Making Egg Donation More Fair and Affordable:
Changes in Pricing of CHR's Standard Donor Egg Program (SDEP)

As a logical consequence of two recent national developments with profound new implications for egg donation in the U.S. and because rising costs increasingly price patients out of fresh donor egg cycles, CHR decided to radically reorganize structure and costs of its Standard Donor Egg Program (SDEP). In full disclosure, we here describe changes made in the program, their motivations and the new cost structure. The two national developments creating the impetus were:

- Following settlement of a class action suit, the American Society for Reproductive Medicine (ASRM) withdrew its previous recommendation as to how much IVF centers should pay egg donors for their services per donation cycle. The suit claimed the right of egg donors to let the market determine donor reimbursements. The legal settlement reaffirmed this principle, and CHR, therefore, feels legally obliged to consider market pricing in reformatting its donor egg/recipient cycle program.
- Within a very short time period, frozen egg banks by 2015 have already been supplying eggs for ca. 20% of donor egg cycles in the U.S., even though frozen eggs reduce donor cycle pregnancy chances to a minor degree in comparison to fresh donor eggs. In CHR’s SDEP, patients in return for a $8,000.00 fee used to receive all eggs a donor produced in her cycle, whatever the number was. Donor egg banks, however, have established “commerce” in donor eggs by charging per “sold” mature egg(s).

Donor egg banks have established a market value for donor eggs. Considering this fact and the legal settlement, CHR’s past cost structure no longer appeared fair to either donors or recipients: Instead of a fixed fee per donation, donors should be paid proportionally to their egg production, while recipients should be responsible for fees to pay more attention to the role of the immune system in female infertility.

More on the Importance of the Maternal Immune System

Regular readers of these pages may recall that we recently discussed a study that had appeared in the literature, which suggested that women infected with certain parasitic helminthes (the scientific name for worms) were more fertile than either uninfected women or women infected with a different worm. In our comments on this paper we suggested that this study represented further evidence for how important the maternal immune system was for successful female reproduction, and that it seemed high time to pay more attention to the role of the immune system in female infertility.

Also in this issue:

- Three-parent IVF
- More (bad) news about PGS
- More important CHR publications
- CHR profile: David F. Albertini, PhD
- In Focus: Images from the CHR lab
Maternal Immune System: Continued from Page 1

If a certain helminth can improve female infertility, it, likely, does so by challenging the maternal immune system in ways that enhance the chance of implantation and successful pregnancy.

Read about parasitic worms & fertility: http://kaywa.me/Z4w62

Despite being “foreign” and, therefore, subject to potential immune attacks and rejection, worms, of course, are parasite, which are “experts” in surviving in humans. The way they achieve survival is, likely, by inducing certain immune responses (pathways), which activate mechanisms within the host’s immune system that actually block such immune attacks, - i.e. induce immunological tolerance toward the helminthes. Induction of such pathways is, however, exactly what the implanting fetus also needs in order to survive because, like the helminth, it, too, is really a “foreign” body for the maternal immune system since it is 50% of paternal origin. Above cited study in South American Indian tribal women, thus, suggested that certain worms, in order to fend off attacks from women’s immune system induce certain immune pathways, which also are helpful to the establishment of pregnancies.

That this is not a farfetched thought was last month (June 19) also discussed by Moises Velasquez-Manoff in the Sunday Magazine of the New York Times in an article that attracted wide attention under the headline, “The Parasite Underground.” In that piece the author reported on the concept that infecting patients with certain helminthes who suffer from intractable autoimmune diseases often obviates clinical symptoms of the disease. The title of the article referred to the fact that an underground industry has evolved around infecting autoimmune patients, who cannot get relief from traditional medicine, with helminth larvae, which penetrate the skin and end up in the patients’ gastrointestinal tract.

Like in pregnancy, the concept here is again that helminthes induce tolerance-producing pathways in the immune system. Such tolerance is exactly what autoimmune patients need because presence of autoimmunity means that a patient’s immune system has lost its ability to be immunologically tolerant toward self-components of the body. As a consequence, the patient’s immune system attacks certain tissues in the body, and an autoimmune disease evolves. By inducing and/or enhancing autoimmune pathways, those helminthes not only protect themselves against their host’s immune system but they at the same time also restitute self-tolerance against the body’s own tissues and, thereby alleviate disease symptoms.

But this is not yet the end of the story about tolerance-inducing pathways for today: Just very recently, we discussed in the pages of the VOICE another article, which reported the remarkable observation made by medical colleagues in infectious diseases that administration of Influenza vaccine during pregnancy reduced stillbirths by 50%. In discussing this publication in these pages, we made the point that this observation may suggest that administration of Influenza vaccine during pregnancy may prolong the period of immunological tolerance of the fetal-semi-allograft by the maternal immune system because most stillbirths are likely the consequence of pregnancy complications caused by premature termination of tolerance (preeclampsia/eclampsia, premature labor, etc.).

We further speculated that, like helminthes, Influenza vaccinations also induce immune response pathways that enhance tolerance of the maternal immune system toward the female semi-allograft (the fetus) and, thereby, extend the period of tolerance in patients who, otherwise, would experience premature loss of tolerance and pregnancy complications that stem from such premature termination of tolerance.

Read the influenza and pregnancy: http://kaywa.me/yA3DB

Since then we discovered that this was not the only report suggesting that Influenza vaccinations dramatically reduce stillbirths. Indeed, last year a so-called meta-analysis also reported this fact (Bratton et al., CID 2016;60:e11-19).

Assuming that our hypothesis was correct, we also discussed in the VOICE piece the likelihood that Influenza vaccination not only can prevent stillbirths late in pregnancy but also premature labor, which represents the single largest cause of perinatal morbidity and mortality around the world. Low and behold, only weeks later a large observational study was published from South East Asia, which reported exactly that. Indeed, prematurity rates, once again were reduced by approximately half if women were vaccinated in pregnancy, and the effect was maintained after adjustment for covariates (Olsen et al., Clin Infect Dis 2016; May 3, pii: ciw290).

Combined these data increasingly suggest that...
Three-Parent IVF

From quite a number of articles during 2015, most readers of the VOICE will already be familiar with the term three-parent IVF. For those who have not previously heard about this technique, here is a short explanation: All of the body’s cells except for red blood cells contain a good amount of small tubular structures, called mitochondria. They can be viewed as the “batteries” of our cells because they provide over 90% of the energy that our cells consume in fulfilling their various functions. Interestingly, mitochondria also have their own DNA. Other than the nucleus of every cell, mitochondria are the only other structures that contain genes.

Differences between nuclear and mitochondrial genomes are, however, quite remarkable: While the nuclear genome is made up of 3.2 billion base pairs encoding for ca. 20,000 genes, the mitochondrial genome is only construed of 16,569 base pairs encoding for only 37 genes. Moreover, while nuclear genes of mother and father are passed on to future generations, only maternal mitochondrial genes are passed on to offspring.

Mitochondrial diseases

Like nuclear gene mutations, mitochondrial gene mutations can also lead to severe diseases, called mitochondrial diseases. Fortunately, with an estimation of 1 in every 2500 births, these diseases are quite rare. When mitochondria fail in their function in various mitochondrial diseases, less energy is generated in cells, resulting in cell injury and often cell death throughout the body. This, in turn, leads to failure of whole bodily systems, diseases and even death. While these diseases primarily affect children, first diagnoses at adult ages are increasingly common.

In addition to energy generation, mitochondria have many additional functions. Though, as noted before, mitochondrial DNA encodes for only 37 genes, remarkably, it takes approximately 3000 genes to make a mitochondrion. Ca. 2963 of these genes, thus, encode in the cell nucleus, and resultant proteins are transported to the mitochondria. Roughly 2900 of the 300 genes are, thus, involved in other, non-energy producing function of specific cells/tissues in which these mitochondria are situated.

Individuals affected by mitochondrial diseases either inherited a mutated gene from their mothers or were victims of a new mutation in mitochondrial (mtDNA) or nuclear DNA (nDNA). Because of the large number of mitochondrial functions, hundreds of different mitochondrial diseases have been described, with almost all presenting in a wide spectrum of clinical phenotype (i.e., symptoms), which can be highly confusing especially in early disease stages. Because so many genes often interact in these diseases, identical mutations in mtDNA will not always produce identical clinical presentation, then called genocopies. The opposite can also happen, when different mtDNA or nDNA mutations lead to the same clinical presentations, called phenocopies.

Preventing mitochondrial diseases

Efforts to prevent the inheritance of mitochondrial diseases have been under consideration for a good number of years. In the U.S. all research efforts were, however, blocked by the Food and Drug Administration (FDA), which declared all such clinical efforts to be under their regulatory jurisdiction, and so far refused all requests for consideration of the subject.

As Cohen and Adashi recently reported in JAMA (June 09, 2016. doi:10.1001/jama.2016.4930), a recent Obama administration action very likely further cemented the FDA’s refusal to even address this issue.

Continue reading on Page 4
In an unexpected development (and without attention by media), President Obama signed into law a policy rider that precludes modification of the human germ line. Incorporated under section 749 of the Consolidated Appropriation Act of 2016, the rider directs the FDA to refrain from considering “applications for an exemption for investigational use …. In research in which a human embryo is intentionally created or modified to include heritable genetic modification.” Possibly targeted at the prospect of editing the genome of a human embryo (see also below), the rider, nevertheless, is equally applicable to mitochondrial replacement therapy. This conclusion has been affirmed by an agency spokesperson who said that the FDA had resolved to delay on adjudication of mitochondrial replacement therapy for the rest of the current fiscal year (i.e., 2016).

As the authors also note in their article, the longevity of past government interventions into reproductive medicine do not bode well for this intervention: The so-called Dickey-Wicker Amendment, which prohibits all public funding of human embryo research, has been in place unchanged for over 20 years, and has been responsible for IVF having become the only routine medical treatment in the U.S., which cannot be supported by federal research funding. The even better known Hyde Amendment, prohibiting public funding for abortions, has been in place for almost 40 years.

Both of these prohibitions, however, only deny federal financial support, without prohibiting either activity, when funded by other sources. This recently signed policy rider by the Obama administration, however, sets a very unfortunate precedent for government interference into scientific research and medical practice by outright blocking all research activities in this arena, even if funded by private sources. Since the FDA had already declared that no such research could be pursued without prior agency review and approval, by instructing the FDA from refraining from all such reviews, the Obama administration put the whole enterprise of mitochondrial therapy in the U.S., likely indefinitely, on hold. That this would come from a Democratic administration is nothing but surprising!

In principle, two potential clinical treatment options have been proposed: The older proposal involved the so-called three-parent IVF, where basically in embryos known to be affected by a mtDNA mutation, the affected mitochondria are exchanged for healthy mitochondria from a third party egg donor. Already in March of 2015, the Human Fertilisation and Embryology Authority (HFEA), which is the administrative counterpart to the FDA in the U.S. in supervising human embryo experimentation in the U.K. based on parliamentary authority, requested more evidence of safety of the procedure before further consideration of the procedure’s clinical use in the prevention of transmission of mitochondrial diseases into the next generation. In a study published in early June in the prominent science journal Nature, colleagues from Newcastle, UK, under the leadership of Prof. Doug Turnbull and Prof. Mary Herbert, now reported that, utilizing a technique called pronuclear transfer, they could create embryos with less than 5% mutated mtDNA. Indeed, approximately 80% of embryos had less than 2% mtDNA. In other words, the resultant embryos had DNA from three different people (therefore, the term three-parent IVF): nDNA, half from the mother and half from the father; mtDNA in 95-98% from the healthy donor and mtDNA on 2-5% from the carrier mother (Hyslop et al. Toward clinical application of pronuclear transfer to prevent mitochondrial DNA disease. Nature 2016; June 8. Doi: 10.1038/nature 18303).

Modifying a previously published nuclear transfer technique, the investigators achieved greatly improved rates of blastocyst-stage embryo generation with no apparent effects on ploidy (chromosomal abnormalities) and gene expression in these early-stage embryos. Maximal reductions in maternal contribution of mtDNA (i.e., carryover) is desirable because expression of disease directly relates to the degree of heteroplasmy (i.e., amount of presence of mutated mtDNA).

Further studies on a stem cell line created from so produced blastocyst stage embryos, however, raised serious questions about the potential clinical applicability of this technique in preventing inheritance of mitochondrial diseases because the initial heteroplasmy of 4% mtDNA in the stem cell lineage significantly increased with continuous culture.

Similar results were, indeed, only one week earlier reported by a group of investigators from the New York Stem Cell Foundation under the leadership of Dieter Egli, PhD, Senior Research Fellow at the Foundation who, using human mitochondrial replacement stem cell
More (bad) news about preimplantation genetic screening (PGS)

We decided to put “bad” into parentheses in the heading because we have been advocating against the routine use of PGS in IVF for so long, that we actually welcome reports which confirm our arguments. Though “bad” news for PGS and its proponents, we consider such reports actually “very good” news for opponents of PGS and especially for IVF patients who, hopefully, will face less pressure from IVF centers to spend additional money on a basically useless, sometimes even harmful, procedure.

Remarkably, Human Reproduction (HR), the official organ of the European Society for Human Reproduction and Embryology (ESHRE) issued a rare “HR ALERT” in advance of publication of a study by colleagues from Stanford University under the leadership of Prof. Ruth Lathi, which apparently demonstrated “no advantage for preimplantation genetic screening over expectant management in recurrent pregnancy loss.” (Murugappan et al., Intent to treat analysis of in vitro fertilization and preimplantation genetic screening versus expectant management in patients with recurrent pregnancy loss. Hum Reprod 2016; pii: dew135) In other words, selecting out and avoiding transfer of allegedly aneuploid (chromosomally abnormal) embryos did, even in women with recurrent prior pregnancy loss, widely believed to be at especially high risk for aneuploidy in their embryos, not improve subsequent miscarriage rates.

These outcome data, of course, did not surprise us because, as we pointed out so many times in multiple publications, the procedure of PGS is really unable to determine accurately whether an embryo is euploid (chromosomally normal) or aneuploid (chromosomally abnormal). In addition, CHR investigators recently assessed national miscarriage rates after IVF with and without PGS (an abstract has been submitted for presentation to the Annual 2016 ASRM Conference), and found absolutely no difference. If PGS, indeed, as claimed, were able to eliminate aneuploid embryos from transfer, PGS cycles should have demonstrated clearly lower miscarriage rates.

Though much smaller in patient numbers than the CHR study, this upcoming publication from Stanford is for a number of reasons still of considerable importance. First, and the authors are to be congratulated on this fact, the study was correctly based on “intent to treat,” which means that outcomes were assessed with reference point cycle start. Practically all studies claiming outcome benefits for PGS failed to follow this proper study design, and calculated outcomes with reference point embryos transfer. When this is done women who did not reach embryos transfer (usually poorer-prognosis patients than those who do reach embryo transfer) are excluded from statistical outcome evaluations, greatly and falsely exaggerating pregnancy and live birth rates with PGS.

Secondly, we are impressed that this study was accepted by Human Reproduction and became subject of an HR ALERT because studies critical of PGS have had a very difficult time getting accepted in medical journals dedicated to infertility since reviewers of submitted PGS manuscripts at those journals are usually strong proponents of the procedure. Therefore, kudos go to Human Reproduction, and since the authors are American, one wonders whether Fertility and Sterility, the official organ of the American Society for Reproductive Medicine (ASRM) did not reject the manuscript before it was submitted to the European journal. This would not be surprising, considering the very strong, almost unabashed pro-PGS biases editors of Fertility and Sterility have exhibited on this subject. Those who are interested in gaining further insights into these biases may be interested in exploring the official forum of the journal over the last few weeks, where a fierce debate has taken place between CHR investigators and journal editors relating to this subject.

It is also important to point out that the study further suggests that PGS does not accelerate time to conception, as one would expect from any procedure that improves pregnancy and live birth rates. Once again, this does not come as a surprise to CHR, but it is nice to see such data also finally being reported by others.

Finally, this study is important because it puts yet another nail into the basic concept of PGS. With a number of additional studies in the publication pipeline, which demonstrate the futility of PGS even in good prognosis cycles and in its new 2.0 incarnation, we are hopeful that the new academic year 2016/2017 will see the ultimate demise of the PGS concept. It has already taken too long!
Dear Colleagues and Friends,

This Conference has the principal goal of offering an authoritative 2016 update for reproductive scientists and clinicians about important new translational developments in reproductive biology/physiology and clinically relevant patient care issues, while at the same time pointing out paradigm changes and imminent new potential developments of significance. By targeting clinicians as well as basic scientists as audience, this Conference will offer both groups a unique and intimate framework for interaction and exchange of ideas.

David F. Albertini, PhD | Ali H. Brivanlou, PhD, MD | Norbert Gleicher, MD | Zeev Shoham, MD

August 1, 2016 Abstract deadline for inclusion in the Journal of Assisted Reproduction and Genetics (JARG) and eligibility for Young Investigator Award of $5,000

Due to limited space and limited numbers of discounted hotel rooms available during the pre-Christmas season, we recommend early registration and hotel reservation.

Pre-Conference Workshops:

In vitro follicle/oocyte maturation age: From primordial stages | A new paradigm in clinical IVF: Age-specific stimulation and embryology | An in vitro implantation model: Peeking into the “black box” of implantation | The biological basis for the demise of preimplantation genetic screening (PGS)

Sessions:

The future of fertility care | Paradigm change I: Expanding infertility treatments from the gonadotropin-sensitive to earlier stages of follicular maturation | Paradigm change II: Early diagnosis of premature ovarian senescence, offering women more and better reproductive options | Paradigm change III: Reconsidering embryo selection | Paradigm Change IV: Individualization of infertility care | Skeptical of current clinical practice? Here are some answers!

For the full Conference program, registration, and abstract submission, visit the official Conference website: [http://frm.cme-congresses.com/](http://frm.cme-congresses.com/)
More Important Recent CHR Publications

Four more manuscripts with contributions from CHR investigators appeared in print since publication of the May VOICE. Here they are:

Treating older women with IVF

The first in order, was an invited review by the prestigious Journal of Endocrinology, in which the editors of the journal asked CHR investigators to summarize recent improvements in IVF treatments of older age women (Gleicher et al., Improvements in IVF in women of advance age. J Endocrinol 2016; pil: JOE-16-0105).

Since very few IVF centers offer treatments to older women, and even fewer published their experiences in treating such women, CHR investigators primarily had to present CHR data in this review, though, wherever possible, also drew on other centers’ reports. While the authors stressed steeply declining pregnancy and live birth chances with advancing female age, especially after ages 42-43 years, they also pointed out that outcomes were significantly better than generally perceived by most colleagues because, as most colleagues themselves do not treat older women, they rely in their consultations on outdated outcome data. Consequently, patients frequently are poorly advised as to what their real chances are, as the figure above (from another CHR paper published in late 2015 in the journal Fertility & Sterility) demonstrates.

AMH as a therapeutic agent

Two recent papers involving CHR investigators offer evidence that anti-Müllerian hormone (AMH) might offer significant therapeutic benefits. Both studies, therefore, served as substrate for three U.S. patent applications.

The first study involved collaboration with Aritro Sen, PhD, Assistant Professor and Laboratory Head at the University of Rochester School of Medicine and Dentistry in Rochester, New York and his laboratory's staff (Dr. Sen is also a Visiting Assistant Scientist at CHR and, based on a formal collaboration agreement between the University and CHR for a number of years a close collaborator with CHR). In this study the investigators determined in a mouse model intracellular mechanisms of AMH in regulation of follicle development. The study in addition demonstrated that AMH pretreatment prior to superovulation with gonadotropins improves oocyte yields. AMH as a therapeutic addition to gonadotropin stimulation may, therefore improve egg numbers [Hayes et al., Intra-cellular mechanism of anti-Müllerian hormone (AMH) in regulation of follicular development. Mol Cell Endocrinol 2016;433:56-65].

In a completely separate study of human IVF cycles at CHR, which initially was only meant to investigate whether statistical models could at various age predict whether a woman was a good, intermediate or poor prognosis patient in regard to clinical pregnancy and live birth rates, interesting additional AMH observations were made. This study, published in the prestigious Journal of Translational Medicine [Gleicher et al., Definition by FSH, AMH and embryo numbers of good-, intermediate- and poor-prognosis patients suggests previously unknown IVF outcome-determining factor associated with AMH. 2016;14(1):172], demonstrated among other findings relevant to the initial goal of the study that AMH at different levels appears to have distinctively different impact on outcomes in IVF cycles. At “best” levels, which are mid-range levels, AMH greatly appears to increase pregnancy and live birth chances; but at excessively high levels it appears associated with increased miscarriage risks.

AMH as a therapeutic agent may, thus, increase oocyte yields but may also at certain levels
proportionally to the number of eggs they receive in a cycle.

In reorganizing its SDEP, despite these developments, CHR still considers the commercial trade in human oocytes with considerable ethical concerns. As till now, CHR will forego profit from managing the process of egg donation between donor and recipient, and will continue to offer donor matching services as an unreimbursed courtesy to the center’s patients. CHR, therefore, will price the anonymous exchange of eggs between donors and recipients in its program at cost, and without profit margin. In full disclosure, we here offer a detailed description of the new financial structure for oocyte donors and recipients.

Principles of the pricing changes
The principal change in CHR’s revised SDEP is that egg donors will now be reimbursed based on the number of eggs they produce, and recipients will pay for donor eggs based on the number of mature eggs they receive. This, of course, immediately raises the questions, what does an egg donor receive per egg, what are the cost to the recipient per fresh donor egg, and how did we come to those numbers?

Let us start with the last question: CHR came to the new donor egg cost structure by looking at the center’s historical data, and determining the historical average number of mature oocytes in fresh donor egg cycles (n~10). Considering that CHR for over 10 years has maintained a reimbursement rate of $8,000 to egg donors for egg donation, independent of egg numbers produced, this established an average historical reimbursement of $800 per egg to donors. We then calculated CHR’s overhead costs in maintaining an independent donor pool of over 200 egg donors, and came per matched donor to approximately $2,000 ($200/egg) to $2,500 ($250/egg), depending on egg numbers. Combined, these numbers then established a cost for recipients of $1,000 - $1,050 per oocyte.

CHR, thus, in principle has not changed the pricing of fresh donor eggs but now distributes benefits and risks more fairly for donors and recipients.

What egg donors need to know
In practical terms this means that, with starting date August 1, 2016, the following donor reimbursements and recipient cost schedules will be implemented: Unchanged from prior procedure, recipients will, once they choose an egg donor, still be required to deposit $8,000 in anonymous escrow for donor reimbursement.

For this reimbursement, they will be entitled to 8 mature oocytes. Should they wish to receive more, they will have to make a balance payment to CHR for those additional mature eggs per below listed recipient charges prior to cycle start. If a donor produces fewer than 8 mature oocytes, the recipient will be entitled to a proportional refund.

Egg donors, in turn, will still be guaranteed $8,000 for a donation, as long as they produce at least 10 mature oocytes (the average number of eggs donors have produced at CHR in the past). If they produce fewer mature oocytes, their donor fee will be reduced proportionally in accordance with below listed donor reimbursements. If they, however, produce more mature oocytes, they can increase their cycle reimbursement to up to $12,000 for 15 or more mature oocytes. We hope that this new reimbursement schedule will motivate CHR’s egg donors even more than in the past to maximize their cycle performance.

Donors will be informed about the number of mature oocytes they produced on the day after egg retrieval since some immature oocytes may still mature overnight. The timing of donor payments remains unchanged. The table describes the new donor reimbursement schedule and recipient charges for varying oocyte numbers.

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Continue reading on page 11
At a recent meeting held in Brussels, Belgium, David Albertini, Ph.D., CHR’s Director of Laboratories and Senior Scientist, delivered two lectures on a promising area of research in human assisted reproductive technology (ART). The meeting was sponsored by the European Society of Human Reproduction and Embryology (ESHRE) on the subject of “Oocyte maturation: from basics to clinic,” and was attended by 137 scientists and clinicians, representing 35 countries from around the world. He delivered the plenary lecture on the history of in vitro oocyte maturation (IVM), and another talk on the breakthroughs in basic research that are leading the way to important clinical applications for the treatment of infertility.

As recently published by ESHRE in the May 2016 issue of the society’s official magazine, Focus on Reproduction, Dr Albertini’s remarks were summarized as follows: Rarely does an opportunity arise at a time when the confluence of basic science and clinical advance energize ART to the level of practicality. This ESHRE workshop took participants from the basic mechanisms of oocyte maturation to promising clinical findings which reflect the safety and suitability of IVM for understanding the mechanisms of developmental competence. While much remains to be refined before large scale clinical application, this meeting synergized the available evidence into a workable paradigm that will in the near future translate into clinically valuable dividends.

Guided by the natural physiology behind ovulation induction in women, retrieved oocytes in a majority have ripened and matured to a state ready for fertilization and embryo development. This, however, does not apply to all retrieved oocytes. As many fertility patients experience at CHR, even unripe immature eggs can be given a chance to prepare for fertilization by culturing them overnight in an enriched medium that often results in IVM, adding to the patients’ pools of eggs to be fertilized and, hence, to the number of embryos they would end up transferred into the uterus or frozen for later use. By some, this process is called “oocyte rescue,” and CHR investigators recently published their experience with this technique [Lee et al., Rescue in vitro maturation (IVM) of immature oocytes in stimulated cycles in women with low functional ovarian reserve (LFOR). Endocrine 2016;52:165-171].

Using animal models designed to identify the best culture conditions that will support the process of oocyte maturation, Dr. Albertini has pioneered the use of IVM for embryo production for over 25 years. In 2001, he for the first time began moving his animal research into clinical IVF, working in Boston with the laboratory of Catherine Racowsky, PhD at the Brigham and Women’s Hospital at Harvard University, who is an invited speaker at the upcoming Novembers scientific conference in New York City organized by the Foundation for Reproductive Medicine and co-sponsored by CHR.

Here at CHR, we are already routinely utilizing “oocyte rescue” for selected patients requiring fertility preservation, in women with inherent defect in the oocyte maturation processes and especially in poor responder patients who produce only few eggs and embryos. As CHR investigators in above cited study demonstrated, in such patients “oocyte rescue” can make the difference!

New informational material on treatments or news coverage on fertility breakthroughs, the best way to stay up to date on CHR’s activities is via our social media channels. Follow us, and never miss important news!
lines, demonstrated that low levels of heteroplasmy, introduced into human oocytes by mitochondrial carryover during nuclear transfer, often vanish. Instead, a gentotypic drift of mtDNA and reversion to the original genotype is observed (i.e., heteroplasmy returns to pathological levels) (Yamada et al., Genetic drift can compromise mitochondrial replacement by nuclear transfer in human oocytes. Cell Stem Cell 2016;18:749-754). These authors, therefore, warned that, although functional replacement of mtDNA is possible, even minor remaining heteroplasmy can affect the stability of the subsequent mtDNA genotype and, therefore put at risk the efficacy of the initial treatment. Dr. Egli will be CHR’s first GrandRounds speaker in the new academic year in September, further expanding on his group’s findings.

Interestingly, above noted British investigators in a way reached similar conclusions when they concluded in their manuscript that pronuclear transfer as a technique to replace an abnormal mitochondrial genome may have the potential to reduce the risk of mtDNA diseases but may not guarantee prevention of disease.

A better method to prevent inheritance of mitochondrial diseases
To some investigators in the field, these results are not too surprising. Indeed, suspicion about the potential limitations of cytoplasm exchange (a term under which the technique of nuclear transfer and other proposed techniques of mtDNA replacement have been bundled together) were a principal reason why some investigators have recommended a very different approach to preventing inheritance of mitochondrial diseases.

Their suggested approach is the selective elimination of mutated mtDNA from the germline using either mitochondria-targeted restriction endonucleases or TALENs. Already in April of 2015, a group of investigators at the Salk Institute for Biological Studies in La Jolla, California, under the leadership of Prof. Izpisua Belmonte, reported success in preventing transgenerational transmission of mitochondrial diseases in a mouse model using these techniques (Reddy et al., Selective elimination of mitochondrial mutations in the germline by genome editing. Cell 2015;161:459-469). We have previously extensively reported on this group’s efforts. As we repeatedly reported in these pages, CHR, indeed, initiated a collaborative effort with them.

Above reviewed two recent publications increasingly suggest that the prevention of transgenerational inheritance of mitochondrial diseases will, likely, not succeed via cytoplasmic exchanges but will have to rely on the surgical excision of abnormally mutated mitochondrial genes from the germline, and their replacement by normal genes.

Rapidly improving genetic editing techniques strongly suggest that this approach is likely clinically feasible already today. As above noted experience of our British colleagues from Newcastle well demonstrates, however, outcomes of practical clinical applications do not always follow earlier theoretical considerations. Careful preparatory investigations are therefore essential, and our British colleagues are to be congratulated on having done exactly that in their recently published study in Nature. CHR and our collaborators at the Salk Institute, in this context, are still looking for women in their reproductive years who are known carriers of mitochondrial

IN FOCUS

This feature presents microscopic images from CHR’s laboratories, edited by our Director of the Division of Laboratories and Senior Scientist, David F. Albertini, PhD.

This picture shows two oocytes and their companion granulosa cells one of which has undergone in vitro maturation (left) and one of which we refer to as being immature (right). The different colorations between each of these reflect major changes in the biochemistry and physiology of oocytes when they proceed from the immature GV state (right) to the mature M2 state (left), distinctions made in the IVF laboratory by embryologists following oocyte retrieval. Research at the CHR led by Dr. Albertini aims to optimize in vitro maturation for patient treatments when indicated. (For a related article on Dr. Albertini, see page 9.)
What recipients need to know

It is important for recipients to understand that under this new pricing scheme, they too, will be subject to a fairer fee structure, with all cycle fees being normalized to the number of mature oocytes a patient chooses to “purchase.” In practical terms this means that a recipient who, under the previous program would “purchase” all mature eggs her donor produced, now has the option to “purchase” as few as 4 eggs or, still, all the eggs the donor produces in the cycle. If she purchases only 4 eggs, she will greatly reduce her cycle costs, while, because of high pregnancy chances with fresh embryos from donor eggs, still experiencing an excellent pregnancy chance. At the other extreme, recipients who want to purchase all of the donor’s eggs in a given cycle, likely, will have higher cycle costs than in the past but will not only have the advantage of a higher cumulative pregnancy chance but also the chance of having frozen embryos for future siblings to a first child.

Potential additional egg donor income & recipient expenses

Cost reimbursements for travel and maintenance in New York City for long-distance donors will remain unchanged. Long-distance donors will remain marked in CHR’s donor pool, so that recipients will be aware of these additional donor costs for travel.

To further recognize varying “market values” of donors, CHR also introduces a new option, already widely used by many donor agencies and donor egg banks, by designating the so-called “high demand donors” (HDDS) who will be allowed to charge additional donor fees of either $1,000 or $2,000. Once donors are designated as HDDs, they, at their choosing, will be permitted to charge these additional fees, though, based on market forces, some donors may choose not to in order to be matched more quickly.

Eligibility for the designation of HDD will be determined by CHR, based on successful prior completion of at least one IVF cycle and/or special educational or other demand-enhancing achievements and/or qualities. To make recipients aware of these designation, donors awarded the HDD designation are also marked accordingly in CHR’s donor listing.

All other donor egg cycle costs remain unchanged. Please do not hesitate to contact us if you have further questions about our reorganized SDEP by calling 212-994-4400.
Influenza vaccination in pregnancy, indeed, extends the period of tolerance for the fetus by the maternal immune system. This, of course, raises an important additional question: **If the Influenza vaccine (and, maybe other vaccines or even helminthes) are able to extend the period of tolerance, can they also help in the initial induction of tolerance?**

With appropriate timing, the likely answer is yes because, like there are patients with premature termination of tolerance, there undoubtedly are also patients with initial difficulties in inducing tolerance for the implanting fetus.

**A new clinical trial**

Such patients currently are believed to suffer from so-called implantation failure and/or from repeated miscarriages. CHR, therefore, is initiating a new clinical trial, which will be presented to the center’s Institutional Review Board (IRB) for approval in its July meeting. Since CHR has a policy of recommending Influenza vaccinations to all women attempting pregnancy, CHR will prospectively randomize women to receiving this vaccination either before or after tentative implantation of embryos. In women with implantation failure, we hope to be able to establish that vaccination improves implantation rates and, therefore, pregnancy rates in association with IVF. In women with repeat miscarriages, we hope, to establish that vaccination reduces miscarriage risks.

The new trial will, likely, initiated in September with arrival of the annual Influenza vaccine. CHR will provide immunizations free of charge. Patients who are interested in participating in this trial, please call 212-994-4400, and let our staff know that you would like to participate in the “Influenza Trial.”

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improve clinical pregnancy and live birth chances. At excessively high levels, on the other hand, it may serve as an abortifacient.

**More PGS**

Approximately a year ago, when almost the whole world was still enamored with PGS 2.0, a prominent European colleague, Prof. Karen Dora Sermon from Vrije Universiteit, Brussels, Belgium, decided to conduct a worldwide query of 30 key opinion leaders in the field. One of those was CHR’s Medical Director and Chief Scientist, Norbert Gleicher, MD, except for a Dutch colleague, Sebastian Mastenbroek, PhD, the only PGS skeptic among this group.

The summary of opinions of these key opinion leaders were now published in Molecular Human Reproduction (*Sermon et al., The why, the how and the when of PGS 2.0: current practices and expert opinions of fertility specialists, molecular biologists, and embryologists. 2016; pii: gaw034*).

This paper will likely become a classic in the medical literature in demonstrating why opinions of “experts” are considered the lowest level of evidence in medical sciences. It, for that reason alone, is a worthwhile read. -The CHR

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