-called *full mutation* exists and, especially males, will demonstrate significant medical problems, in the medical literature described as the *fragile X syndrome*. This syndrome is the most common genetic cause of mental retardation and autism in males. While rarely affecting females, women with this genetic abnormality still, in approximately 70% of cases, demonstrate borderline, or below that, IQ levels and, even with normal range IQ, affected women still often demonstrate executive function deficits. The most typical presentation of fragile X in women is, however, POF.

Even at lower CGG repeat numbers, in the so-called *premutation zone* (defined by 55-200 CGG triple repeats), significant medical abnormalities may occur. While these, again, are seen primarily only in males (the so-called fragile X tremor/ataxia syndrome, FXTAS), they, in contrast to the classic presentation of the fragile X syndrome with full mutations, occur later in life. Women only rarely develop FXTAS but, once again, at premutation triple repeat ranges (and even lower repeat numbers, the so-called *intermediate*, or *gray-zone*, range of 45-55 repeats), a significant increased risk of POF has been reported.

The association of these abnormally high numbers of CGG triple repeats with POF has recently lead to recommendations by various professional organizations that women with a medical, or family history, compatible with abnormalities in the FMRI gene, or with evidence of premature ovarian aging (POA), as evidenced by elevated FSH levels or resistance to ovarian stimulation with fertility drugs, be tested.

CHR, of course, has a considerable volume of POA patients. Once a testing policy for *FMRI* was implemented, data started accumulating quickly. Since POA has for a number of years been a major research interest, CHR investigators, under the leadership of CHR's Medical

Director, Norbert Gleicher, MD, quickly asked a very basic question: if premature ovarian senescence is statistically associated with high CGG triple repeat numbers (primarily in premutation and full mutation ranges), *maybe ovarian function, in general, relates statistically to the number of triple repeats on the FMRI gene?*

When this question was investigated, low and behold, ovarian function, defined by FSH and anti-Mullerian hor-



mone (AMH) levels, indeed, statistically correlated in a highly significant way with the number of CGG repeats on a woman's X chromosome.

Indeed, the study suggested that *the risk for POA starts at, what currently by everybody is considered an entirely normal triple repeat range-above 30 repeats.*

This is, however, not where the study ended: aside from the statistical association with abnormal expansions on the *FMRI gene*, POF is also known to be increased in association with abnormal *automimmune function*. (For those interested in detail on this subject, we strongly recommend Parts I and II of a recent review by CHR staff; *Gleicher et al., Expert Rev Obstet Gynecol 2007; 2:453-464 and 465-475*). The second obvious question that now arose, therefore, was: *since both, expanded triple repeats on the FMRI gene, and abnormal autoimmune function, can lead to POF, are these two*

etiologies linked?

To answer this question, women with known fragile X status, were now separated into two groups, those with, and without, autoimmune abnormalities. CHR investigators then compared triple repeat numbers in these two groups of patients. The results were, once again, dramatic: by separating infertile women based on autoimmune history, two distinctively different groups of infertile women were defined. On the one side were women with autoimmune abnormalities, who usually had normal triple CGG repeats, lower FSH and higher AMH levels, while on the other side were women with abnormally high triple repeats, higher FSH and lower AMH levels.

In other words, the study clearly demonstrated that the *FMRI gene and abnormal autoimmune function, independently, can lead to POA/POF. CHR investigators, thus, have for the first time defined two distinct predictors of POA/POF. Moreover, preliminary prevalence calculations would suggest that, combined, these two etiologies are the cause of a majority of POA/POF cases.*

By testing the number of triple CGG repeats in a young woman and testing for abnormal autoimmune function (unfortunately not as exact a science as the former test), we can now determine whether she is at increased risk for POA. If these screening tests suggest an increased risk, a female can be placed on a closer monitoring schedule. Should her risk convert into factual evidence of POA, such as prematurely rising FSH levels and/or decreasing AMH levels, she can either choose to complete her family early or, alternatively, take fertility preserving steps, such as egg freezing.

The potential importance of these findings goes, however, beyond the obviously greatly improved potential for accurate diagnosis. The close statistical association between ovarian function a CGG triple repeat numbers, strongly suggests that the gene product of the *FMRI gene*, the so-called *fragile X mental retardation protein*, may be involved in ovarian aging processes. If confirmed, this, of course, would open dramatic avenues, not only in regards to improved diagnosis of ovarian function, but also for the treatment of aging ovaries, whether premature or not.

The Center for Human Reproduction

650 W. Lake Street
Suite 200
Chicago, IL 60661

26 YEARS LEADING INFERTILITY CARE

Editors: Tom Weidner- tweidner@thechr.com
Alexis Scarpinato- ascarpinato@thechr.com

We're on the Web!

CenterForHumanReprod.com

PATIENT TESTIMONIAL

Dear CHR,

Dr. Gleicher and CHR helped my husband and I conceive twins with PGD about 3 1/2 years ago. I just wanted to send a note and tell you how grateful we are for the work you and the rest of the clinic and lab are doing. Allison and Rachel are very happy, healthy, bright, beautiful two-year olds and we could not imagine our lives without them.

Earlier this year my husband was diagnosed with Huntington's Disease. While his diagnosis is a very difficult thing for our family, I can not put into words how grateful I am that I do not have to worry about my daughters having this devastating disease. I also know that as my husband faces his own illness he does not have to suffer with the guilt of passing it onto his children. And what a blessing for them to not have to grow up in fear.

I sat in a support group meeting on Monday and listened to a woman say that she just started to notice symptoms in her nine-year old son. It made me think how very lucky I am and how grateful I am for your work.

-Kelly

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

Tel. 312-876-1506
Fax 312-876-1804
ascarpinato@thechr.com

