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 worldwide 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-

**Ovarian Function and Triple Repeats on the FMR1 Gene**

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” 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...
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.

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 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:


CHR NEWS
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Continued from page 1 “A New Correlation?”...

a minute portion of the X-chromosome, - the so-called fragile-X gene (FMR1). 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 mildly high numbers of CGG triple repeats.

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Indeed, the study clearly demonstrated that the FMR1 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 FMR1 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.
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