Clinical Care | Research | Education

March 2022

THE VOICE

SO MANY EMPTY CRIBS BECAUSE OF WASTED EMBRYOS

(see "CHR Publications")

IN THIS ISSUE

March 2022

The VOICE

With Spring per schedule knocking on the door, the mood in the world feels anything but spring-like. The deadly and cruel Russian war machine is already for weeks invading the independent country of **Ukraine**. As these words are put to paper, thousands have died on both sides of the war, including innocent Ukrainian civilians, - many innocent children. Many more have been wounded and, according to media reports, much more and much worse to come. Over 2.6 million Ukrainians, mostly women and children, have fled into neighboring countries as this is written and, there too, more can be expected. According to U.N. sources, the numbers may rise to 5 million, while even current numbers already represent the largest refugee stream in Europe since WWII.

And this is not all that reminds us of WWII: We are not only witnessing **the largest military assault on an independent neighbor nation in Europe since WWII,** history presents extremely concerning similarities to what happened prior to WWII between October 1 to October 10, 1938, when Hitler's Germany, under the pretext of defending an allegedly by Czechs abused German minority, occupied the Sudetenland, only to conquer the rest of the Czech part of Czechoslovakia by March 1939. Mimicking Hitler's 1938 strategy, Russia's Putin has been accusing the Ukrainian government for years of genocide against the Russian minority in the country. Already in 2014, under that pretext, he annexed the Crimea, until then an integral part of the Ukraine, and two border enclaves in Ukraine in the Donbas region. He did it in a so-called hybrid military approach, where allegedly local Russian militias (in reality often Russian military without Russian military insignia, so-called "little green-men") declared two newly "independent regions/enclaves" from Ukraine.

Receiving then little resistance from world powers, Hitler's next victim was Poland, which Germany invaded on September 1, 1939, thereby officially initiating WWII, when France and England declared war on Germany. Considering Putin's often publicly expressed opinion that granting in December of 1991 the individual nations that had made up the Soviet Union, independence represented "*the greatest political catastrophe of the 20th century,*" concern has been mounting that, as Hitler did not stop after the Czech landgrab, Putin, in an effort to "reunite" the old Soviet empire, will not stop after conquering the Ukraine.

As an unpolitical medical center, the CHR usually does not take sides in political conflicts. But when, as in this case, "good" and "evil" are so obvious, remaining quiet and not speaking out against "evil" makes one an enabler or, even worse, a co-perpetrator. The CHR, therefore, in strongest possible terms in this conflict sides with the heroic population of the Ukraine and condemns in strongest possible ways the inhumane activities of the Russian military against the people of the Ukraine and the national integrity of the country.

The CHR has many friends, colleagues, and collaborators on both sides of the conflict in the Ukraine as well as in Russia. We have been privileged to enjoy the incredible hospitability of natives in both nations and have had the pleasure of hosting many members of both communities over the years at the CHR in Chicago and, more recently, here in NYC. Based on these personal experiences, we know that most Ukrainians and Russians are peace-loving, hardworking, and very cultured people who outright condemn this senseless war. **Until this madness stops, and the Ukrainian people are given the opportunity to rebuild their lives and country, the CHR will, however, stop all commercial activities with Russia.** At the same time, we, however, remain available and, indeed, encourage friends, colleagues, and collaborators on both sides of the conflict who are victims of this atrocity and need personal help, to contact us. **We will do our utmost to offer this help.**

Despite this pain in the world, work at the CHR must, of course, go on uninterrupted, and so is the work of *the VOICE*. We, therefore, are pleased to offer here the March 2022 issue of this newsletter. Our lead article this month will explain what defines good-, intermediate- (or "regular"), and poor-prognosis in an infertility patient and why these distinctions matter. The CHR's Medical Director and Chief Scientist, **Norbert Gleicher, MD,** and several prominent colleagues from Israel and the U.S. just saw publication of an important article in *NATURE Medicine*, one of the world's most highly cited medical journals, with release from embargo only on March 21, which finally allows us to comment on this article in this newsletter (see "*CHR Publications*"). In his monthly "*A Piece of My Mind*" article, Gleicher will this month explore, **why medicine so often wastes efforts and money on treatment that simply do not work?** In addition, March is **"Women's History Month," "Endometriosis Awareness Month,"** and **"Developmental Disabilities Awareness Month**," motivating short, related articles. And then, there are, of course, the usual **literature reviews** of recently published articles we here at the CHR consider relevant and important for our specialty. **We hope you enjoy the March issue!**

- The CHR

Good-, average-, and poor-prognosis in IVF: *what does it mean and why does it matter?*

If it is not the first question patients ask, then it is one among a few very early questions after receiving any diagnosis in medicine**: "*Doctor, what is my prognosis?"*** In association with IVF, the same question may be worded slightly differently - ***doctor, what are my pregnancy and live birth chances?***

As simple as they sound, these questions, however, are not always easily answered. Medicine is always multifactorial in that outcomes are affected by more than a single determinant. But **especially female infertility is characterized by being complex multifactorial because treatment outcomes, besides many secondary factors, depend so heavily on female age and ovarian reserve at time of treatment**. To start the discussion, let us, however, first clarify some basic definitions:

Defining prognosis in IVF

A patient's prognosis is meant to define a woman's chance to conceive and deliver a healthy offspring with fertility treatments, in here presented framework with IVF. **Good-prognosis patients** will have the best chances, **average- or intermediate-prognosis patients** will be in middle ranges, and **poor-prognosis patients** will have below average chances. CHR investigators several years ago established that **this trifecta of outcomes exists in all patient populations**, even populations like the CHR's which, almost exclusively, only encompasses very poor-prognosis patients due to very advanced ages and/or low functional ovarian reserve (LFOR, as defined by abnormally high FSH and/or abnormally low AMH values). We repeatedly reported in *the VOICE* that CHR's patients have by far the highest median age (in the February issue we, for example, reported that 53% of the CHR's IVF cycles in 2021 were in women above age 43) and, likely, also have lower FOR than other centers' patients.

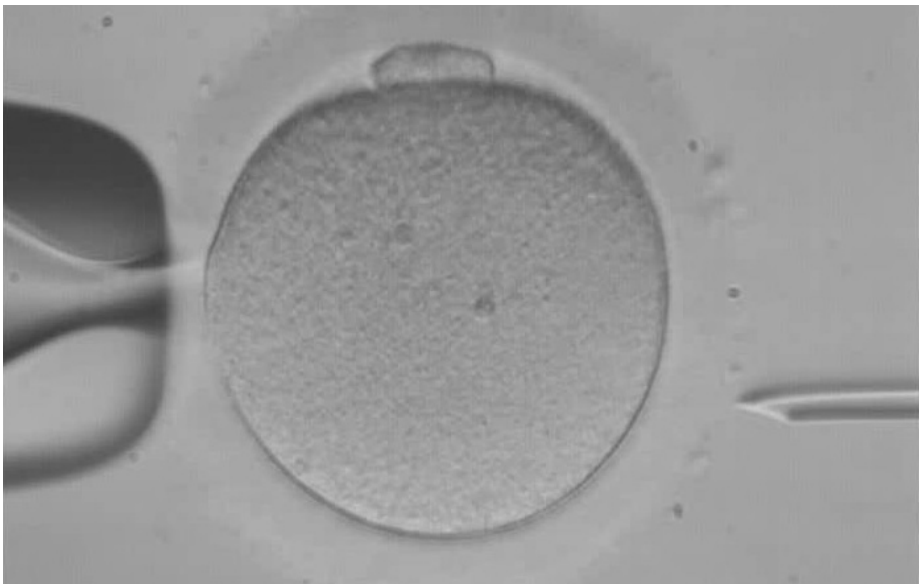
Though obvious differences can be found in patient populations IVF centers serve, when areas under the curve are studied with varying cut-off levels, **in all patient populations, good-, intermediate-, and poor-prognosis patients represent ca. 5%, 70%, and 15%, respectively, meaning that most patients will have average outcome chances and only relatively small minorities of patients will represent very-good- or very-poor-prognosis patients.**[1]

Let us, based on the CHR's patient population, explain why this classification is of importance: Because the CHR serves such a significantly poorer-prognosis population than most other IVF centers in the U.S. (and likely elsewhere in the world), **expectations would be that IVF cycle outcomes in all three of these patient categories at the CHR *should be lower* than at IVF programs with overall better-prognosis patients.** If one compares IVF cycle outcomes between the CHR

and other IVF centers, one, however, will notice that this is not the case and that the CHR's outcomes are comparable despite these differences in patient populations. **This, of course, then suggests that the CHR overperforms or that other IVF centers underperform.**

Because individual IVF centers serve at times very different patient populations, outcomes cannot just be simply compared between centers without taking into (statistical) consideration what kind of patients individual centers serve. This is the principal reason why the two U.S. national IVF outcome reports from the *CDC* and the *ASRM/SART* point out that **their reports should not be used, "*to compare IVF centers*."** Since statistical comparisons should compare only apples with apples, **true outcome comparisons between IVF centers will become possible only once the IVF cycle outcomes of individual centers can be reliably adjusted for the "severity" of a center's infertile patient population** (i.e., how "good" vs. "poor" the population's prognosis is prior to treatment start). Unfortunately, neither *CDC* nor *ASRM/SART* reports, however, do offer this currently.

This shortcoming is not only important for interpreting individual centers' outcome reporting in those two registries, but the CHR believes that **these inadequate reporting systems also have very negative impacts on general IVF practice in the US by incentivizing IVF centers to adjust practice patterns to artificially improve reported cycle outcomes, rather than to improve true patient outcomes.** Here are some examples: IVF centers that, for example, automatically promote women above age 42 into egg-donation, thereby exclude their worst-prognosis patients from their autologous oocyte cycle pool,



Beginning of an ICSI procedure

automatically upgrading the chances of remaining patients in all three prognostic categories. Similarly, IVF outcomes to registries have in the past been artificially improved by disproportionally transferring better prognosis patients in fresh cycles, while banking embryos from poorer-prognosis patients for future transfers, a practice not uncommon among even leading IVF centers. [2,3]

What are considered **good-, intermediate- or poor-prognosis patients at any given center, therefore, must be expected to vary.** Consequently, since the effectiveness of every treatment is depending on the treated population, **effectiveness of treatment protocols must also vary between IVF centers.**

All of this, of course, appears entirely logical: For example, in medical oncology and other medical specialties, it is a widely accepted concept that treatments should be adjusted according to patient characteristics, a concept now frequently given the term "**precision medicine**." **In association with IVF this kind of individualization of care is, however, only rarely applied** and **represents among the many differences in treatment approaches between the CHR and most other IVF centers, the most consequential one.** Yet, surprisingly, **practically all the clinical infertility literature is ignorant of these facts and presents outcome claims in often highly selected (usually primarily good-prognosis) patients and then applies those conclusions to all patient populations equally**. For that reason, most IVF centers stimulate most patients in IVF with the same protocols, trigger ovulation and, therefore, time retrievals identically in 25 -year-olds and 43-year-old patients, culture the embryos of everybody to blastocyst-stage, and perform PGT-A on all embryos that reach blastocyst-stage, **while the CHR, of course, does none of this.**

That IVF outcome claims from even prominent authorities in prestigious medical journals can be automatically integrated into one's own practice set-up is, therefore, a fallacy: similar outcomes will only be obtained in similar patient populations and, since study populations are usually highly selected for good-prognosis patients, those outcomes will usually not be matched at other IVF centers who apply the same protocols to mostly average-prognosis patients. Examples for this abound, with likely, as previously repeatedly pointed out in these pages, the most prominent being the practice of

routine extended embryo culture to blastocyst-stage, which originally was demonstrated to marginally advance time to pregnancy in highly selected good-prognosis patients,[4] and, after that, was never able to demonstrate the same effects in unselected general patient populations.

Another good example for how patient populations determine effectiveness of treatment outcomes in IVF is offered by another CHR experience; The CHR has been following for over two decades a rigid policy that determines how changes to current (generally very successful) IVF practice are made. There are only two options: either a change has been tested out at the CHR with routine CHR patients in randomized fashion and found to have favorable outcome effects (in cases of new supplies the threshold may be non-inferiority) and/or a detailed literature review offers adequate data that allows extrapolation to the CHR's unique patient population. For example, when the IVF field went a little "crazy" about **time-lapse embryo imaging systems,** the CHR resisted buying those systems because **the literature did not demonstrate any outcome benefits.** The CHR, however, agreed to purchase such a set-up, should it in prospective studies at CHR demonstrate outcome benefits in either **regular patients** (the center's usually very poor-prognosis patients) or in **best-prognosis patients** (i.e., young egg donors) and, therefore, was offered a loaner-instrument to conduct a study at the CHR. When the study was analyzed, there were no outcome benefits in egg donors. In the center's poor-prognosis patients, the hands-free automated incubation was, however, clearly inferior to the CHR's traditional manual embryology.[5] **The CHR, therefore, to this day does not employ time-lapse imaging in routine clinical practice.**

What "precision treatment" means at the CHR

At the CHR, "**precision treatment" means individualization of care at every step,** starting with history taking and laboratory investigation as well as other diagnostic workups. **Treatment planning does not start until a clear, likely causally related diagnosis has been established** (in this context, the CHR does not accept the concept of **"unexplained infertility"**[6]). Once one or more diagnoses have been established, patients are informed of those diagnoses since, surprisingly frequently, patients reach the CHR without diagnosis after prior treatments at multiple IVF centers. At that point **the patient's/couple's prognosis is discussed, defined as their probability of conception and live birth on a per cycle basis and cumulatively within 3-4 cycles.** Since the CHR primarily serves an older patient population and women with LFOR, this is also the point when **prognosis is explained as a function of how many oocytes/embryos are obtained in an IVF cycle** and as a function of what treatments are chosen (if there is more than one choice).

The CHR offers options and makes recommendations; **all final decisions about treatment choices are, however, the patients'. The CHR also exercises no mandates** (i.e., we, as an example, recommend Covid-19 vaccinations to all patients but do not mandate such vaccinations as a condition of treatment at the CHR). Patients at the CHR, therefore, will never be confronted with a mandate to use PGT-A as a condition for being offered an IVF cycle (as some IVF centers unfortunately do). The opposite, however, is also true: Even though the CHR, as is well known, opposes the utilization of PGT-A, the center offers the procedure if patients are insistent, despite appropriate informed consent process. Fortunately, that, however, happens only rarely.

Patients at the CHR, consequently, receive **greatly varying ovarian**

stimulation protocols, experience **variable trigger timing and, therefore, cycle length** according to the CHR developed HIER protocol.[7,8] **Embryo transfer timing is also individualized** and, in women with small oocyte/embryo numbers, will occur at cleavage stage (days 2,3), while women with larger egg/embryo numbers may be transferred at **cleavage or blastocyst-stage.** Even in the embryology laboratory, procedures are patient- and even egg-specific. For example, immature oocytes are never automatically discarded but always undergo attempts of ***in vitro* maturation rescue**.[9]

And individualization of care, of course, also applies to the male and all **male-infertility** and to **medical complications in women** that can interfere with conception and/or normal pregnancy progress. No disease grouping is, of course, in women of reproductive age more relevant than **autoimmune diseases**. Research in autoimmunity and the treatment of women with autoimmune diseases has been one of the CHR's primary interests for over four decades. Few IVF centers in the world, therefore, have the knowledge and practical clinical expertise the CHR's physicians have acquired in this area of medicine over those years.

The CHR also does not order at exorbitant costs huge quantities of unvalidated and, therefore, by insurances not covered tests. Most of these tests are not only technically worthless but unneeded to reach appropriate immunological diagnoses. Instead, the CHR attempts to offer a balanced diagnostic and therapeutic approach to **women with hyperactive immune systems** that lies between **"immunology deniers,"** of which there are many in the infertility field, and **"immunological cowboys,"** who symbolically often sell snake-oil, not only in what they test, but also in how they then treat.

Considering how controversial the practice of **reproductive immunology** has remained, the CHR considers this middle of the road approach appropriate as of this moment. It also is representative of the CHR's conviction that **experimental treatments should be given to patients only in formal clinical trials with appropriate informed consents**. Like other medical diseases, **autoimmune diseases in association with infertility have prognoses and, therefore, can with considerable probability be judged in advance.** No other disease group, possibly except for cardiac diseases, is as interdependent with reproductive processes as autoimmune diseases. In practical terms this means that **autoimmune diseases can greatly affect reproductive success**; but it also means that **fertility drugs and pregnancy can have significant impacts on autoimmune diseases**. Once again, therefore, **precision medicine with individualization of care is of utmost importance.**

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patient testimonial.

"

Dear Dr. Gleicher,

I just wanted to thank you so much for all that you did for me during my time at CHR. No doctor before you could diagnose me with PCOS and I still remember that day I received your second opinion report stating. I was thrilled to find an answer and knew CHR was going to be the place where I would have success. I will never forget your last words to me on our first consultation – "Don't worry, you'll be OK." That was really the first time I truly believed I could be pregnant with my own babies one day.

Why are we still using treatments in IVF that we know do not work?

By Norbert Gleicher, MD
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The CHR, New York N.Y.

I just had the opportunity to attend a large international conference on infertility that was the first well attended gathering in the infertility field since Covid-19 paused all such events. I had also attended an in person a conference in Berlin, Germany a little more than a month earlier; but attendance at that meeting had been so poor that the organizers were surprised to see me. Most other speakers had cancelled their attendance in the last minute because of an upswing in Covid-19 cases all over Europe. It, therefore, was good "to be back" among colleagues after two years "in isolation," giving only "electronic" lectures and watching colleagues' presentations only on computers. It also helped that this was my first visit to Egypt and that the conference was in Cairo, just a short car ride (ca.16.5 km) away from the Pyramids of Giza (see photo).

It was magical; but that is not the subject of this article. It was also work because I was giving three talks, one among them as part of a thematic session on **"add-ons" to IVF**, with special emphasis on **preimplantation genetic testing for aneuploidy (PGT-A)**. The Organizing Committee had balanced the session well, with a prominent speaker from the UK giving the introductory lecture on "add-ons" to IVF in general (she was among those who originally coined the term "add-ons"), followed by an Italian colleague widely known as a strong proponent of PGT-A; and then it was my turn as a strong opponent of PGT-A utilization, to present a counterpoint.

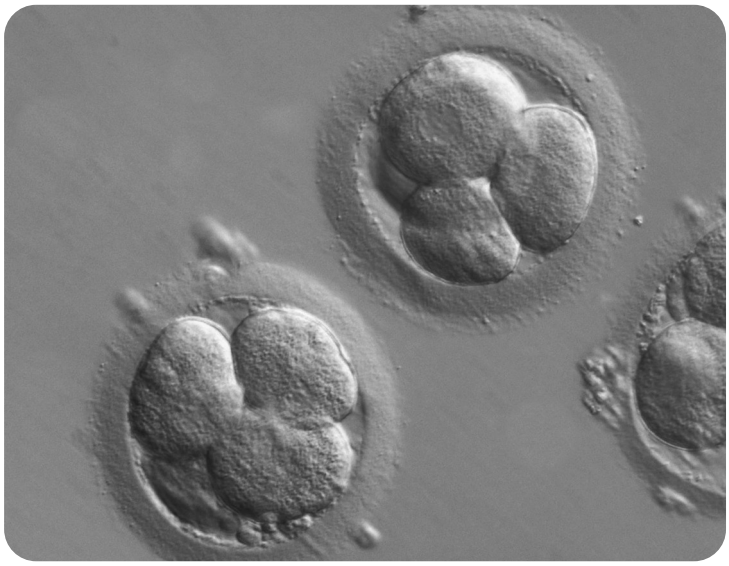
From their many publications, the Italian team's work on PGT-A was well known to me. I also over the years participated in several debates with members of this Italian group. Though we usually fiercely disagreed, I always respected the colleagues' creativity and enthusiasm. This time the energy level was, however, different; the speaker sounded "tired," presenting outdated arguments without supportive evidence and ignoring the evidence against, while offering misleading citations. When challenged about those citations, the response was, "*this is not necessarily my opinion but is what the literature says,*" - as if quoting studies does not reflect a speaker's opinion. He also seemed unaware of important recent literature on the subject, as two important papers had appeared over three months earlier in *The New England Journal* that directly contradicted many of the opinions he

had unabashedly offered in defending the clinical utilization of PGT-A.[1,2]

The response of the audience in the panel discussion that followed the lectures confirmed these impressions, raising the question, **why would a prominent and well-regarded physician-scientist, still, defend the indefensible, when even he apparently has come to acknowledge that there no longer exists any intellectual basis for such a position?** As I was pondering this question, I realized that the real question that must be raised regarding current IVF practice is bigger and much more important: ***why are we still using treatments in IVF that we know do not work?*** And this is how the idea for this column was born!

This newsletter has repeatedly addressed the issue of **unnecessary care in IVF**. Our British colleagues coined the term **"add-ons"** to describe additions to standard IVF treatments, which in a large majority of cases were introduced without prior validation of claims made for these "add-ons."[3,4] But as if introducing unvalidated tests and treatments into routine IVF practice is not bad enough, **many of these "add-ons" have since been seriously "un-validated." The most abhorrent example is, of course, PGT-A, which finally has been recognized for what it is**: A useless *ca*. $5,000 addition to already exorbitant IVF cycle costs that does not improve IVF outcomes but, for many patients, indeed, reduces pregnancy and live birth chances with IVF.[5,6] Moreover, incorrect PGT-A results, often, prematurely push women into third-party egg donations. Who then can be surprised that **voices demanding that PGT-A be restricted to experimental protocols are getting louder.**[1,7-10]

But PGT-A is by no means alone. Interested readers should look up here referenced studies by **Joyce Harper, PhD** [3,4] as well as other studies she published on the subject of "add-ons." Considerable evidence exists now that **other newly evolved mainstays of IVF also cause more harm than good**: **Routine extended embryo culture to blastocyst-stage** makes little statistical sense, as repeatedly reviewed in prior issues of this newsletter. **Elective single embryo transfer** is, after PGT-A, likely, **the second-most-important cause for declining live birth rates all over the world**.



Other causes include literally "crazy" concepts, like "mild" stimulation or "natural" IVF cycles, which not only have no experimental data to support their utilization, but, simply logically, make no sense. And then there are the great sounding hypotheses, **like time lapse embryo imaging,** on which IVF clinics spent millions of dollars based on the expectation that these instruments would improve embryo selection. By now we know that they offer no outcome advantages and, moreover, only increase the need for laboratory manpower, which they were supposed to reduce. Or take the concept of **all-freeze cycles with embryo banking and delayed transfer**. This "genial" idea not only extends every IVF cycle into two because of the need for a later frozen-thawed cycle, thereby delaying pregnancy and increasing costs, but it is **not even close to improving IVF outcomes**, as claimed by its original proponents.[12,13]

We, indeed, could go on and on about other worthless tests besides PGT-A that are now offered to IVF centers and, often, to patients directly through clever Internet marketing. But that is, again, not the primary purpose of this article. **What we here are trying to explain is why physicians, still, order useless tests and perform useless procedures in association with IVF?**

Cynics, of course, would say it's the money: PGT-A adds ca. $5,000, almost evenly split between IVF center and PGT-A laboratory (what a genial marketing move of the genetic testing industry, circumventing fee-splitting laws!). As noted, all-freeze cycles lead to additional frozen-thawed

cycles, also adding at least another $5,000 to the IVF cycle bill. Though there may be colleagues who are motivated by so-created additional revenue flow, **I, personally, do not see this as the primary motive why so much irrational treatment is dispensed in association with IVF** (though a very knowledgeable businessman in the field recently told me that without current PGT-A income, a third of U.S. IVF centers would, likely, have to restructure or go out of business).

That we do so many things, of which we know (or should know) that they do not work, in my opinion has mostly other, much more complex motivations, largely unrelated to financial gains. This behavior to large degrees appears to me like a reflection of the times we live in, **overloaded with information but increasingly poor in knowledge**, since **the information we are receiving often cannot be trusted**. Our field of medical practice in this sense is just a reflection of what is happening in society in general. Our medical journals are not different from newspapers and news magazine, where **articles have been getting shorter and shorter, headlines bigger and bigger and biases stronger and stronger**. We have more medical journals than ever before; **but who still reads beyond the headlines?** Abstracts are no longer enough as a summary of an article; even highly regarded medical journals now often list **"key-points,"** so that one can inform oneself even quicker (and more superficially). **Our knowledge is, thus, increasingly derived from abbreviations of abbreviations, thereby getting shorter and shorter and, obviously, increasingly more superficial.** Who really can determine the quality of a published study by just reading the headlines? And who, therefore, can be surprised that most physicians, simply, no longer are able to judge what to believe and whom to believe.

The consequence is a paradox, in that, **at a time when the medical establishment is claiming that medicine is increasingly becoming more evidence-based, the opposite is really the case.** Most **physicians, more than ever before, are dependent on expert opinions (the lowest level of evidence in the evidentiary pyramid)** because they, themselves, are unable to sort things out. **How well "experts" serve society when given too much power was, of course, nowhere more evident than during the Covid-19 pandemic**. Experts are often short-sighted and, therefore, biased because their field of special expertise is usually quite restricted and, by being ignorant of confounding outside factors, they overemphasized their biased viewpoints. And **experts are also "purchasable"** because **who does not want to be a "consultant" these days!**

Industry knows all of this and **uses their "consultants" smartly as opinion leaders** in selling their products with, concomitantly, greatly increased sophistication in direct marketing to the consumer. We physicians are for industry as much consumers as our patients are, and industry knows how to sell us their products and how to induce us physicians to use them on our patients. **Once a product is on the market, industry really does not care very much how well it works; what matters are sales. Does that clarify the original question?**

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IMPORTANT WOMEN IN IVF

Everybody, of course, knows the physiologist Sir **Robert G. Edwards** because of his contributions to in vitro fertilization (IVF) for which he won the *Lasker-DeBakey Cinical Medical Research Award* and, later, the *Nobel Prize for Physiology and Medicine*. Similarly, everybody knows his clinical partner in achieving the first IVF birth in the world, the gynecologist **Patrick Steptoe**, even before that known as a pioneer in gynecological laparoscopy, who undoubtedly would have shared in all the honors Edwards received, had he still been alive at the time. But almost nobody ever heard the names of two women who made essential contributions to IVF. Since March is "Women's History Month," the CHR wants to bring them to the attention of our readers.

Miriam Friedman Menkin (8/8/1901 - 6/8/1992)

She was born in Riga, Latvia, into a Jewish family that two years later moved to the U.S., where her father became a successful physician in NYC. After an undergraduate degree from *Cornell University* in histology and comparative anatomy, she within one year earned a master's degree in genetics from *Columbia University* but, as a woman, failed to be accepted into medical school. In 1924, she married Valy Menkin, a *Harvard* medical student and, because the family required financial support, she earned a second undergraduate degree in secretarial studies, so her husband could complete his medical degree. Her plan remained to earn a PhD in biology, and **she twice finished all *Harvard* PhD requirements, but never received the degree because she could not afford the course fees**.

After working for several years as a secretary, she became a research fellow at *Harvard Medical School* and was offered a job **as a laboratory technician** in the laboratory of the biologist **Gregory Pincus**, the inventor of the combined contraceptive pill. When Pincus lost his tenure at *Harvard*, she applied for a research position with **John Rock**, a fertility specialist who would become one of the most important researchers in the history of reproductive physiology and medicine. Their goal was to learn when ovulation was taking place. Since Rock had no laboratory experience, he hired Menkin for that purpose. By March 1938, Menkin initiated the first experiments relating to IVF. To understand the timing of ovulation, Rock and Menkin asked women who were scheduled to undergo hysterectomies (surgical removal of their uterus) to have unprotected intercourse. They then went on to time the surgery just before ovulation, so they could get eggs from preovulatory follicles during the surgery.

Menkin followed a routine schedule: Egg retrievals on Tuesday, trying to fertilize them with sperm on Wednesday, pray on Thursday and look under the microscope at the results on Friday.[1] **It took her till February 3, 1944 to achieve *in vitro* fertilization** and then subsequently **observe cell cleavage to 2- and 3-cell stage** in several embryos. This achievement was published in an article in *Science* on August 4, 1944. **Menkin and Rock never attempted to transfer those embryos into a uterus, but they were the first to fertilize an egg *in vitro* and observe cell division.**

Jean Purdy (4/25/1945 – 3/16/1985)

Transfer of human embryos into uteri was successfully done only in 1977 by Steptoe, Edwards and **Jean Purdy**. Purdy was a nurse and embryologist who worked with Steptoe and Edwards in developing IVF. Her role in that process has, however, mostly been ignored, though, as has now become apparent, it was substantial.[2,3] She in 1968 applied for a position as a lab technician in Robert Edward's *Physiology Laboratory at Cambridge*. Steptoe the following year became Director of the *Centre for Human Reproduction* in Oldham, UK (**if the name sounds familiar, it is no coincidence!**), where he collected oocytes from volunteers during laparoscopies for research in Edward's laboratory. Purdy became so essential to this research that, when she had to take time off to care for her mother, the work in the lab simply stopped.[2]

In a public comment in 1998, Edwards offered an appropriate tribute to Purdy when stating: "*There were in 1977 three original pioneers in IVF, and not just two, Dr. Robert Edwards, Mr. Patrick Steptoe and, Miss Jean Purdy and their supporting staff.*" Had Purdy not died at such young age from melanoma, she, most certainly, would have shared Edward's Nobel Prize in Physiology and Medicine. She co-authored 26 papers with Steptoe and Edwards and, supposedly, 370 IVF pregnancies were conceived at *Bourn Hall Clinic* (in 1980 co-founded by all three) while she was responsible for embryology.

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1. Gross RE. January 5, 2020 https://www.bbc.com/future/article/20200103-the-female-scientist-who-changed-human-fertility-forever
2. Gosden R. *Hum Fertil (Cambridge)* 2018;21(2):86-89
3. Johnson MH. *Reprod Biomed Soc Online* 2018;8:1-6

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IVF Nurse Coordinator

We, a strongly academically oriented internationally renowned fertility center with international clientele in NYC (Manhattan) are seeking an LPN (or equivalent training) to fill additional nurse-coordinator position in the center's busy IVF program. Prior IVF experience and knowledge of a foreign language preferred but not an absolute prerequisite, as training will be required even with prior experience. This position involves a large amount of close and independent interaction with patients and, therefore, requires a professional and pleasant demeanor, good interpersonal and communication skills and ability to multitask. We offer a highly collaborative work environment between physicians, clinical coordinators and embryology staff, competitive salaries and benefits as well as opportunity to participate in important research.

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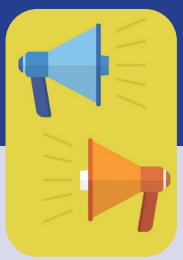

It is Endometriosis Awareness Month

and we, therefore, want to summarize in short bullet points what every woman should know about this condition.

• Endometriosis is a condition, in which endometrium (the lining of the uterine cavity) in little islands can be found outside the uterus, most frequently in ovaries, fallopian tubes, and utero-sacral ligaments; but really anywhere in the abdominal cavity, including bowel, omentum, the diaphragm, and even in lungs

• Since these islands are under the same hormonal control as the endometrium, they "menstruate" when the uterus menstruates.

• When those islands "menstruate," the woman's immune system perceives them as open wounds and proceeds to heal them, in the process forming scar tissue.

• If this scar tissue involves fallopian tubes and ovaries, it can cause infertility and/or pain.

• Pain and other symptoms can also be caused by endometriosis, infiltrating deeply into pelvic regions. If endometriosis infiltrates the rectum, it can cause rectal bleeding during menstruation.

• The pain associated with endometriosis has strange features: it does *not* correlate with severity of the disease; mild disease can cause severe pain, and severe disease may be asymptomatic.

• Severity of disease is described in disease stages I-IV.

• Pain may occur in association with periods in the menstrual cycle and/or only during sex. Pain during sex is especially strong during deep penetration.

• Endometriosis to this day has no clear etiology (cause), but is highly associated with inflammation and autoimmunity.

• A strict anti-inflammatory diet, avoiding gluten, dairy, and sugar can be very effective in reducing disease load and symptoms in many women.

• When endometriosis is in the ovaries in the form of cysts, those are called endometriomas or chocolate cysts. Their biggest risk is that they rupture and cause peritonitis.

• In women who still want to conceive, the CHR, however, in most cases strongly recommends against performing surgery to remove those cysts because such surgery often also removes remaining healthy ovarian tissues, basically sterilizing the patient.

• It has been reported that 10% of women have endometriosis. At the CHR we consider this number likely an underestimation. Certainly, among infertile women, this number is much higher

• A likely diagnosis can be often made based on history, symptoms and pelvic exam, but a definite diagnosis can only be made by laparoscopy.

• Endometriosis has no cure but usually "burns-out" during pregnancy (often only temporarily) and with advancing age, the latest with menopause. This means no new islands of endometriosis are forming, and the old ones are undergoing scarring and sometimes calcification.

• Temporary medical interruption of menses over several months can also result in a temporary "burn-out;" but there is no permanent medical cure available for endometriosis. Moreover, temporary treatments do not allow for pregnancy attempts during that time period of treatment.

• Consequences of scarring are usually not reversible without surgery. The CHR, however, recommends surgery to infertile women usually only if their clinical symptoms are intolerable. In almost all other circumstances, except for obvious clinical emergencies, the CHR recommend against surgery

If you have further questions or if you suffer from endometriosis and do not believe you receive the right treatment, call for an appointment with one of CHR's physicians by calling 212-994-4400.

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What *patients* ask about

This is where we answer the most interesting questions received over the preceding month. Please write to us at social@thechr.com if you want your question(s) answered in this rubric.

Is surrogacy affected by epigenetics?

This is an excellent question, **and the unequivocal answer is a big YES**. But before we go into more detail, here is a brief explanation of what the meaning of **epigenetics** is: Our understanding of what genes do has dramatically changed over the last few decades. There was a time when we believed that every gene had only one function; we now understand that genes have many different functions, often in combination with other genes. Epigenetics, however, has a different meaning. What this term refers to is the fact that **genes work like thermostats, - they can be off or on, or they can be set at varying levels of activity**. The field of science that addresses these aspects of our genes is called **epigenetics**.

While we inherit our genes from our genetic parents, what these genes later in life do (i.e., how much they are on or off) is, thus, determined by epigenetics and is dependent on **effects the environment has on our genes.** This is important to understand because what this means is that, while we inherit our genes from our parents, how they work depends to a significant degree on the environment in which we exist. And here comes the most important point: **The most important period in our lives for epigenetically determining the function of our genes are the nine months we spend in our mothers' wombs.**[1]

One other very important point regarding epigenetics: The thermostat settings we acquire epigenetically will at least partially be passed on to next generations. In other words, **carrying a pregnancy every pregnant woman, including all gestational carriers (surrogates), have not only major influences on future children but also on their children and grandchildren.** This is the principal reason why **we want patients as well as gestational carriers who are planning to conceive to be as healthy as possible** and why we, here at the CHR, recommend to our patients who use gestational carriers to allow us to interview them before they commit to any surrogate carrier.

REFERENCE

1. Toraño et al., *Biomed Res Int 2016;2568635*

Do hormonal contraceptives cause the Polycystic Ovary Syndrome (PCOS)?

Here, **the very clear answer is a big NO**! We, nevertheless, were very happy to receive this question because several patients recently pointed out to us that, probably advanced by well-paid influencers, this claim has become very popular on social media, **allegedly being promoted by an industry that is trying to sell "post-birth-control remedies."**

Oral contraceptives or other hormone combinations are, indeed, frequently used to treat PCOS, especially if affected young women have irregular periods and/or very heavy periods. **What causes PCOS is still unknown** but investigators at the CHR have recently developed evidence that what currently is called PCOS, with considerable likelihood represents **two distinct clinical entities**, **one characterized by metabolic** and **the other by immunological problems**. But one thing is for sure, neither one is caused by hormonal contraceptives.

Is it correct that chromosomal-abnormal embryos can self-correct?

And **the answer to this very important question is again, unequivocally, YES**. Though first documented several years ago in mice,[1] a recent study by *Rockefeller University* investigators in collaboration with investigators from the CHR for the first time also **confirmed in human embryos that embryos often self-correct downstream from blastocyst-stage.**[2] One of the arguments opponents of PGT-A have, indeed, made for years has been, **what would the purpose be of diagnosing embryos as aneuploid at blastocyst-stage if they, downstream, can still self-correct?**

March is also ***Developmental Disabilities Awareness Month***. We, therefore, in such a context are pleased to reaffirm that human embryos can avoid disabilities by correcting their chromosomal make-up.

REFERENCES

1. Bolton et al., *Nat Commun 2016;7.11165*
2. Yang et al., *Nat Cell Biol 2021;23:314-321*

RECENT PUBLICATIONS
from *the CHR*

Gleicher N, Albertini DF, Patrizio P, Orvieto R, Adashi EY. The uncertain science of preimplantation and prenatal genetic testing. *Nature Medicine 2022; doi: 10.1038/s41591-022-01712-7*

We in these pages two months ago noted a front-page article in *The New York Times* by **Sarah Kliff** and **Aatish Bhatia** on January 1, 2022,[1] in which they correctly pointed out the irresponsible behavior of the genetic testing industry when it comes to **early prenatal testing in pregnancy for chromosomal abnormalities.** Many of these tests are unvalidated and produce **large numbers of false-positive results** that can lead to **unnecessary terminations of pregnancies** (see also below, "*Regulating unregulated laboratory-developed tests*"). To demonstrate the seriousness of the allegation, the headline of their article was: ***"When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong."***

In the February issue of the highly prestigious medical journal *Nature Medicine*, an unsigned editorial based on this article picked up on the subject and concluded that, ***"it was time to close a loophole that allows so-called laboratory-developed tests to be exempt from regulatory oversight, putting people at risk of making consequential medical decisions on the basis of unreliable results."*** [2] And on March 21 at 12:00PM, the same journal released an article from embargo[3] in which CHR investigators in collaborations with colleagues from the U.S. and Israel addressed both of these issues but made the additional connection that **the same issues are even more relevant and disturbing and much longer ongoing in association with PGT-A,** where large numbers of perfectly fine embryos with significant pregnancy and live birth potential are either refused transfer or are even disposed of because of a similarly unvetted testing procedure. They further concluded that, in addition to tightening oversight of the genetic testing industry in reproductive medicine by professional organizations in the field, and if that does not occur, by the *FDA*, **the clinical utilization of PGT-A should be restricted to experimental protocols,** as recently also suggested in an article in *The New England Journal of Medicine* that attracted considerable attention.[4] Their article, furthermore, warned about expanding efforts of the genetic testing industry into a brand-new field of so-called **polygenic risk testing of embryos**, only recently **by a major genetics society in Europe defined as unethical**.[5] Yet, nevertheless, polygenic risk testing is in the U.S. already being offered clinically. **Shameful!**

The complete article information is provided below in bold,[3] and copies of the article can, as always, be ordered by calling 212-994-4400 or e-mailing to social@thechr.com.

REFERENCES

1. Kliff S., Bhatia A. *The New York Times*, January 1,2022. https://www.nytimes.com/2022/01/01/upshot/pregnancy-birth-genetic-testing.html
2. Editorial. *Nat Med* 2022;28:215
3. **Gleicher N, Albertini DF, Patrizio P, Orvieto R, Adashi EY. The uncertain science of preimplantation and prenatal genetic testing, *Nat Med 2022*; doi: 10.1038/s41591-022-01712-7**
4. Mastenbroek et al., *N Engl J Med* 2021;385:2096-210
5. https://www.focusonreproduction.eu/article/ESHRE-News-PRS

patient testimonial.

"

My husband and I ended up coming to CHR after our local clinic told us we had no other options besides egg donation. Dr. Barad changed our lives - CHR listened, and tailored my treatments to my specific issues. They also monitored me much closer than my previous clinic, and the results speak for themselves. After multiple tries (with adjustments after each) we were able to retrieve eggs, got embryos, and I am now many months pregnant with a baby. This would NOT have happened at my old clinics, CHR respected our plans and worked with us to achieve our goals. Well worth the trips to NY, and I will be always eternally thankful.

General news
Clinical Reproductive Medicine

Regulating unregulated "laboratory-developed tests"

When Congress first authorized the *FDA* to regulate medical devices and diagnostic laboratory tests in 1976, a small number of tests, designed, manufactured, and analyzed in the same lab, were purposefully excluded by the *FDA* from all regulatory controls, - so-called **"laboratory-developed tests" (LDTs).** This exclusion made considerable sense at that time because these tests were usually simple screening tests, developed by physician offices in the country, hospitals, researchers, and academic medical centers for their own rather limited uses.[1] After the U.S. exempted such tests, other countries, including the *European Union*, also picked up this exclusion.

This was, however, when **the laboratory testing industry**, sensing a gigantic loophole in *FDA* and *EU* regulations, stepped in and started abusing this loophole by manufacturing tests on large scales, never ever imagined by the *FDA* when excluding LDTs from supervision. And in absence of oversight, medical practice always develops problems, which this newsletter has now been covering for over two decades because this is how long CHR's investigators have been pointing out **the damage the genetic testing industry has been causing to IVF** through what initially was called **preimplantation genetic screening (PGS),** now called **preimplantation genetic testing for aneuploidy (PGT-A)**, recently also well summarized by others.[2]

We elsewhere in this issue of *the VOICE* report on this month's publication of an article by CHR's investigators in collaboration with U.S. and Israeli outside colleagues in the highly prestigious medical journal *Nature Medicine*, in which the authors point out **the need for finally reigning in the genetic testing industry in reproductive medicine**, not only regarding PGS/PGT-A but also regarding **prenatal testing for chromosomal abnormalities in early pregnancy**, as well as regarding expansion plans for embryo testing, involving the testing for polygenic conditions through so-called **polygenic risk scoring** , from eye color, to physical talents and disease risks,[3] **an idea recently described by the *European Society of Human Genetics (ESHG)* as unproven and, therefore, unethical.**[4] A practically identical opinion was offered in an unsigned editorial in the February issue of *Nature Medicine*,[1] while the rather disturbing ethics of PGS/PGT-A were in detail reviewed in a recent article in *The New England Journal of Medicine*,[2] which we, after it appeared in print, in detail addressed in the pages of this newsletter.

Especially problems with PGS/PGT-A (wastage of large embryo numbers with excellent pregnancy potential) and **early prenatal testing for chromosomal abnormalities (terminations of pregnancies because of false-positive results),** after a recent *New York Times* article,[5] **appear to have finally reached no longer ignorable exposure.** Even Congress appears to have recognized the problem, as a large group of members of Congress and Senators apparently indicated in a recent letter to the *FDA*.

The CHR has warned for years that, unless we, as a medical specialty, police our field of practice with help of our professional organizations, it will be left to government to step in to prevent abuses. There may, still, be time for *ASRM/SART* and *ESHRE* to step in, but considering those organizations' close relationships with (and dependency on) the genetic testing industry and large investor-owned IVF-practice networks, we are skeptical that this will happen. **It will, likely, be left to the *FDA* to reign in the current abuses** and, whenever government steps in, **the danger exists that the medicine is worse than the disease.**

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1. Editorial. *Nat Med* 2022;28:215
2. Mastenbroek et al., *N Engl J Med* 2021;385:2096-2100
3. Gleicher N, et al. *Nat Med* 2022 doi: 10.1038/s41591-022-01712-7
4. https://www.focusonreproduction.eu/article/ESHRE-News-PRS
5. Kliff S., Bhatia A. *The New York Times*, January 1,2022. https://www.nytimes.com/2022/01/01/upshot/pregnancy-birth-genetic-testing.html

Artificial intelligence (AI) in medicine

All medical specialties are buzzing with articles about AI, - reproductive medicine is no exception. As a recent article in *Nature Medicine*, likely, correctly noted, ***"AI is poised to broadly reshape medicine."*** [1] In following the literature in reproductive medicine, we, however, often wonder whether some of the authors understand the powers and limitations of AI and whether expectations

are not at times exceeding realities. This is a main reason why we recommend this recent paper which was written by authors from the Department of Biomedical Informatics at *Harvard University*, Department of Computer Science, *Stanford University*, and *Scripps* Translational Science Institute (can it get any better than that?), for two years tracking key developments in medical AI and now reporting their observed key findings.

The recognition we especially often find missing is that, **if AI is to contribute, potentially causally associated co-dependencies must be present.** If those do not exist, AI will, of course, have nothing to discover. This is an important point, for example in **embryo selection**. It is entirely possible that more advanced AI, utilizing multifactorial cluster analyses, will, for example, be more successful than even sophisticated single factor association analyses which have *not* been able to produce outcome benefits for IVF with **time lapse embryo imaging**.[2] We, however, urge caution because that would require that there exist significant enough differences at either cleavage or blastocyst-stages that can affect IVF cycle outcomes. And this is not something we can be sure of, considering that **most embryo quality is oocyte-dependent**, and that oocyte quality is the product of weeks to months of follicle maturation. By the time an embryo reaches cleavage- and/or blastocyst-stages, one can imagine that quality of remaining embryos may be too similar (of course, except for distinct findings like true aneuploidy) to allow distinctions even through AI.

REFERENCES

1. Rajpurkar et al., *Nat Med* 2022;28:31-38
2. Perrotta M. Geampana A. *Soc Sci Med* 2020;258:113115

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Biology & Embryology

Spindle instability in human oocytes

Melina Schuh, PhD, now the director of the *Schuh Laboratory* and Department of Meiosis at the *Max Planck Institute for Multidisciplinary Sciences* in Göttingen, Germany which also has a secondary lab at *Bourn Hall Clinic* near Cambridge in the UK (originally founded by Edwards, Steptoe and Purdy; see also, "*Important women in IVF*") is now widely recognized as one of the world's leading experts on **meiosis errors** that lead to **chromosomal abnormalities** and has developed revolutionary **single cell imaging technologies** that have formed the basis for many groundbreaking discoveries.

Her lab just published another important paper in *Science*, in which the authors relate mechanisms in spindle pole organization to chromosomal instability in human oocytes.[1] In this study they identified the molecular **motor KIFC1 (kinesin superfamily protein C1)** to be spindle-stabilizing in other mammalian oocytes (with lower aneuploidy rates than human oocytes) but not in human oocytes. Depletion of KIFC1 in those other mammalian oocytes resulted in spindle instability like in human oocytes. As a control experiment, the authors then injected recombinant KIFC1 protein into human oocytes. Live imaging of spindle assembly in those oocytes, indeed, demonstrated the by now expected stabilization of the spindle and, concomitantly, reduced chromosome segregation errors.

These observations, therefore, confirmed that KIFC1 stabilizes the oocyte spindle in humans, while deficiency of KIFC1 causes instability. They also suggest potential treatment options for oocytes to reduce chromosome segregation errors in infertility. We also recommend this manuscript for the, as always from this lab, impeccable imaging studies.

REFERENCE
1. So et al., *Science* 2022;375(6851):eajb3944

What causes oocyte aging and what to do about it?

A just published study from Israel offers also interesting and potentially clinically valuable information on oocyte physiology. Here, the investigators asked the very basic question, **what causes oocyte aging?** They concluded that the **loss of heterochromatin-associated chromatin marks, that cause DNA damage and impair oocyte maturation, apparently play an important role.**

The authors reached these conclusions after demonstrating in mice that, prior to development of significant aneuploidy, **heterochromatin histone marks are lost, and oocyte quality becomes impaired**. This loss involves constitutive and facultative heterochromatin marks but not euchromatic active marks. Human aging, in prophase-1 arrested oocytes also experiences heterochromatin loss. In the mouse heterochromatin loss if, furthermore, accompanied by increases in RNA processing and is associated with increases in L1 and IAP retrotransposon expression, DNA damage and nuclear localization of DNA repair proteins. These findings, like in above-described spindle study, were further confirmed: **By inhibiting the heterochromatin machinery in young oocytes, retrotransposon expression and oocyte maturation defects increased,** - not an uncommon finding especially in older women.

The opposing experiment also confirmed the hypothesis: **Inhibition of retrotransposon reverse transcriptase with the HIV drug azidothymidine (AZT) rescued the maturation defects of older oocytes partially, and activated the DNA repair machinery.** Activation of the heterochromatin machinery by treatment with the SIRT1-activating molecule SRT-1720, or by over expression of Sirt1 or Ezh2 by plasmid electroporation into older oocytes, resulted in **downregulation of retrotransposon expression and elevated oocyte maturation rates**.

Oocyte pretreatment with AZT for 6-8 weeks prior to IVF cycle start, therefore, theoretically should rescue maturation defects and activate DNA repair in oocytes of older women. A clinical trial of such treatment would appear of importance.

REFERENCE
1. Wasserzug-Pash P et al., *Aging Cell* 2020;00:e13568

More on models for human embryos

We in a prior issue of *the VOICE* reported on the exciting upcoming paper out of **Nicolas Rivron's** laboratory at the *Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA)* in Vienna, Austria, in which he reported the ability to mass-produce **human** blastoids from stem cells that strongly resemble human blastocyst development.[1] Now this paper appeared in print,[1] and Li et al from **Juan Carlos Izpisua Belmonte's** laboratory at the *Salk Institute for Biological Studies* in La Jolla, California (a friend and onetime collaborator with the CHR), penned an interesting preview commentary on the subject of **blastoids that resemble human blastocysts to model implantation** in the journal *Cell*.[2]

This commentary, like the paper they are commenting on, are "must reads" for everybody interested in preimplantation-stage embryos and the implantation process because, considering all the restrictions and limitations on experimentation with human embryos, **the practical future of**

research in this area, very likely, lies in blastoids and other artificial human embryo models, not under such restrictions.

REFERENCE
1. Kagawa et al., *Nature* 2021;601(7894):600-605
2. Li et al., Cell 2022;185:561-564

A little more on stem cells

It has been known for some time that **pluripotent stem cells (hPSCs) in maintenance frequently become aneuploid (there also have been reports on self-correction)**. It has also been established that, like in embryos, aneuploidies usually mostly happen during mitosis, caused by segregation errors. Now, a still unreviewed preprint on *bioRxiv* by researchers from *Dartmouth Geisel School of Medicine* in Lebanon, NH, report **inherently low segregation fidelity in hPSCs**. The principal reason appears to be lagging of chromosomes with improper merotelic chromosome microtubule attachment in anaphase. The authors furthermore claim that they can reduce lagging chromosome rates and/or destabilize chromosome microtubule attachments using small molecules that prolong mitotic duration, thereby **offering a strategy in preserving genome stability**. They also demonstrate that segregation fidelity, moreover, depends on developmental stage of a cell since **miotic errors correlate with developmental potential, decreasing upon differentiation and loss of pluripotency and, conversely, increasing again after reprogramming to pluripotency.**[1]

These findings, if confirmed in peer review, have significant relevance to aneuploidy in human embryos because they further suggest that **there must be physiological purpose to aneuploidy** if the most immature cell stage favors aneuploidy and aneuploidy disappears (like in embryos after implantation) with increasing maturity of cells.

REFERENCE
1. Deng et al., *bioRxiv* preprint. https://doi.org/10.1101/2022.03.01.482524

Cell surface fluctuations regulate early embryonic lineage sorting

Lineage segregation during early embryo stages is determined by time and space. Though significant progress has been made in understanding the process on a molecular level, **the physical mechanisms are not well understood** yet. Now comes a large international team of investigators from Europe, the U.S. and Asia, reporting that segregation within the **inner cell mass** of **primitive endoderm** (producer of the yolk sac) from the **epiblast** (producer of the fetus) **is dependent on cell surface fluctuations.**[1]

If correct, the authors propose that cell surface fluctuations may represent a general feature of self-organization across organisms, clearly a concept deserving of further exploration.

REFERENCE
1. Yanagida et al., *Cell* 2022 185:777-793

Viable offspring from unfertilized (parthenogenic) mouse oocytes

Chinese investigators from Shanghai and Beijing, apparently **succeeded in producing normal mammalian offspring mice that were derived from only a single unfertilized egg**. Because of genetic imprinting, parthenogenesis in mammals is generally considered limited. How, then, did these investigators achieve this milestone?

They basically rewrote the animals' DNA methylation pattern by rewriting even imprinting control regions. This tour-de-force is because of its technical density at times difficult to follow in the manuscript; but it must be considered **a major accomplishment that potentially opens several opportunities, not only in medicine and infertility** but also in, for example, agriculture. **The authors are to be congratulated!**

REFERENCE
1. Wei et al., *PNAS* 2022;119(12):e2115248119

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Riboflavin (as Riboflavin-5-Phosphate Sodium)	5 mg	385%
Niacin (as Niacinamide)	25mg NE	156%
Vitamin B6 (as Pyridoxal-5-Phosphate)	8mg	471%
Folate (as [6S]-5-Methyltetrahydrofolic Acid Glucosamine Salt) (Quatrefolic®)	1010 mcg DFE	253%
Vitamin B12 (as Methylcobalamin)	50 mcg	2,083%
Biotin (D-Biotin)	350 mcg	1,167%
Pantothenic Acid (as Calcium Pantothenate)	25 mg	500%
Choline (as Choline Bitartrate)	550 mg	100%
Calcium (as Di-Calcium Malate and Dicalcium Phosphate)	200 mg	15%
Iron (as Ferrous Bisglycinate Chelate)	30 mg	167%
Iodine (as Potassium Iodide)	150 mcg	100%
Magnesium (as Magnesium Bisglycinate Chelate Buffered Magnesium Bisglycinate Chelate, Magnesium Oxide)	130 mg	31%
Zinc (as Zinc Bisglycinate Chelate)	25 mg	227%
Selenium (as L-Selenomethionine)	100 mcg	182%
Copper (as Copper Bisglycinate Chelate)	1 mg	111%
Manganese (as Manganese Bisglycinate Chelate)	4 mg	174%
Chromium (as Chromium Picolinate)	200 mcg	571%
Molybdenum (as Molybdenum Glycinate Chelate)	25 mcg	56%
Vitamin K2 (as Menaquinone-4) (MK-4)	60 mcg	*
Dehydroepiandrosterone (DHEA)	25 mg	*

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COVID-19

SARS-CoV-2 infection in pregnancy

We in prior issues of *the VOICE* have repeatedly pointed out studies in the literature demonstrating **higher disease severity of Covid-19 in pregnant than non-pregnant women**. Now more detailed information is becoming available, and explanations are offered why that is the case. A multicenter study from the U.S. involving 17 hospitals now reports that, "***among pregnant and postpartum women SARS-CoV-2 infections were associated with increased risk for a composite outcome of maternal mortality and/or serious morbidity from obstetric complications***."[1]

Why that may be the case may have been at least partially explained by the paper of another group of U.S. investigators from Boston and Baltimore. What these investigators reported is that acute severe disease in pregnancy is associated with placental **shedding of placental angiotensin-converting enzyme 2**.[2] This was based on finding decreased placental ACE2 protein, the main receptor for the SARS-CoV-2 virus. The study, thus, points out the importance of studying the dynamics of ACE2 expression on the placenta; and the authors noted the many functional and structural parallels placental and lung tissue share. Practically unlimited placental tissue, therefore, could serve as an excellent substrate for research on Covid-19 pathogenesis.

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Some more news on Covid-19 vaccinations and infertility treatments

In an article, currently only available as a pre-proof in *Fertility & Sterility*,[1] Israeli investigators in analogy to other prior reports from Israel on male infertility[2] and IVF cycles,[3] demonstrated absolutely **no outcome differences between 200 vaccinated and 200 unvaccinated patients in fertility treatment outcomes.** Though this study is reassuring, some caution in interpreting these results should in our opinion be exercised, since reliable demonstration of absence of effects usually in IVF studies, considering variabilities of patient populations, requires larger numbers of study subjects to avoid type 2 errors.

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Omicron's lingering mysteries

In a "feature" article in *Nature* magazine, under the title above used for this comment, **Amber Dance** offers a very concise summary of the many new mysteries the **Omicron variant** has brought to our understanding of the SARS-CoV-2 virus.[1]

With this variant, the virus has dramatically changed: it, as she notes, **enters cells differently and infects lungs differently.** Therefore, the virus has become even more contagious than its predecessors and causes milder disease. She also notes that how Omicron affects the immune system has remained controversial.

What will happen to the virus is, of course, also still undetermined. She quotes some experts who offer two possibilities: one, that Omicron continues to evolve into potentially worse than currently already detected variants BA.1 and BA.2., or that another unrelated variant evolves. Experts agree that **the SARS-CoV-2 virus demonstrates unusual plasticity and, therefore, has different evolutionary options**. Practically this means that **we may not have seen yet the end of the Covid-19 story.**

Current BA.1., BA.2., and the still almost unknown BA.3 Omicron sub-lineage are very well summarized in a recent short manuscript in the *British Medical Journal (BMJ)*.[2]

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Finally, some information on T cell memory

We have repeatedly pointed out our disappointment about how Covid-19 research has been disproportionally concentrating on antibody-mediated humoral immunity, while largely ignoring cellular immunity, which also plays a very large role in immunity to viruses. Since it is now established that antibody-mediated immunity after SARS-CoV-2 vaccinations vanes within months, **to this day no test exists to reliably assess how immune an individual is to Covid-19 because innate cellular immunity cannot yet be tested easily**.

Comes now a group of international investigators who investigated **T cell memory following Covid-19 vaccinations** and report that **the vaccines induce such immunity and that this immunity cross-recognizes virus variants from the initial Alpha to Omicron.**[1]

This is, of course, of considerable importance because the ability to preserve over longer-term a majority of T-cell responses (in contrast to antibody-mediated immunity) may offer **an important contribution by the innate cellular immune system as a second-level defense against diverse variants of the virus**. Only more reason to start investing in more research on cellular immunity!

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1. Tarke et al., *Cell* 2022,185:847-859

Again, is it the Huanan Seafood Market in Wuhan?

In recent weeks we have been witnessing an upsurge of reports, **again pointing toward the Wuhan animal market as the site of origin for the Covid-19 pandemic**, well summarized in two recent articles in prominent journals.[1,2] All proposed evidence for this **old-new theory of origin for the pandemic** stems from three papers, all still at preprint-stages and, therefore, not peer-reviewed, and not yet formally published. They, nevertheless, have attracted considerable attention in science magazines as well as in the lay press.

In principle **for two reasons, we, however, remain skeptical:** The most important reason is, of course, **the secrecy the Chinese government imposed on the whole subject.** What would be the purpose for such secrecy if the pandemic, indeed, originated at the seafood market? And the second reason is that **no transitional animal carrier sold in the market has so-far been identified,** even though multiple animal species have been identified as potential carriers of the SARS-CoV-2 virus. Moreover, all three studies rely on epidemiological data of human traffic at and around the seafood market. With the busy market, however, geographically close to the *Wuhan Institute for Virology*, would one not expect employees at the *Institute* to shop at the market, and would that then not be a logical site for **a secondary human-to human transmission** that would present with **identical epidemiological picture, concentrated on the market, as if an animal-to human transmission had taken place at the market**. Stay tuned, but don't believe everything you read!

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