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IN THIS ISSUE

THE CENTER FOR HUMAN REPRODUCTION

THE VOICE

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With Thanksgiving just around the corner, we here at the CHR for the second year in a row are missing out on the hectic last-minute preparations for our **annual conference in New York City on reproductive biology and endocrinology,** *the CHR* until 2019 co-hosted in collaboration with the *Foundation for Reproductive Medicine (FRM)* on the long weekend before Thanksgiving. In 2020, the COVID pandemic forced cancellation of the conference after lengthy preparations, including recruitment of faculty that already had taken place much earlier. Considering how long in advance lecture schedules must be established to be able to recruit many of the most prominent physicians and scientists in the field, we, wisely, did not even start preparations for 2021. With the COVID pandemic weakening and the recent *Pfizer* announcement of a new oral antiviral drug that reduces risk of hospitalization and death from *COVID-19* by 89% (for further detail, see the *COVID-19* News later in this issue of the VOICE), we suspect that medical conferences, at least to a degree, will retreat from the singular virtual format they have taken on during the pandemic since nothing can replace the person to person contact the ***CHR/FRM*** Conference has become famous for. Our intent is to commence planning for the 2022 Conference immediately after the holidays.

This November, therefore, still offers the opportunity to concentrate on other important issues, many, indeed, also direct consequences of the COVID pandemic which has changed life in so many unexpected ways, including how medical services are provided. Likely the most consequential effect of the pandemic for the CHR has been the interruption of travel, causing for far too long an almost complete cut-off of travel for many of the center's long-distance patients from outside the U.S. Traditionally, approximately one-third of the center's patients have come from outside the U.S. Though with special medical visas some have been able to travel to New York City, for a large majority this has not been possible. With **this month's full reopening of travel to the U.S. for vaccinated individuals,** we expect accelerated demand for services from patients who delayed cycles because of travel restrictions. Considering the newly announced loosening of travel restrictions for COVID-vaccinated patients, **there no longer should be any obstacles to traveling for medical care to the CHR in New York City!** We, therefore, are looking forward to busy year-end.

As always, we in this issue of *The VOICE* cover a variety of issues. Our lead article attempts to explain why so many infertility patients appear misinformed about the risk of having a **chromosomal-abnormal pregnancy.** True **risks are just a small fraction of what most patients believe.** We here correct the numbers and try to trace the source of this rapidly spreading misinformation. Because November is **National Family Stories Month**, we also thought it may be a good idea to report on a few very unusual cases, where the CHR was able to help where other centers failed repeatedly. And, as usually, there is much more, based on questions we receive from patients, and what we read in the literature.

THE REAL AGE-DEPENDENT RISK FOR CHROMOSOMAL-ABNORMAL PREGNANCIES:

Why Are Most Patients So Misinformed?

Patients dealing with infertility are among the best-informed patients in medicine. They, however, often appear enormously misinformed about one of the most important basic biological questions they all are curious about, - ***what is the risk of ending up with a chromosomal-abnormal pregnancy after infertility treatment?*** Especially over the last decade with explosive growth in utilization of **preimplantation genetic testing for aneuploid (PGT-A)**, this question has increasingly moved to the forefront, and we will in a short moment explain why. But before we do that, here are a few basic biological facts that must be understood first: In many species, for example in the mouse, chromosomal abnormalities in embryos are very rare. **In early preimplantation stages of human embryos, in contrast to mice, chromosomal abnormalities are very common;** so common, indeed, as recent research has demonstrated that **presence of chromosomal-abnormal cells at those early developmental stages must be viewed as a normal physiological state**, even raising the question whether chromosomal abnormal cells may not contribute to an embryo's ability to implant.[1] In association with cancer, aneuploidy (the scientific name for chromosomal abnormalities) in cells has, indeed, been demonstrated to be a principal driver of invasiveness (i.e., metastases).[2]

When discussing aneuploidy in early-stage human embryos, it is also important to understand that, based on when an "error" happened in how chromosomes align in a cell, aneuploidy can occur in two different forms: If the error occurs after fertilization of an egg by sperm, but before the first cell division takes place (a so-called **meiotic aneuploidy**), this error will remain present throughout all later cell divisions; in other words, **every cell of this embryo will demonstrate the aneuploidy.**

Such meiotic aneuploidies were believed to represent most chromosomal abnormalities in human embryos. We now, however, know better and consensus exists that **most aneuploidies, indeed, are mitotic**. This means that they arise later in early embryo development at any time during sequential cell divisions. Because they can arise during any cell division, they will be only inherited by cells derived from the cell where the error occurred. In other words, mitotic aneuploidies, therefore, will be only present in **a clone of cell (a small island of cells).**

Mitotic aneuploidies do not increase with advancing female age and, as a recent study by investigators from *Rockefeller University* and the CHR demonstrated **often self-correct downstream from blastocyst-stage.[1] Meiotic aneuploidies, however, do increase with advancing female age and usually do not self-correct.** Consequently, it is absolutely correct that, **as women get older, their embryos will be meiotic aneuploid more and more often and will not self-correct.** At very advanced ages, almost all embryos, therefore, may be aneuploid and it may take a large number of embryos to find one that is **euploid (chromosomal-normal)**.

Here is, however, where a major thought error has found its way into the discussion: **Just because the number of aneuploid embryos significantly increases with advancing female age, this does not mean that the number of chromosomal-abnormal pregnancies increases in parallel. The risk of a pregnancy being chromosomal-abnormal, indeed, increases with advancing age only to relatively minor degrees,** and the reason is the wisdom of nature which has an evolutionary interest that we humans do not produce abnormal offspring.

Nature, therefore, has created **two distinct defense mechanisms to prevent chromosomal-abnormal pregnancies:** (i) **Most chromosomal-abnormal embryos simply cannot implant;** and (ii) those few that breach this first line of defense, face a second barrier to pregnancy success and g**et miscarried relatively early,** often even already as **chemical pregnancies.**

The consequence then is that, if one looks at ongoing pregnancies beyond fetal, heart, there is unquestionably a statistically significant increase in the risk of a chromosomal-abnormal pregnancy with advancing female age, but that risk goes from extremely low in the 20s into the 1-2% range around age 40 and remains in low single digits till age 47. **A Korean study in 2013 likely defined this best by reporting, based on chorionic villous sampling (CVS) and amniocentesis, a 1.37% risk at age 36 and a risk of 6.67% at age 47.**[3]

One therefore must clearly differentiate between risk of a chromosomal abnormality in a given embryo and the risk for a chromosomal abnormality in an established and ongoing pregnancy after positive fetal heart, with the former at age mid-40s in the literature reported to be in the 80-90% range, while the latter is still in relatively low single digits. Yet, this differentiation is frequently not made.

When asked what they thought at age mid-40s the expected presumed risk for a chromosomal abnormality was, the answer we receive almost uniformly is 80-90% which, of course, is ridiculous! Because these numbers have been known for decades, **where this very obvious and rather substantial misdirection comes from, is difficult to understand.** We hear those false numbers, however, quoted more and more frequently and, when trying to determine the source, we not infrequently are told that **these are the numbers patients were provided during genetic counseling for PGT-A.** Though we hope that this is not the case, it would not surprise since avoidance of miscarriages caused by aneuploid pregnancies, is really the only remaining argument left for proponent of PGT-A utilization in association with IVF since all other claims, like improved implantation, pregnancy and live birth rates have been clearly debunked. And even whether PGT-A reduces miscarriages is highly questionable.

The real message to remember, therefore, is that **even at very advanced female ages, the risk of a chromosomal abnormality in an ongoing pregnancy after positive fetal heart is quite low.** Moreover, even those rare cases can now very early in pregnancy easily be diagnosed through **cell-free DNA testing** in blood.

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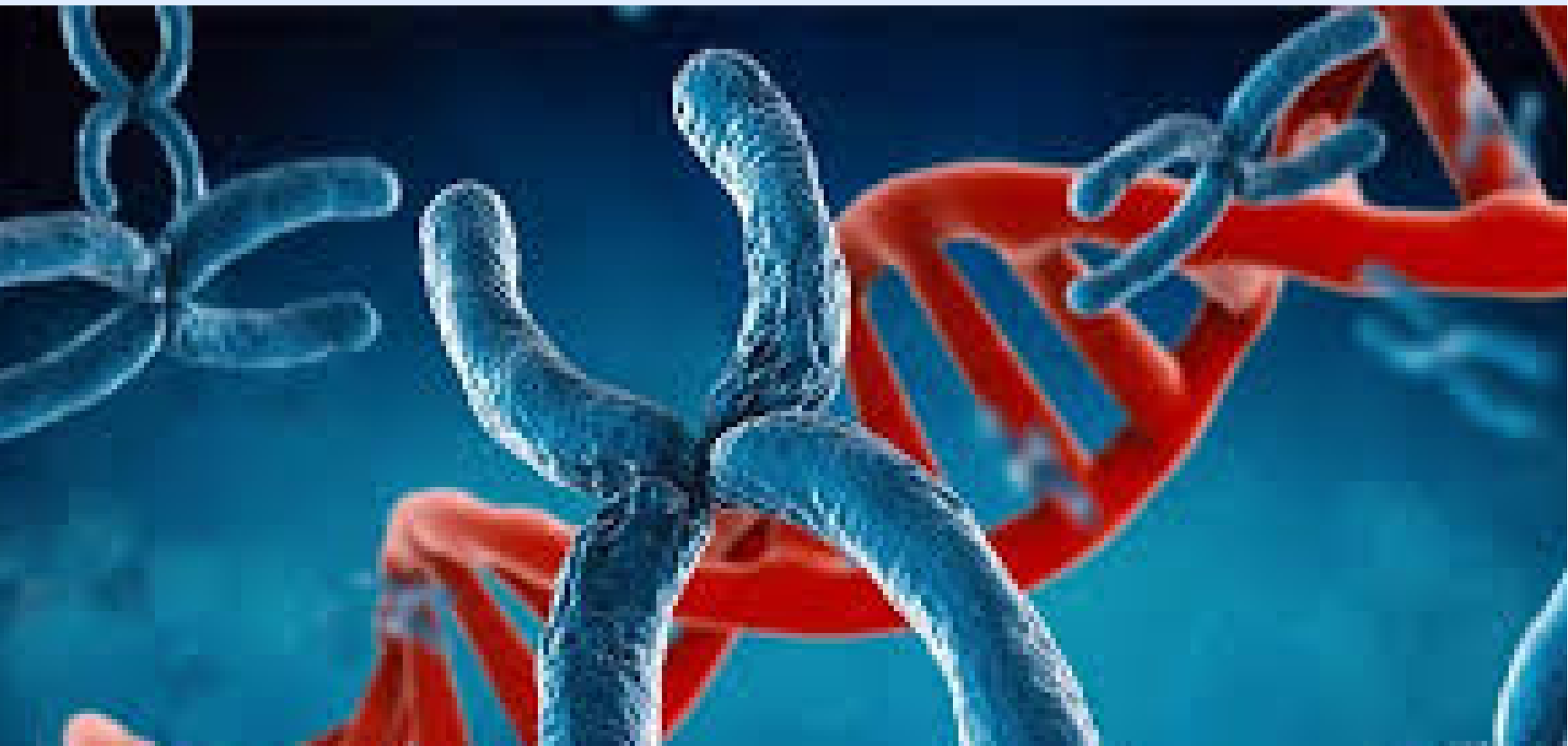

HOW THE CHR BUILDS FAMILIES EVEN WHEN OTHERS FAIL

A noted in the introduction section of this newsletter, November is **National Family Stories Day**. Attempting to demonstrate that **creating "family stories," is what the CHR does every day,** we, therefore, here present a few recent experiences at the CHR that are somewhat outside of the ordinary and bear witness to the fact that when things don't work out elsewhere, and before giving up or being prematurely pushed into egg donation, it may be worthwhile to contact the physicians at the CHR.

WHEN PARTNERS ARE GENETICALLY TOO SIMILAR

Recently a couple from another state reconsulted with the CHR after almost five years of absence, when, the woman in her late 30s, was discharged from the CHR with a **twin pregnancy after IVF**. The couple had initially presented to CHR a few months earlier after they had failed three IVF cycles at a local IVF center.

They also reported two **chemical pregnancies** (i.e., very early miscarriages before a pregnancy could be seen on ultrasound). Moreover, they reported that whenever these short-lived pregnancies happened, the female developed a **rash on her neck and upper chest.** Because of these very early miscarriages and the reported rash,

CHR's physicians suspected that this couple may have an immune rather than fertility problem. The reason was that CHR investigators in 2011 reported a group of women who with their pregnancies developed exactly this kind of a rash and repeatedly miscarried their pregnancies as soon as the rash appeared.[1]

In further investigating this group of patients, they made several interesting discoveries: First, most of these women demonstrated evidence of a **hyperactive immune system** (most often evidence of **autoimmunity**); and, second, most of these couples were found to be "**genetically too similar.**"

What that means is that the couple, possibly would be excellent organ donors for each other because organ donation requires good **histocompatibility in so-called HLA loci;** but **for pregnancy, too much HLA compatibility is bad and has been associated with significantly increased miscarriage risk.**[2]

The CHR's physicians, therefore, decided to pursue the possibility that this couple may have more of a miscarriage than an infertility problem and initiated an **in-depth diagnostic miscarriage work-up** in addition to routine infertility diagnostics.

Low and behold, **they were found to share three Class II HLA loci** and, consequently, had to receive **immunosuppressive treatment** in order prevent the female's immune system from rejecting the fetus. Such treatment was initiated at a relatively low level because the female did not demonstrate significant autoimmune abnormalities upon testing, and she did not conceive in her first IVF cycle.

Treatment levels were increased, and **the patient conceived in a second cycle**, went to positive fetal heart, and was discharged into obstetrical care. **Unfortunately, she, however, miscarried** a few weeks later and returned to the CHR for a third IVF cycle. This time **she conceived twins** and received **aggressive immunosuppressive treatment for almost 3 months into her pregnancy.**

She went to term and was delivered by Cesarean section because the patient developed around 38.5 weeks mild **preeclampsia**, a condition also associated with excessive Class II HLA sharing between partners.[3] Having still 10 embryos cryopreserved at the CHR from prior cycles, the couple represented recently with the desire for another pregnancy, though this time they want only a singleton pregnancy, - and who can blame them?

LESSONS TO BE LEARNED:
(i) Getting a detailed past medical history is of crucial importance.
(ii) Infertility can also be caused by miscarriages.
(iii) A correctly functioning maternal immune system is crucial for establishment and maintenance of a normal pregnancy.

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HOW UNEXPLAINED IS "UNEXPLAINED INFERTILITY"?

Though it sounds like an oxymoron, "**unexplained infertility**" is to this day considered a real infertility diagnosis, with the literature claiming that a whopping **30% of all infertility is unexplained**.[1] In contrast to most colleagues, the CHR's physicians already for decades have made the argument that **unexplained infertility does not really exist;** it only depends how deeply a diagnostic work up is pursued.[2]

We here want to reemphasize this point by briefly providing a summary of two recent cases CHR physician encountered that reemphasize this fact. They then diagnosed women after many failed IVF cycles elsewhere with a rare but easily to treat medical problem that had been missed before. Because these cases are subject of a recently submitted paper, we cannot go into too much detail. Therefore, only so much: In the same year, **two women presented to the CHR with a diagnosis of "unexplained infertility." The first** was 34 years old and had failed 2 IVF cycles at another center. Upon diagnostic evaluation CHR's physician were struck by how low her androgens (male hormones) were.

Moreover, her **estradiol**, produced by follicles, was undetectable (suggesting no follicle development), as was her **ACTH** hormone, produced by the pituitary gland and controlling the adrenal glands.

The patient's medical history furthermore revealed that because of persistent skin rashes she was on long-term treatment with a very potent **topical steroid.** It turned out that these steroids suppressed her ACTH and, with it, interrupting **androgen hormone production in adrenal glands.** With androgens significantly falling, **follicles stopped growing,** because follicles require good androgen levels at small growing follicle stages between secondary and small-antral follicles.[3] With no follicles growing, estradiol production ceased. **Once the patient was taken off her steroid cream, her ovarian function fully recovered.**

The second 40-year-old patient also presented with "unexplained infertility," after failing 5 IVF cycles at other centers. Like the previous patient, she had v**ery low androgens** and **no detectable estradiol** at time of presentation. She, too, was on steroid medication, this time on an inhaled steroid for severe asthma. Once taken off her steroid, she, too, fully recovered her ovarian function.

We, here present these two cases because we are unaware that ever before **exogenous corticosteroid treatments** have been reported to lead to **secondary ovarian insufficiency (SOI)** because of failing androgen production in adrenal glands. The most frequent cause of adrenal androgen insufficiency is believed to be **autoimmunity,**[4] and this diagnosis is also frequently overlooked.

Moreover, as CHR's investigators pointed out before, there are several other diagnoses that are frequently missed, leading to the oxymoronic diagnosis of "unexplained infertility." Among the most frequent ones are **failure to diagnose tubal disease** on hysterosalpingography and **immunological infertility**.[2]

LESSONS TO BE LEARNED

(i) A detailed medical history is essential.
(ii) The assessment of androgens, usually not part of a routine diagnostic work-up in infertile women, can be very important.
(iii) "Unexplained infertility" does not exist. If this diagnosis is raised, insist on a more thorough diagnostic work up or come to the CHR.

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PATIENT TESTIMONIAL

“The CHR team is a wonder: attentive, organized, and always giving you the information you need when you need it. As a doctor, and someone who believes in science, Dr Gleicher and his team are the real deal, which for me means that they don’t treat your reproductive system like a specialty car that needs fixing or fixing up, they understand it in the context of the entire body first and then through the specific lens of each patient. They know what they don’t know, which is so important in a field this new, and this allows them to really be at the cutting edge. They are always kind, compassionate, and never make false promises. I have complete confidence in them and am so grateful they helped us bring Alma Anne into the world! Thank you ever so much CHR!”

MORE PATIENT TESTIMONIALS

Dr. Gleicher,

Thank you! We wouldn't have our beautiful daughter without all of the hard work + genius of you and your staff. CHR will forever be in our hearts.

Hope you are well!

Thank you!

-CHR Patient

I reached out to CHR because I'm 45 and after 8 months of trying, was looking for assistance in getting pregnant. After my phone consultation with Dr. Gleicher, I was sent a list of lab appointments, (via their portal), I had to complete extensive blood tests and other requested information to determine the next steps. This is all VERY normal. Most healthcare offices have their portal as a way of communicating. I read someone's review complaining about having to "take computer classes" to be able to communicate with CHR??? People will complain about anything if they didn't get their expected outcome. Anyway, once my blood tests came back, Dr. Geicher notified me that my FSH numbers were really good and started me on his recommended supplements to improve egg quality/quantity, in preparation for IVF. After 3 months of being on his supplements, I got pregnant naturally. Dr. Barad and Dr. G closely monitored me for the first 10-12 weeks, (with weekly ultrasounds), making sure everything was going as it should, and Marijana, (who assisted Dr. G and Barad), would constantly check-up on me when I would forget to send my weekly updates in the portal. Not once did I feel like I was "just another patient," even though I was. With each visit and every interaction, I felt I was not only working with very intelligent people but also that they cared. Once they confirmed my pregnancy was going well, they helped me decide on an OBGYN in my network and released me. TBH, I was very scared to leave because I became dependent on them, and their knowledge and wasn't sure if my next Dr. would be on their level. My experience couldn't have been a better one, not because I got the outcome I wanted, but because I felt extremely confident, from the initial phone call with Dr. G to the very end, that I was dealing with the "experts" in this field. They don't tell you on the first call that you need an egg donor, which most Dr's would do. They assess your situation and decide the best course of action for you. I'm now 4 months pregnant and even though it happened naturally, I don't think it could have ever happened without the guidance of CHR. More people need to know about this place. Period.

WANT TO SUBMIT YOUR STORY?

email us at
social@thechr.com

Meet David Barad, MD, MS, FACOG

David H. Barad, MD, MS, FACOG, is an OB/GYN and board-certified reproductive endocrinologist serving patients at the CHR. He has published extensively in the field and is a fellow of the American College of Obstetricious and Gynecologists and a member of the American Society of Reproductive Medicine, Society of Reproductive Endocrinology and the Endocrine Society.

In 1999, he was recognized by the American Infertility Association for his continuing dedication and support to individuals experiencing infertility. In May 2003, Dr. Barad was awarded a Masters of Science in Clinical Research Methods at the Albert Einstein College of Medicine.

WHAT PATIENTS ASK ABOUT

We in this section address several questions which in recent weeks and months appear to have gained special interest. If you wish to contribute to this section, please send your questions to social@thechr.com

The use of artificial intelligence (AI) in infertility practice

Where AI utilization in infertility practice stands apparently does not only interest many of our patients but was also a main subject of this year's annual meeting of the *American Society for Reproductive Medicine (ASRM)* that took place last month in Baltimore, MD. We will return to some of the presented abstracts later in this newsletter under "News from ASRM 2021." Here we, however, want to address a few principal issues about AI utilization in medicine in general, concentrating especially on the hype we have been observing to develop around the subject.

We repeatedly have made in these pages the point that **a good-sounding hypothesis does not mean that this hypothesis will be found to be correct.** Consequently, just because a hypothesis sounds "brilliant," for ethical, but also for practical reasons, **it should not be offered in routine clinical care, - unless and until sufficient evidence has been generated in publicly pronounced investigative efforts to validate the hypothesis.**

Unfortunately, this is not what happens in medicine all the time, especially when it comes to introduction of tests that do not require prior regulatory approvals by local or federal government agencies, like the Food and Drug Administration (FDA). Consequently, **ever increasing numbers of tests are offered in clinical practice (and often directly to consumers) that remain unvalidated yet are freely offered as commercial products.** Though a medicine-wide problem, **reproductive medicine has been especially badly affected,** as some of these tests have become integral parts of IVF practice. To list just a few: **Preimplantation genetic testing for aneuploidy (PGT-A)** is, likely, the most telling example[1] and has in these pages been repeatedly addressed. Other tests include the **ERA (Endometrial Receptivity Analysis),** in several studies demonstrated[2'3] not to improve IVF outcomes, yest still widely advertised and promoted.[4]

Now the field is threatened by another onslaught of tests, claiming benefits from AI when existing evidence is, at best, insufficient to claim outcome benefits. Good examples are **AI analyses of time-lapse** observations of embryos in culture. Several start-up companies have already formed around the idea of selecting "best" embryos from among embryos cultured to blastocyst-stage, based on AI of time-lapse observations on large numbers of embryos. In this context it is, however, worthwhile to remember that ca. a decade ago several start-ups formed around the concept of time-lapse embryology and **not a single time-lapse study ever was able to demonstrate any significant outcome benefits from time-lapse observations.**

It is, therefore, noteworthy that the commercial marketplace is already "offering AI." For example, a company called ***Future Fertility,*** offers a service called ***Egg freezing with Violet™*** as an **AI-driven egg assessment tool for young women who wish to use egg-freezing as a fertility preservation tool.** The company claims that their product offers *"the first AI-powered egg assessment tool that will help patients gain insight into the quality of the eggs they are freezing."* The company further represents that *"their clinically proven software solution can detect patterns in oocytes that the human eye cannot see, with over 20% more accuracy than embryologists."* [5]

What the company, however, does ***not*** state is much more interesting than **what it say. Will *Violet*™ make any outcome difference for the patient who freezes her eggs** (of, course, except for making expensive egg-freezing even more expensive)?

We chose this example of **overselling AI in reproductive medicine** because the CHR's investigators, probably more so than any other investigators in the world, have for years made the argument that, **if embryo selection among a single cycle cohort of embryos is at all feasible, it must go upstream and include egg quality from which an embryo is derived.** They made this point already in a 2015 publication[6] and, just this year, offered further evidence in two additional papers.[7],[8]. The CHR, therefore, better than anybody else knows **how fragile the concept of embryo selection is at its basis** and, therefore, **how far away AI is at the present time from really becoming a commercial product that will be able to improve IVF (and in this instance egg-freezing) outcomes.**

Our concerns, therefore, are that, like PGT-A and genetic testing in general, the ERA and many other useless and sometimes even harmful tests before, **AI will become the new "fashion of the moment," adding more and more cost to an already prohibitively expensive IVF process without improving IVF outcomes.**

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Male infertility in the age of COVID-19

Probably never before has a virus (and the vaccine against it) caused as much commotion and **concern about human fertility** as the SARS-CoV-2 virus. But what is even more fascinating is that the rumors regarding effects on male fertility are almost as pronounced and weird as the rumor mill surrounding female fertility. In other words, **something in the COVID-19 pandemic got the world seriously concerned about male fertility** and we have been unable to figure out why.

Since from the earliest days of the pandemic we have in this newsletter extensively written on effects of the virus (and vaccines against it) on female fertility and especially pregnancy, it seems high time to also address briefly what has been happening to male fertility because of COVID-19. And there is really not much to report, considering all the crazy rumors that have been circulating on the Internet.

Let's first start with the question, **what happens when a male catches the virus?** Since men, at least for the moment cannot yet conceive, they do not face **increased disease severity from pregnancy, as women do. That pregnancy turns COVID into a more severe disease (as also the flu does), is immunologically a highly interesting observation** because it strongly suggests that pregnancy induces pathways in a woman's immune system (tolerance pathways which make the 50%-genetically "foreign" fetus invisible to the maternal immune system) which also facilitate survival of the SARS-CoV-2 virus in the host.

Men do not have to deal with this weakness of the immune system; yet, overall, **COVID is a much more serious disease in men than women**; and we still do not know why?

High fever in many medical conditions may affect male infertility. Because men steadily produce semen into advance ages, **sperm production is subject to environmental insults**. A good example is that high fever can interrupt the production of fresh sperm. Consequently, following high fevers, ca. 8 weeks following the fever period, sperm counts in ejaculate may be temporarily low. That also, of course, would apply to males who have high fever due to a COVID infections. As the temperature normalizes, the patient will, however, start recovering in his sperm production and, usually, within 1-2 months sperm parameters have normalized in counts and other semen analysis parameters.[1]

Though the SARS-CoV-2 virus has been isolated from semen,[2] most reports suggest that this is only a very rare finding. Since usually not penetrating the testicular barrier, there is little risk that semen may be infected and that the infection, therefore, can be transmitted sexually and/or could affect fertility treatments. In short, if a male survives COVID-19, his fertility will likely return to normal. Moreover, vaccinations against the virus have not shown effects on semen parameters.[3]

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A PIECE OF MY MIND

by

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Usually not a big fan of **Ross Douthat's** writings as editorial columnist at ***The New York Times***, I was not only surprised but deeply moved by a piece he published in *The Times* on Sunday, November 7, 2021, titled, *"How I Became Extremely Open-Minded."*[1] Considering that the author, like most of this newspaper's editorial opinion writers, is fervently liberal, it was the title of the article that attracted my curiosity because I assumed that, as a liberal commentator, he would consider himself to be born an "extremely open-minded" individual. An acknowledgment in the title that he was not, and that something happened that finally made him see things clearer, was a brilliant signal he sent to readers that this, likely, was an unusual and atypical opinion piece, worthwhile their attention. And that it was!

He in this piece for the first time goes public about a multiyear health struggle he has been facing with **Lyme disease** and in the process not only in deeply moving ways describes his own experiences during this journey, but also astutely how the medical establishment failed him. It is this latter argument that led me to this commentary because his observations are highly relevant for what is going on these days in all of medicine, unfortunately including reproductive medicine.

Douthat brilliantly describes how the **"rational him"** concluded that clinically *"he was bad but not that bad"* to subscribe to treatments that appeared non-sensical and clearly out of the mainstream and how the **"needy him,"** nevertheless, succumbed to some of the most paradoxical treatments, including one called the **Rife machine**, named after **Royal Raymond Rife**, and American inventor who in the 1930 claimed the discovery of an oscillatory rate that would shatter various pathogens in the body (in this case presumably **Borrelia burgdorferi**, the **spirochete**, responsible for Lyme disease).

Medical entrepreneurs then took up the idea and started producing machines that generated vibrations at different frequencies with the promise that they would shatter infectious organism causing whatever infectious disease (in this case Lyme disease). Though after reading up on the subject convinced by his "rational him" that all of this was **"quackery and snake oil,"** his lengthy suffering in the end, however, gained the upper hand to his "needy him," and he purchased the machine. Among 873 preprogrammed channels for various medical conditions, 2 supposedly addressed Lyme disease, each containing innumerable frequencies.

And, surprisingly, it worked!

Still conscious of his "rational him," he even performed little experiments, blinding himself to allegedly "working" frequencies and his body still responded favorably when he used those frequencies by others in the community (in intellectual crowdfunding) noted to have worked. The Rife machine, therefore, became an integral part of his recovery.

In somewhat hesitantly reporting this experience in the editorial pages of *The Times*, knowing that it would be interpreted as a *"classical psychosomatic placebo effect,"* and he be viewed as, *"poor Ross, taken in by the quacks,"* he made two important points: First, he felt obliged to communicate, *"what its like to fight for your health for years,"* and did not consider it right, *"to leave the weird stuff out."* But the second point he made really became the impulse for this essay because Douthat felt obliged to communicate how *"falling through the solid floor of establishment consensus (by which he felt abandoned) and discovering something surprising underneath, is extremely commonplace."*
As scientists who conduct research we instinctively know this, - or at least should know because often it is exactly that surprising something underneath the existing consensus that we are searching for in conducting research; yet having lived through almost two years of a pandemic, **where establishment consensus not only has reigned supreme but has made large swaths of the population feel equally abandoned by the medical establishment to how Douthat felt in his singular battle with Lyme disease,** one starts understanding the striving we have witnessed in the population for a Rife machine against the SARS-CoV-2 virus.

It, thank God, is at the core of human nature to search for new cures and this search will increase in urgency as time passes under an ineffective consensus regime.

Considering how many important discoveries in medicine were made by accident and/or by outsiders who, obstructed in the peer-review process by prevalent consensus, often could not get their papers published in timely fashion further emphasizes this point. Douhat astutely interprets these strivings as follows: *"Interaction between (differing) believes instilled by these experiences and the skepticism they generate from people for whom the floor has always been solid is crucial to understand cultural polarization in our time."*

Solid floors exist only in religions and ideologies. In every other sphere of life, floors constantly cave, to bigger or lesser extend revealing unexpected findings.
Consequently, just as paradoxical as it appears that a progressively more areligious world is becoming increasingly more ideological, so is it almost comical to observe the allegiance politicians on left and right have been swearing during the COVID pandemic to **"following science."**

One cannot be more anti-scientific than to believe in an absolute truth; yet demand for consensus is exactly what we are witnessing more and more in national politics as well as medicine.

As Douhat concluded in his essay, adapted from a forthcoming book "*The Deep Places: A Memoir of Illness and Discovery*" which I cannot wait to read, his seven-year experience with a severe chronic disease has made him "*more open-minded about the universe and at the same time more skeptical about anything that claims the mantle of consensus.*" Everybody in medicine, including colleagues in reproductive medicine, should follow his example. **There is especially much to be skeptical about in current IVF practice!**

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NEW PUBLICATIONS FROM THE CHR

Gleicher N, Orvieto R. Transferring more than 1 embryo simultaneously is justifiable in most patients. Reprod Biomed Online. Sep 20:S1472-6483(21)00401-6. Doi. 10.1016/j.rbmo.2021.08.0

Reproductive Biomedicine Online, one of the more popular medical journals in the infertility field initiated a new by the editors of the journal invited series of publication called **Countercurrent Contributions.** The intent of these papers is to challenge currently prevailing opinions.

CHR's Medical Director and Chief Scientist, **Norbert Gleicher, MD**, was invited to address the currently widely practiced concept of **elective single embryo transfer (eSET)** based on his and the CHR's longstanding opposition to the concept of eSET for all. Since **Prof. Raoul Orvieto** from the *Tel Aviv University Sackler Medical School Faculty* is known to share in this opinion, Dr. Gleicher invited him to join in the writing of the manuscript.

Though Gleicher in collaboration with other colleagues from CHR and from other institutions over many years has published several articles on the subject explaining why **routine eSET for all patients** should be abandoned, this manuscript adds some interesting updates to the subject. The original reasoning has remained the same: (i) **Identical treatments for all patients in medicine almost never make sense** and, with increasing emphasis on individualized medical care in all of medicine, make less and less sense now. (ii) Indisputably, **eSET reduces pregnancy chances in comparison to 2-embryo transfer.**

.(iii) Therefore, **eSET must offer a compensatory benefit** to make it a worthwhile treatment. (iv) That **compensatory benefit has been alleged to be risk reduction for mother and offspring** since 2 embryo transfers create twinning risk and twin pregnancies carry higher fetal as well as maternal risks. (v) Though eSET, indeed, reduces twin pregnancies, **a real compensatory benefit, however, does not** exist because most risk comparisons in outcomes between singleton and twin pregnancies compared one singleton to one twin pregnancy. This is, however, an incorrect statistical comparison because outcomes differ. For a proper statistical comparison, one twin pregnancy must be compared to two consecutive singleton pregnancies and, if this is done, significantly increased risks for twin pregnancies basically disappear.

Even though data against routine use of eSET appear indisputable, like in other areas of IVF practice (for example, **PGT-A**) the **routine medical practice of eSET continues.** The two authors, therefore, argue in their paper that worldwide **continued practice in face of contradictory evidence can only be interpreted to mean that expert opinion in medicine still often outweighing evidence.** In other words, as elsewhere discussed in this newsletter by The CHR's Medical Director and Chief Scientist, Norbert Gleicher, MD, **consensus opinions are not always correct.** Considering over especially the last decade the **emphasis of opinion leaders in medicine (reproductive endocrinology included) on evidence-based medicine,** one cannot but wonder how serious this effort really is? Apparently not too serious, especially when evidence contradicts consensus opinions. **Expert opinion in the medical evidence-hierarchy representing the lowest level, therefore, still appears to rule medical practice and nowhere more so than in reproductive medicine.** No wonder then that, like in increasingly many medical journals, the *ASRM's* primary medical journal allocates over a third of its pages in every issue to expert opinions

Interesting news in clinical reproductive medicine

More on frozen eggs

The October *VOICE* in very much detail addressed many important points regarding egg-freezing. Here is a little bit of a follow-up from the most recent literature. While by the ASRM no longer considered "experimental," **social egg-freezing**, recently given the new acronym **"planned" egg-freezing, by the CHR is still considered an experimental procedure**. The principal reason for CHR's decision to maintain this procedure under and experimental mantel is that **outcomes cannot yet be predicted with adequate accuracy.** In other words, when a patient requests fertility preservation via egg freezing, we still do not know how many eggs a woman must cryopreserve at a given age to have an X% probability of delivering at least one child from use of those eggs.

Medicine in general considers medical intervention to be "experimental" until patients can be given relative accurate predictions about outcome chances because how would they, otherwise, be able to offer informed consent? A recent study in *Fertility & Sterility* again reemphasized this point by confirming what has been suspected for quite some time:[1] (i) **At what age eggs are cryopreserved matters; the earlier the better** since older eggs lead to progressively lower pregnancy rates. (ii) This, in turn, means that women who want to assure an X% chance for one birth **must freeze increasing numbers of eggs as they age**. (iii) As one also would expect, **with advancing female age at conception, "good" perinatal outcomes declined**. Available information is thus improving; but this manuscript confirms that **there is still substantial additional knowledge to be acquired before planned egg-freezing in the CHR's opinion can be considered a no-longer experimental procedure.**

Eric Flisser, MD, a physician at *RMA-NY*, in a well-thought-out accompanying commentary raises interesting additional questions.[2] He, for example, asks **why IVF outcomes of frozen eggs from supposedly fertile young women not exceed those of age matched infertile patients**, suggesting that fertility preservation through egg-freezing ***"converts fertile women at time of oocyte cryopreservation into infertile versions of their younger selves."*** He also noted the unusually short time (1-2 years) between cryopreservation of oocytes and their use in many patients, asking the astute question whether this really represents fertility preservation or is just **a surreptitiously performed mode of infertility treatment** under the name "short-term" infertility preservation. There is more to this excellent commentary, which we recommend to be read in its full length.

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And more on PCOS

We in these pages quite often complained about international **diagnostic criteria for the polycystic ovary syndrome (PCOS) to this day not including anti-Müllerian hormone (AMH)**. But the CHR in this regard is not alone. Several authors have in recent years recommended that elevated AMH levels become such a diagnostic criterion.[1,2] A recent collaborative study by investigators from several European countries demonstrated that AMH levels are robust in determining **polycystic ovarian morphology (PCOM)**, which is a criterion for the diagnosis of PCOS.[3] In the introduction the authors remind us of PCOS being a very frequent condition with a prevalence of 8-13% in the population but with only approximately 30% of cases diagnosed. Simple and effective diagnostic tools, therefore, would be welcome. **Failure to diagnose is especially common among phenotype-D PCOS** patients who do not have any of the external stigmata of the phenotype-A (the by far most frequent phenotype also called the "classical" phenotype) and after age 35 only rarely suffer from anovulation.

But any such efforts must make sense. Based on seemingly satisfactory ROC curves, the authors suggested, **to find consensus around a single level (in this case an AMH level of 3.2ng/ml (23pMol/L).** This, however, makes little sense, considering that AMH levels change with age, and this level, therefore, means very different things at ages 15, 25, 35 and 45. That AMH, like other hormones, must be viewed adjusted for age, is widely accepted. **Whenever AMH will be included among clinical criteria to define the PCOS, the hormone must, therefore be age specific.** Curiously, an accompanying editorial also argues for a universal AMH threshold, this time of 4.0 or even 4.5 ng/mL (28.5 or 32.0 pMol/L).[4] **Strange, how even experts cling to the concept of universal hormone threshold that are applicable to all ages!**

In the same October issue of *Fertility & Sterility,* investigators from Taiwan explored a different PCOS-related theme by demonstrating that **cysteine-cysteine motif ligand (CCL) 5 levels and cysteine -cysteine receptor type 5 (CCR5) expression in peripheral mononuclear cells (MNCs) and adipose tissue are associated with hyperandrogenism and insulin resistance in PCOS.**[5]

Mr. PCOS in the U.S., **Ricardo Azziz, MD, MPH, MBA,** then offers an insightful commentary[6] summarizing the study as suggesting how **chronic subclinical inflammation** may play a role in previously reported adipose tissue dysfunction and hyperandrogenism in PCOS.[6] He, also astutely observes that this study in the process also offers new evidence that **inflammation may play a bigger role in infertility than is widely appreciated.**

This is a point the CHR's investigators have been making for several years. One also must recognize that inflammation often is asymptomatic. Clinical evidence for existence of inflammation, therefore, can in asymptomatic cases only be obtained by checking inflammatory markers, like **sedimentation rate (ESR), C-reactive protein (CRP)** and **Interleuin-6 (IL-6).** Within this context it is also important to note that inflammation is only one among several possible reflections of a **hyperactive immune system** and **hyperactive immune systems are also associated with increased miscarriage risk.**

One more final point that, unfortunately applies to many, if not most PCOS publications must be made: Neither authors of the paper nor the commentator addressed the fact that PCOS is not one unified condition but, as the term "syndrome" indicates, represents an amalgam of several conditions, called **phenotypes (A, B, C and D)**. Among those, all except for phenotype D (after age 25) are hyperandrogenic. **Phenotype-D, however, between ages 25-35 is usually normo-androgenic** but after age 35 even become hypo-androgenic. In this phenotype, hyperandrogenism, therefore, cannot be considered linked to a hyperactive immune system; yet phenotype D has by far the highest association with a hyperactive immune system among all PCOS phenotypes.[7,8] We, therefore, suggest caution in uncritically accepting the conclusions of the paper and the attached commentary. There is still very much to be determined when it comes to PCOS!

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And, of course, more on PGT-A

We in this issue of *The VOICE* discuss an unusual number of articles from the latest issue of *Fertility & Sterility* which, overall, was likely the journal's most interesting issue in several years and in a series of articles also addressed **preimplantation genetic testing for aneuploidy (PGT-A)**, - the chromosomal testing of embryos prior to their transfer into uteri. That this is a constant topic of prominence at the CHR and, therefore, in *The VOICE*, will by now be obvious to all readers of this newsletter; but we never commented very much on PGT-A related papers in *Fertility & Sterility* because we always felt that **editors of the journal were biased toward submissions that favored PGT-A and, at the same time, discriminated against opponents of the procedure.**

That, even after a senior editor change, this unfortunately appears still the case, was again at display when **three invited articles about PGT-A were uniformly assigned to strong proponents of PGT-A in the past** [1–3] and no opposing voice was offered the opportunity. Meant to address the interpretation of so-called "mosaic" testing results of human embryos after PGT-A, it is important to note that the *ASRM* only relatively recently released an official guidance on the interpretation of "mosaic" results[4] which, at the initiative of members of the CHR's staff, was strongly rebutted by a spontaneously coalesced group of researchers from all over the world.[5]

But then something funny happened, when two especially ardent proponent of PGT-A in the past, **James A. Grifo, MD, PhD** from *NYU's Prelude Infertility Center* and **Nathan Treff, PhD,** from *Genomic Prediction Inc* and *Rutgers University,* both in New Jersey, suddenly, in their respective pieces sang to a very different tone in comparison to their many earlier printed statements. But let us address this three-manuscript section in sequence.

The first article by Treff and Marin[1] already in the abstract defines PGT-A as ***"one of the most controversial topics in reproductive medicine"*** and includes among unresolved issues, ***"what patient populations, if any, benefit from PGT-A, the true frequency of chromosomal mosaicism, whether embryonic aneuploidies self-correct, and how practitioners manage embryos designated as 'mosaic.'"*** In addition, the authors note that, ***"uninformed introduction of 'mosaic' diagnoses has led to a significant reduction in the accuracy of PGT-A."*** They go on by saying that, ***"the inclusions of 'mosaic' diagnoses results in overestimation of the presence of chromosomal abnormalities*** (and) ***false-positive 'mosaicism' undoubtedly plays a significant role in the failure to demonstrate improved outcomes with PGT-A."***

Those are remarkable position changes for Nathan R. Treff, PhD (and Diego Marin, PhD) who in the past has been one of the most outspoken proponents of utilization of PGT-A in association with IVF,[4] and rather vigorously has clashed with CHR's Medical Director and Chief Scientist, **Norbert Gleicher, MD**, in public debates on the subject. What remained missing is, however, the logical next step after finally reaching all these opinions, - namely asking the question publicly, **why is PGT-A still routinely performed in association with IVF?** According to these authors' paper, over 40% of IVF cycles in the U.S. already involve PGT-A. Others claim even higher percentages.

Viotti et al, in contrast, conclude that the status of current knowledge suggests that, ***"specific features of "mosaicism" detected via PGT-A are associated with variable clinical outcomes*** (and that therefore) ***mosaicism should be considered for improved embryo selection."***[2]

The authors of this manuscript are likely correct that it should become possible to establish **a transfer hierarchy for alleged chromosomal abnormalities after PGT-A**, based on pregnancy and live birth chances.

CHR investigators, indeed, recently submitted a manuscript for publication describing pregnancy and live birth rates in over 50 transfers of chromosomal-abnormal embryos where other IVF centers had refused their transfer and, in many cases, even had advised patients that their only chance of conception left was **egg donation. Pregnancy rates were in the mid 30s and live birth rates in mid-teens** and there, indeed, was a potential hierarchy evolving, though much larger numbers are required to really do so.

But that is not even the question because what really must be asked are two basic questions: (i) **What are really the risks of transferring human embryos untested?** And the answer at current knowledge levels is clearly, **minimal to none.** (ii) **At what hierarchy point would an embryo go from "transferrable" to "disposal?"** We would argue that **such a point does not exist** because most patients who have tried for years to conceive and/or have bene advised that motherhood was only achievable through egg donation would, of course, transfer embryos with even only minimal birth chances rather than dispose of low chance embryos. **What then is the purpose of a transfer hierarchy?**

The third paper in the series by Besser et al[3] had James A Grifo, MD, PhD, as its senior author who is a well-respected fertility specialist in NYC who over the years has demonstrated raw emotional attachment to PGT-A and its forerunners with more heart and soul than anybody else in the field. **Some of the acknowledgments made in this manuscript, therefore, came as a really surprise.**

First, these authors acknowledge that, **to them, births of healthy offspring from transfer of by PGT-A as chromosomal-abnormal diagnosed embryos came as a surprise.** Though they withheld credit for the first reported healthy births from the CHR and collaborators who reported such births first[5] and gave it to Italian colleagues who reported such cases only a few weeks later,[6] we view this as a considerable concession because the NYU-group for the longest time refused such transfers to their patients and only very recently started offering them, though limited to so-called **low-percentage mosaics** (a topic for another day, though the **CHR does not accept the senseless differentiation between grades of alleged "mosaicism"**).

Second, the authors acknowledge that PGT-A is offered commercially as an unvalidated test by noting that, ***"results may vary based on which laboratory performs the analysis."*** CHR's investigators made this point already in 2015.[5] They furthermore acknowledge that the primary purpose of PGT-A to this day is, ***"to maximize chance of implantation and reduce chance of spontaneous abortion."*** ." If that is the case, then **PGT-A has failed in over 20 years** of utilization because not a single professional organization in the world (except for the official "PGT-A Union," the *Preimplantation Genetic Diagnosis International Society, PGDIS*) ever concluded that PGT-A improved any IVF outcomes. Most importantly, the authors, however, acknowledge by now healthy euploid births in the thousands after transfer of embryos by PGT-A described to contain aneuploid cells and, at least until recently, therefore destined for destruction. They, indeed, also point out that **not a single abnormal birth has occurred because of such transfers and not even a single pregnancy had to be terminated.**

One, therefore, must ask, **if even strong proponents of PGT-A can no longer deny evidence against use of PGT-A in association with IVF, how come the utilization of PGT-A continues to grow?** And here we must refer to another opinion article in the same issue of Fertility & Sterility, penned by one of the most influential academic infertility gurus in the U.S (and Peoples Republic of China), **Richard S. Legro, MD** from Penn State College of Medicine in Hershey, PE. In this piece in which he was invited to speculate about the future of reproductive medicine post-COVID-19, he speculated that, ***"molecular diagnostic methods will only expand."***[7]

What, however, caught our attention (and not in a positive way), was his explanation, ***"why the use of PGT-A will only increase regardless of the scientific efficacy or cost efficiency of the practice, because of the reassurance that it provides."***

If a thought-leader in our specialty still believes that PGT-A offers assurance of any kind to women undergoing IVF, how can we expect that the public comes to understand PGT-A as the worthless and, at times even harmful, test it is. To accept this argument as an explanation for increasing utilization of PGT-A is beyond the pale. Aside from all other considerations, **facilitating adding $5,000-6,000 (not covered by any insurance company) to already exorbitant medical IVF costs, appears to us not only as clinically inappropriate but as unethical.**

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Clinically potentially relevant news regarding mental or physical status of mothers and offspring

Several interesting studies appeared in recent weeks addressing the brain function of pregnant women and/or of their offspring. We, therefore, decided to dedicate this month a separate section in our monthly literature review to these subjects. Much of the data presented in those studies is still preliminary and, therefore, should be consumed with caution; but these papers demonstrate some of the concern investigators are currently trying to confirm or reject.

Does maternal treatment with hydroxyprogesterone cause cancer in offspring?

U.S. investigators just published a potentially disturbing finding in suggesting that in utero exposure to **17-alpha hydroxyprogesterone caproate** may increase cancer risks in offspring.[1] Offspring of mothers who received this medication demonstrated almost a doubling in cancer rate. This drug (brand name **Delalutin**, Bristol-Myers Squibb, New York, N.Y.) was in the 1950s and 1960s routinely administered to pregnancy women and was *FDA-approved* for women with threatened abortions and/or repeat miscarriages. **By 1973 the FDA concluded that the drug was ineffective** and suggested that its use may be associated with **increased congenital heart defects in offspring.** Approval of the drug was finally withdrawn in the year 2000 at request of the manufacturer.

Eleven years later, **the *FDA*, however, again approved the drug**, now marketed under the brand name **Makena** (Covis Pharmaceuticals, Waltham, MA), this time alleged **to prevent preterm birth**. As documented by statements from the *Society for Maternal Fetal Medicine* (*SMFM*, 2017)[2] and the *FDA* (2019)[3] document, this indication has, however, remained highly controversial, though *FDA* approval for Makena has been maintained. A recent safety review by Sibai et al., found **no significant safety concerns between the drug and placebo.**[4]

The authors furthermore noted that *FDA* approval requires **post-market surveillance** of approved drugs and that since *FDA* approval almost 310,000 women were treated with Makena and showed no new risk trends. It must be noted that **this review was funded by the manufacturer of Makena.**

In here discussed paper revealed alleged association with cancer risk to our knowledge was never before considered. We, therefore, anticipate another round of heated discussions, whether use of a medication with questionable clinical utility is really worth any risk, even if the alleged risk appears to be very small.

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Effects of maternal psychiatric diseases

Danish investigators in a recent paper in *JAMA* reported on 575,369 Danish public-school children whose mothers during pregnancy took **antidepressants**.[1] In comparison to children of mothers who had not taken such drugs, they were found to have a **statistically significantly lower standardized test score in mathematics by 2 points.** Language scores, however, did not differ.

Though statistically significantly different, the authors concluded that this rather minimal difference may represent **a worthwhile risk to take to prevent acute depression episodes of mothers in pregnancy.**

This study brings to mind another study by British and Hong Kong investigators, already in August of this year also published in *JAMA*, who looked at the consequences on offspring from prenatal exposure to antipsychotic and attention-deficit/hyperactivity disorder treatments.[2] Though too much a hodgepodge of conditions for our taste, the results of this study have relevance to the here discussed theme because they also suggested that **prenatal exposure to antipsychotics did not affect the risk for offspring to develop attention-deficit/hyperactivity disorder (ADHD) or autism spectrum disorder (ASD).** There was also no increased risk for obstetrical complications, including prematurity and small for gestational date infants. **Both here cited studies, therefore, do not support interruption of psychotropic treatments in pregnancy.**

Not all data are, however, equally reassuring: In a study performed at the National Institutes of Health (NIH), the researchers followed 301 women during pregnancy quantitating a 6 time-points their **depression and stress**.[3] After they gave birth, their placentas were investigated for **epigenetic changes known to be linked to depression and stress** and 16 such changes were identified.

Moreover, **several of these epigenetic changes were found to play important roles in brain development and occurrence of psychiatric disorders.** The authors, therefore, concluded that these **epigenic changes in the placenta induced by depression and stress suggest the potential that they may affect fetal brain programming in utero.** Maternal depression and stress, therefore, may affect the long-term mental health of children.

Finally, an observation regarding women who at relatively young ages before natural menopause ages undergo **surgical removal of their ovaries (bilateral oophorectomy).** In a study reported in *JAMA Network Open,* researchers reported that such women experience **mild cognitive impairment and demonstrated poorer performance on cognitive tests approximately 30 years post-surgery.**[4]

This association has been reported before and, indeed, also by these authors. Here presented study, however, not only included 2732 women but also improved upon study design shortcomings of earlier attempts to address this question. **In premenopausal women hysterectomies (surgical removal of uterus), therefore, should not automatically also include removal of ovaries.**

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COVID-19 news

COVID-19 unfortunately remains highly relevant, as reports from Europe and from norther states in the U.S. suggest that **winter, indeed, may bring along yet another fifth wave of the COVID-19 pandemic.** Four circumstances increasingly point out that eradication of the virus under current knowledge will, at least in the short-term, not be possible: **(i)** It appears increasingly **unlikely that vaccines will create herd immunity** for the long-term because immunity against the SARS-CoV-2 virus generated through vaccinations seems to wear off rather quickly. **(ii)** Consequently, we see substantial numbers of **break-through cases** in fully vaccinated individuals, though fortunately, **with significantly reduced morbidity and mortality. (iii)** Not completely surprising, considerable **portions of the population remain on purpose unvaccinated. (iv)** Deservedly, and for several independent reasons (some discussed in more detail below), **science as well as government, have lost the confidence of the people,** thereby creating a vicious cycle of **opposition to even sensible public health recommendations and non-compliance.**

What is wrong with the management of the COVID-19 pandemic?

Readers of *The VOICE* will recall that we have been critical of how the U.S. government as well as the so-called "expert-class" have managed the pandemic from the very beginning. Though **the list of mistakes made is long,** considering the unique presentation of the **SARS-CoV-2** virus, and the limited knowledge at beginning of the pandemic about the virus, one cannot be surprised that mistakes were made. Those mistakes are, however, not the primary reason why scientists and the government have lost the public's trust. That was caused because **science and government did not trust the public and, from the very beginning, failed to be transparent and honest.** The public would have understood had **Dr. Anthony Fauci** on occasion answered a question with, *"I don't know;"* but instead of leveling with the public, he lied when initially opposing the use of mask as *"not useful,"* when trying to preserve the short supply of available face mask in the early days of the pandemic for hospital workers. Though he may have mean well; but who lies once, will automatically be suspected of lying again. And by, over and over again, flip-flopping in his public pronouncements, he made things not easier for himself.

But the primary reason for loss of trust by the public has been **the total politization of the medical and scientific decision-making process in government and media.** When **Trump** was president, it did not matter for Democrats whether he was right or wrong in his decisions. If it came from the Trump administration, it was automatically wrong. And now under the **Biden administration**, Republicans behave in the same way. Under Trump, the vaccines were iffy and both the President- and Vice President-elect would not commit to receiving the "Trump-vaccines." But as soon as they became the "Biden-vaccines," they were presented to the public as the panacea that would finally end the pandemic. **Who, therefore, can blame those who no longer know what to believe and, therefore, believe nothing they are told by government and so-called "experts."** And how does government respond? Instead of recognizing that it lost the trust of many and attempts to regain it by explaining things more and better and being more transparent and less political, **the government issues mandates** which, of course, further erode trust because who likes to be forced?

We in this section offer several recent publications in leading medical journals and media which express similar sentiments regarding a variety of COVID-related issues. They, however, all support the notion that **we better get our act together!** Already in October **Gary Saul Morson**, a professor at *Northwestern University* in Chicago, IL, published an OpEd piece in *The Wall Street Journal,* entitled, **"Partisan Science in America"** (October 12, 2021, pA17) in which he noted that during medieval times infallibility was often claimed after receiving God's direct revelations. He then suggests that starting in the 19th century secular thinkers instead invoked science, directly pivoting to Anthony Fauci by quoting his by now infamous statement, ***"a lot of what you are seeing as attacks on me, quite frankly are attacks on science."*** **There is, likely no more obvious example for the hubris of the "expert-community" than this statement.**

Without having the space to go into too much detail, two more quote by the author must be communicated. In a first, he states that, ***"scientists corrode public trust when they pretend to have authority on social and political matters,"*** and, elsewhere, he notes, ***"the greatest danger to the public's trust in science comes not from the uneducated but from politicians and journalists who claim to speak in the name of science. Still more it comes from scientists themselves, either because of what they say publicly in the name of science or their failure to correct others' misrepresentations of it."***[1]

Cecilia Tomori, an anthropologist and public-health scholar *John Hopkins Bloomberg School of Public Health* in Baltimore, MD, under the banner, "***a personal take on science and society,"*** published recently an essay in *Nature* magazine: **"Scientists: don't feed the doubt machine,"** with the subtitle, ***"from climate to COVID, naivety about how science is hijacked promotes more of the same."***[2]

The first thing we learned from her piece is that there is a so-called scientific field called **agnotology**, which keeps busy with **the study of deliberate spreading of confusion**. The author quoting a researcher in this field, who complained: ***"we spent a long time thinking we were engaged in an argument about data and reason …; but now we realize it's a fight over money and power."***

Though this quote referred to debates on climate change, the argument is applicable throughout science and, of course, especially to medicine. We, indeed, have made similar arguments in these pages when discussing certain practice patterns in reproductive medicine that remain popular, even though evidence not only does not support them but actually contradicts them. To stymy distorting strategies, Tomori argues convincingly for a responsibility scientists have, ***"to consistently highlight correct information and avoid serving as an inadvertent amplifier of flawed information."***

In a very short but powerful opinion piece in *The British Medical Journal (BMJ)*, **Mahesh Devnani,** an associate professor of Hospital Administration, decries overdiagnosis and overtreatment during the COVID-19 pandemic.[3] He points out repeated and unnecessary testing of patients with COVID-19 using RT-PCR, blood test, and other testing as well as irrational medication prescribing patters. He fully acknowledges that during early months of the pandemic lack of knowledge led to defensive empirical practice patterns but is rightly criticizing that many of **these patterns are continuing, even though, almost two years later, we should know better.**

Jennifer Abbasi, a health science writer at *JAMA* tackled a related subject under the headline, **"The Flawed Science of Antibody Testing for SARS-CoV-2 immunity."** Returning to the theme that we do things in medicine we know make no sense because good evidence contradicts them, she points out that physicians do test antibody titers to the SARS-CoV-2 virus in their patients to verify whether they have immunity. Professional organizations and the *FDA* have recommended against such testing because of incongruities between labs and because so-far **no threshold level for neutralizing antibodies has been established**.[4] In other words, **we currently have no reasonable way to determine whether an individual is sufficiently immune to the virus or not. Surprising unmentioned in the medical literature is the daily testing conundrums we face in interpreting test results** because of considerable **false-positive tests** but also because laboratories are using different tests. Add to this that the *FDA* recently authorized several home tests but at the same time, almost as quickly as it approved them, has recalled millions of home testing kits for false-positive reports, the currently ongoing testing mania also requires a reassessment.

Finally, **Paul D. Thacker**, an investigative journalist at *The BMJ* recently published a **shocker of an article**, blowing the whistle on alleged **data integrity issues in *Pfizer's* original vaccine trial**.[5] Interestingly, his quite lengthy manuscript has not received the attention from media as well as social media one would have expected. Considering that the most frequently heard argument against getting vaccinated is the speed of development of especially the RNA-based vaccines, his (peer reviewed) paper has, however, major relevance and we can expect to hear more about the allegations he is making regarding the integrity of *Pfizer's* research.

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Another way to prevent COVID-19

The pharma company *Regeneron* (Westchester County, NY) in early November announced that a single dose of **REGEN-COV,** a monoclonal antibody cocktail, containing 600mg of **casirivimab** and **imdevimab** respectively, for post-exposure prophylaxis (prevention) of COVID-19 reduced the risk for COVID-19 by almost 82% for up to 8 months. The FDA had approved this medication on an emergency basis already in November of 2020 but only for treatment of mild to moderate COVID-19 in high- risk patients. By July of this year the emergency use authorization for the medication was expanded to postexposure prophylaxis.[1] **The results now reported, however, exceeded all expectations in that a single dose of the medication reduced the risk of developing COVID-19 during 8 months by a whopping 81,6% (95% CI, 70.6-88.4%).**

Shortly before going to press with this issue of *The Voice, Pfizer* also reported similar results with a similar drug.

These are results that in effectiveness and length of protection are surprisingly like even best vaccines, The FDA, however, only unlikely will approve REGEN-COV or the Pfizer drug as a replacement for getting vaccinated; but these treatment offer significant promise **especially for immune-depressed individuals who do not easily develop good immunity following vaccinations**. It seems high time that the pharma industry is pursuing additional treatment options against COVID-19 that are not vaccines!

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The American College of Obstetricians and Gynecologists (ACOG), therefore, now not only recommends **routine anti-COVID vaccinations for all pregnant women (and those planning on pregnancy)** but, after a single *Johnson & Johnson/Janssen* vaccine, **recommends a booster** after 2 months and, after Pfizer and/or Moderna m-RNA vaccines, a booster at least 6 months after the second dose.[2] **For those concerned that vaccines can cause harm to fertility and/or pregnancy, be assure that neither is the case.**[3–5] Unvaccinated pregnancy women on the other hand, according to a report in *The New York Times*, made up almost 20% of most critically ill COVID-19 patients in England.[6]

Reports from various health systems unfortunately suggest that, despite efforts by the medical community and governments, **vaccine hesitancy among pregnant women has remained persistently high**. Relating, another interesting paper was just published in *JAMA Internal Medicine*, in which investigators from Sweden reported that family members without immunity to COVID-19 had a 45% to 97% lower risk of contracting the disease as the number of immune members of the family increased.[7] **Even (or especially) within families, vaccinations, therefore help!**

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COVID-19 in pregnancy

A vey interesting recent study investigated the effects of mRNA vaccines on antibody Fc-functional profiles in pregnant, lactating and non-pregnant women and revealed that **in pregnant and lactating women two vaccine doses were required to achieve immune responses equal to those non-pregnant women achieved from only a single vaccination**.[1] These findings at least in part, explain why **COVID-19 in pregnancy is a much more severe disease than in the non-pregnant state** and why **women trying to conceive or already pregnant, should be vaccinated as quickly as possible.**

These findings however, also, once more point out **what a unique immune status pregnancy is** in that it prevents, or at least weakens, the development of highly selective immune responses without affecting the system's overall functionality. The CHR's investigators have explored this concept for several years, hypothesizing that the development of **normal tolerance pathways that protect the rapidly growing fetal semi-allograft from rejection by the mother's immune system** must be defective in some cases of **implantation failure**, and **miscarriages**, leading in those cases to pathological immune responses against the fetus. Their hypothesis also proposes that **women who experience insufficient development of tolerance, also will lose tolerance early in pregnancy and, therefore, will also be at risk for premature labor**. This includes women with **hyperactive immune systems due to autoimmunity and inflammation. All autoimmune and/or inflammatory diseases without exception, therefore, are at increased risks for miscarriages and premature labor.**

And let's not forget, it is flu season!

Remarkably, **in 2020 the whole world went through flu season without anybody getting the flu.** It is still too early to judge this year's season, but preliminary data suggest that this year we will experience some cases but, still, COVID-19 in some way appears to vanish the influenza virus. As noted already before, the flu and COVID-19, however, share the observation that **both diseases have a much more severe phenotype in pregnancy than in the non-pregnant state.** Therefore, all professional organizations also emphasize that the annual flu vaccine should be taken by women planning to conceive and, of course, those who are already pregnant. And both vaccines, indeed, can be taken together. While the CHR cannot administer vaccines against the SARS-COV-2 virus on premises, **we do offer flu vaccinations to our patients.**

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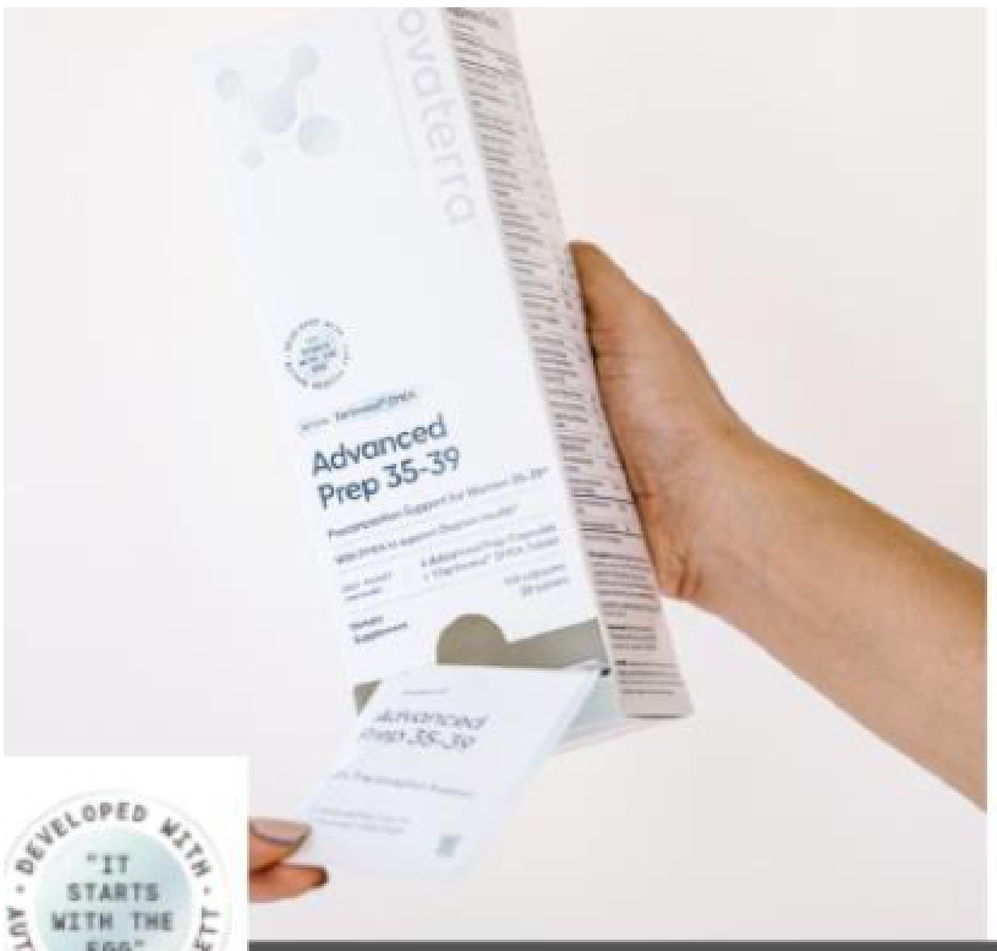

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Vitamin C (as Ascorbic Acid)	500 mg	556%
Vitamin D (as Cholecalciferol from Lichen)	100 mcg	500%
Vitamin E (as D-Alpha Tocopheryl Succinate and Mixed Tocopherols)	134 mg	893%
Thiamine (as Thiamine HCl)	4.2 mg	350%
Riboflavin (as Riboflavin-5-Phosphate 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%
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