



Center for Human Reproduction

Clinical Care - Research - Education

CHR VOICE

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More Older Mothers: Is the World Ready?

Despite more than enough economic and policy issues that would warrant front-page coverage, maternal age, suddenly, appears to have become *the* topic of the moment.

Recently we commented on a very personal account by Holly Finn in *The Wall Street Journal* (July 23, 2011), which portrayed her ultimately unsuccessful attempt at motherhood at older age (www.centerforhumanreprod.com/fertility_crisis_wsj.html). A recent story on single embryo transfer in the popular online magazine *Slate* (August 15, 2011) also quickly expanded into maternal age.

Now, *New York Magazine's* cover of its October 3, 2011 issue features a nude, pregnant woman of a grandmotherly age in the well known Demi Moore pose, accompanied by the question "Is She Just Too Old for This?" (See below.)

Why this sudden interest?

It is no coincidence that *New York Magazine* features this story. New York City, with its concentration of career-orientated women, is the quintessential starting point for this seemingly sudden societal development, which in reality has been quietly growing for over a decade.

Already in a publication in 2007 (*Gleicher et al. Too old for IVF: are we discriminating against older women? J Assist Reprod Genet 2007; 24:639-644*) researchers at CHR pointed out the impending developments, resulting in significantly older women conceiving and delivering, often for the first time: Based on the National Vital Statistics, since before 2003, women between ages 40 to 45 represent the most rapidly growing age group in the U.S. going through pregnancy. The trend has only accelerated since.

By 2004, 4,709 fresh in vitro fertilization (IVF) cycles, 5% of all U.S. cycles, were performed for women over 42. By 2008, 14,162 cycles (9.6%) occurred in women at 41 and 42, 8,893 (6.0%) in women at ages 43-44, and 6,981 (4.7%) in women above age 44. In four years, the proportion of women above age 42, thus, had more than doubled!

By 2008, less than half of all IVF cycles performed in the US (57,508, 38.8%) involved women under 35 and only 60% occurred in women under 38. When IVF was introduced into clinical practice in the early 80s, age 38 was, for all practical purposes, the upper age limit for the procedure!

The developed world, therefore, is in the midst of a reproductive biological revolution, whose consequences so far have not been registered, understood, discussed or investigated by sociologists and/or the medical profession.

It then should not surprise that Lisa Miller, in her otherwise well balanced and well written story in *New York Magazine*, missed the main point: The question is no longer "is she (a hypothetical woman) just too old for this," as the *Magazine* asked. This question has been already answered by thousands of women, with a decisive NO! The real questions to be asked are much more complex. They all relate to the multitude of societal consequences arising from so many older women (and some older men) becoming parents.

Evolutionary consequences

Extension of the female's reproductive lifespan has been a topic of primary interest for almost a decade for CHR. Over the years, CHR has developed a worldwide reputation as a leading fertility center in the world when it comes to "older" ovaries. Our patient population has significantly aged in parallel, with the average age of newly presenting patients now at around 40 years (*Gleicher and Barad. Dehydroepiandrosterone (DHEA) supplementation in diminished ovarian reserve (DOR). Reprod Biol Endocrinol 2011;9:67*). Women in their mid-40s and above now represent a large minority of the center's patients.



Interestingly, CHR researchers have recently identified evidence that evolutionary genetic processes have been working for thousands of year on expanding female reproductive lifespan via genetic mutation of the *FMR1* gene. By defining the so-called ovarian genotypes and sub-genotypes of *FMR1*, CHR investigators demonstrated how, over time, new genotypes and sub-genotypes evolved, and expanded the length of time women are able to conceive, likely by

influencing the speed of follicle recruitment and ovarian follicle depletion.

In this sense, extension of female reproductive lifespan must be viewed as an evolutionary process, carrying significant societal consequences at each stage of extension. Our rapidly developing medical abilities mean that more and more women, who had absolutely no chance of pregnancy only a few decades ago, will have children and dramatic societal changes will take place.

Medical consequences

Extension of female reproductive age will also have major significance for health care, especially in pregnancy management. As older and older women conceive, medical complications of pregnancy are increasing, since pregnancy is a “stress test” for the whole body and all of its systems. This is why CHR’s Founder and Medical Director, **Dr. Gleicher**, who edited *Medical Therapy in Pregnancy* and co-edited (with Uri Elkayam, MD) *Cardiac Problems in Pregnancy*, now a classic, always described pregnancy as a “window into a woman’s medical future.”

Because of increasing perinatal and neonatal risks with advancing maternal age, many medical colleagues often outright object to all pregnancies in older women. What they fail to understand, however, is that they no longer have a choice. The boat set sails a while ago, left the harbor and is on the way towards new lands.

Women will have children at progressively older ages, and medical providers better get ready to offer the required levels of medical expertise. Our responsibility as physician is to correctly inform patients about potential risks. It is not up to us to tell them how to live their lives! The last thing a childless older woman needs is an excessively opinionated health care provider, who makes her feel even guiltier about not having attempted childbirth at younger age. As physicians, it is not our function to “punish” patients for what we consider “incorrect” decisions. Just as we do not withhold care from smokers who suffer from lung cancer or from obese diabetics, it would appear unethical to withhold care from older women, who desire pregnancy.

Therefore, once again not surprisingly, egg donation represents proportionately the most rapidly growing form of IVF. Most recently published national statistics shows that donor egg cycles in 2008 already represented 12.3% of all IVF cycles. This percentage can be expected to grow since egg donation further extends a woman’s reproductive lifespan beyond her natural abilities with use of her own eggs.

Perinatology, neonatology and medical sub-specialties, in general, therefore, better get ready to take care of pregnancies in increasingly older women. In The Netherlands, a university department recently established a first cardiology section within a perinatal unit to specifically address increasingly frequent cardio-vascular problems

in pregnancy. At this point, it may not be exaggerated to expect an evolution of “geriatric” perinatologists in the near future, with special expertise in managing older mothers through their pregnancies.

Societal consequences

So far, the trend towards childbirth at older ages is seen primarily in the developed world, which also has the lowest birth rates. Most of Europe as well as Japan persistently demonstrate birth rates below what is required for population replacement. Even the U.S., which used to comfortably exceed replacement rates, is now just barely reaching them. Since it is practically impossible to grow economies without expanding populations, governments should really welcome the fact that increasing numbers of women are having children in later life.

As more women give birth at older ages, the societal fabric has to change in their support. Ways to achieve that goal, to accommodate the needs of older mothers and encourage them in their pursuits of forming new family units (often as single mothers), urgently need to be studied.

To answer *New York Magazine’s* question “whether there is anything wrong with being pregnant at age 53,” is, therefore, a loud and clear NO (as long as the mother is mentally, physically and socially in appropriate shape, of course). What is clearly wrong is how unprepared society, academia, government and the medical profession are in serving older mothers.

Staff News

Norbert Gleicher, MD, CHR’s Medical Director, had a busy summer with multiple speaker engagements. In addition to presentations at *ESHRE’s* annual meeting in Stockholm in July, in September, Dr. Gleicher was an invited speaker for the biannual meeting of the *Dutch Fertility Society*, a small group of specialists consisting of directors of IVF centers and laboratories in The Netherlands. He presented CHR’s view, now familiar to most readers of the **VOICE**, that twin pregnancies are, for many couples, not only an acceptable but also a desirable outcome of infertility treatments.

David H Barad, MD, MS, CHR’s Director of Clinical ART, was invited to serve as Editor for the new medical journal *Journal of Fertilization In Vitro*.

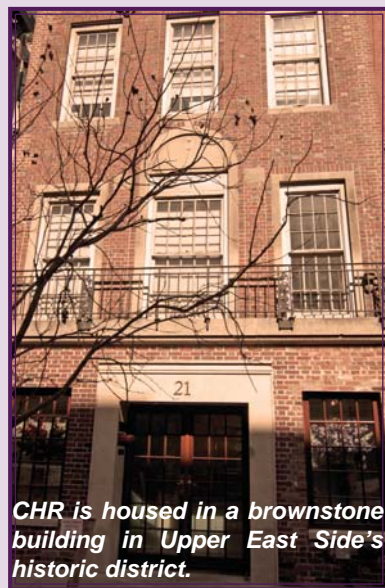


Ping Xia, MD, PhD, HCLD (pictured on left), joined CHR to oversee our embryology laboratory. Having spent six years in the Department of Obstetric and Gynecology at University of California at Davis as Associate Professor and Director of Assisted Reproductive Technology Laboratory before joining CHR, Dr. Xia brings extensive research and clinical experience to CHR.

CHR Celebrates the 10th Anniversary at Current Location

September 2011 was a special month for CHR. Although our history goes back further, the official opening of CHR's current location at 21 East 69th Street was on September 10th, 2001. We celebrated the 10th anniversary with a special GrandRounds event on September 13. CHR's Founder and Medical Director, **Norbert Gleicher, MD**, gave an overview of research accomplishments over the past ten years. CHR's research effort has been mainly translational—the type of clinical research that quickly translates into innovations in clinical care.

Because of time limitations, Dr. Gleicher concentrated on just three areas: (i) the center's work in women with **diminished ovarian reserve (DOR)**, utilizing **dehydroepiandrosterone (DHEA)** supplementation; (ii) the rapidly expanding importance of the **FMR1 gene** and of its **ovarian genotypes and sub-genotypes**, first described and published by CHR investigators; and (iii) the use of **granulocyte-colony stimulating factor (G-CSF)** to improve endometrial thickness. Dr. Gleicher's slide presentation is available at www.centerforhumanreprod.com/grandrounds_presentations.html.



The center's work with DHEA has been ground breaking, and is now clinically benefitting patients worldwide. CHR's discoveries of ovarian *FMR1* genotypes and sub-genotypes and of their specific functions promise to be no less clinically relevant to female infertility, with potential to affect other important areas of medicine. Wait for some astonishing new data, currently being prepared for publication!

Finally, probably no other CHR publication before received as immediate a response from colleagues and patients all over the world as the center's recent CSF publication in *Fertility & Sterility* (Gleicher et al. *Successful treatment of unresponsive thin endometrium. Fertil Steril* 2011;95(6):2123.e13-7.) on women with thin endometrium. Hardly a day passes without somebody contacting us with requests for more technical information or for appointments for consultation with a CHR physician. It is truly remarkable how this publication was immediately embraced, and we are especially pleased by a good number of anecdotal success stories many colleagues have e-mailed to us.

CHR is still in the midst of two clinical trials of CSF. We are, indeed, pleased to report that an interim analysis of

our first randomized CSF trial, which investigates whether CSF improves pregnancy rates in association with in vitro fertilization (IVF), found no inferiority and/or adverse side effects, and concluded that the study should continue. Over 100 patients have enrolled, placing us roughly at a halfway point. Enrollment into our 2nd randomized study, where we assess effects of CSF on chronically thin endometrium that is resistant to traditional treatments is slower, since such cases are rare.

Though Dr. Gleicher did not have the time to point them out, CHR has made numerous other achievements in these 10 years. For example, CHR investigators greatly contributed to the understanding of how **autoimmunity** and reproductive success interact. Many of these publications appeared in respected specialty journals outside of the field of reproductive endocrinology and infertility, especially in rheumatology/autoimmunity (Gleicher et al. *Cutting edge assessment of the impact of autoimmunity on female reproductive success. J Autoimmun* 2011; epub ahead of print.) and dermatology (Gleicher and Barad. *Gestational dermatosis shortly after implantation associated with parental class II HLA compatibility and maternal immune activation: preliminary report of a prospective case series. Dermatology* 2011;222(3):206-11).

Probably most remarkable, however, is the reach of the center's *FMR1* work, which spans a multitude of medical specialties. This is well reflected in publication of two recent CHR papers in the increasingly prestigious general medical journal *PLoS ONE* (Gleicher et al. *Association of FMR1 genotypes with in vitro fertilization (IVF) outcomes based on ethnicity/race. PLoS One* 2011;6(4):e18781 and Gleicher et al. *FMR1 genotype with autoimmunity-associated polycystic ovary-like phenotype and decreased pregnancy chance. PLoS One* 2010; 5(12):e15303).

Dr. Gleicher's interest in reproductive immunology led to a number of interesting publications, which point out the similarities between classical, and yet not understood, complications of pregnancy (i.e., **repeated pregnancy loss**, **preeclampsia/eclampsia** [Gleicher N. *Why much of the pathophysiology of preeclampsia-eclampsia must be of an autoimmune nature. Am J Obstet Gynecol* 2007;196(1):5.e1-7] and **peripartum cardiomyopathy** [Gleicher and Elkayam. *Peripartum cardiomyopathy, an autoimmune manifestation of allograft rejection? Autoimmun Rev* 2009;8(5):384-7.] and such complications of organ and tissue transplants as **graft-versus-host disease (GVHD)** as well as **allograft rejection**. In an invited review in the immunology literature, he demonstrated that practically all autoimmune diseases are characterized by increased risk for **premature labor** (Gleicher. *Does the immune system induce labor? Lessons from preterm deliveries in women with autoimmune diseases. Clin Rev Allergy Immunol* 2010;39(3):194-206.), a previously unknown association.



30 YEARS LEADING INFERTILITY CARE

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DHEA Update

A letter from Australia details a POF patient's experience with DHEA.

We started trying to conceive in 2008, when I was 31. Our first IVF cycle at our Australian IVF center went well, and I now have a beautiful 14-month old son.

In February of this year, we decided to go for another IVF cycle. This time, it was a disaster. We only retrieved 2 eggs, and the only one fertilized embryo didn't progress beyond 4 cells. We had to abandon that cycle--on the eve of my 33rd birthday.

That weekend I hit the internet, after having been told I had premature ovarian failure. I came across your website, and the following Monday at our follow-up consultation I asked my doctor about DHEA. She was all for it and wrote me a prescription.

I took the pills for 3 months. By the second month, my cycle, which was becoming irregular, started to return to normal. In the next IVF cycle in June, I got 11 EGGs. 6 FERTILIZED. ALL WERE EXCELLENT QUALITY!!! I had two embryos transferred. One of the two transferred embryos survived, and it split, leading to identical twins!

I am now 15 weeks pregnant with twins. So far they look fine and we are starting regular scans with a twins specialist next week. Thanks for your wonderful site with all its useful information! It put me on the path to success!

-S. G. in Australia



For an article on *FertilityAuthority.com*, Dr. Gleicher explained the numerous factors

requiring consideration when counseling older women on possible pregnancy (www.fertilityauthority.com/articles/older-mothers-economy-and-fertility-class-divide).

Dr. Gleicher was also interviewed for a *Slate* article exposing the fallacy of single embryo transfer (sET) policies in a majority of fertility patients (www.slate.com/articles/double_x/doublex/2011/08/in_defense_of_ivf_twins.html).

For a list of CHR's press releases, please visit www.centerforhumanreprod.com/about_events.html.