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THE CHR VOICE

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in this issue

May 2022

The VOICE

April was a hectic month at the CHR because the deadline period for abstract submission to the *Annual Meeting of the ASRM* is always hectic. This year these days, however, also coincided with the electronic pre-publication of a CHR paper in *Human Reproduction* [1] that garnered almost as much attention from national media as the paper that had appeared in the preceding month in *Nature Medicine*,[2] including an article in *The New York Times*[3] (see also *Recent Publications from the CHR*). Some of the CHR's investigators, therefore, ended up splitting their valuable time outside clinical practice between abstract preparation and interviews with the media, explaining to journalists **why transferring supposedly chromosomal "abnormal" embryos achieves the surprisingly good pregnancy and live birth rates reported in this paper.**[1]

As every year, CHR's investigators produced a good number of abstracts; now it is up to the *ASRM* reviewers to decide which they wish to accept. These abstracts are frequently the first short drafts of a subsequent paper. Preliminary data are acceptable in abstracts but not in full length papers. Abstracts, therefore, are usually the incentive for investigators to dig deeper into a subject. And this is the reason why "hectic" does not vanish after the deadline for abstract submissions; "hectic" only changes in format from meeting a deadline to producing a best possible study in a full-length manuscript.

As has become routine in recent years, there, of course, had to be at least one abstract regarding **preimplantation genetic testing for aneuploidy (PGT-A)** among submissions. There actually were two this year! Reflecting the CHR's decade-long interest in **immunology**, another abstract reports very interesting and previously unreported observations in female infertility patients during the **Covid-19 pandemic**. Yet another one addresses a new concept on how **polycystic ovary syndrome** is to be viewed. And, finally, CHR's investigators expanded on earlier observations made (and published several years ago [4,5]) in **older ovaries,** demonstrating that the speed of follicle maturation picks up with advancing female age. This observation led to **HIER (Highly Individualized Egg Retrieval)** which at the CHR has become routine. CHR's investigators now furthermore learned that the relevance of **maturity designations for human oocytes** also significantly changes with advancing female age, potentially as important a new discovery as HIER has been. In short, **research at the CHR is continuing to bloom** and is expanding into several very interesting directions, all geared at discoveries with short-term **translational clinical applications** that may benefit CHR's patients.

The CHR is known as a "fertility center of last resort," primarily serving patients who have previously failed treatments elsewhere. Among CHR's areas of special expertise are treatments of "older" ovaries, whether due to advanced female age or premature ovarian aging (POA), immunological problems affecting reproduction, repeated pregnancy loss, endometriosis, polycystic ovary syndrome (PCOS), tubal disease, male factor infertility, etc.

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To benefit CHR's patients, colleagues, and other readers by providing **knowledge relevant to reproductive endocrinology and infertility** is also one of the main objectives of the CHR's *VOICE* which in this May issue again, as we hope, offers a wide potpourri of contributions for the varying interests of our broad readership. As always, we encourage responses and invite independent contributions by writing to social@thechr.com. And, by the way, we very much welcome non-concurring opinions because we all can learn from each other!

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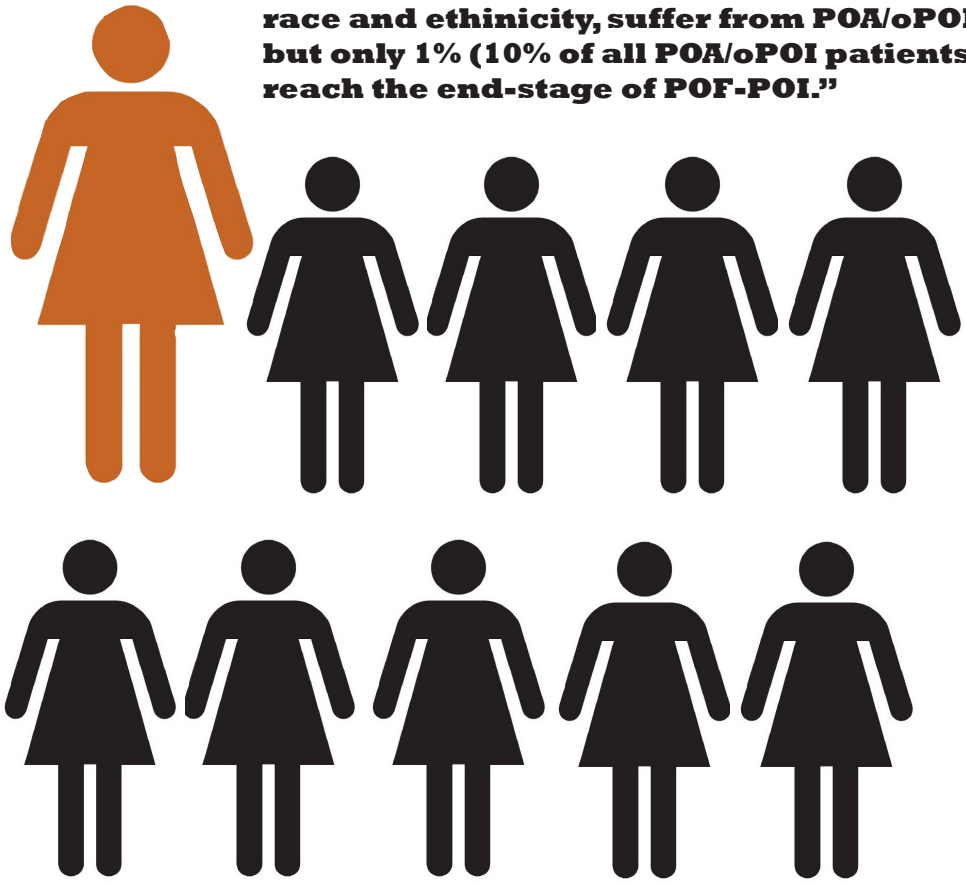
Enjoy the May issue
The editorial staff of the CHR's *VOICE*

Premature ovarian failure (POF) or Primary ovarian insufficiency (POI)

Being among the 1% of women in the world who experience early menopause

"... ca. 10% of all women, independent of race and ethinicity, suffer from POA/oPOI but only 1% (10% of all POA/oPOI patients) reach the end-stage of POF-POI."



A woman reaches menopause when the number of remaining follicles (and oocytes) in her ovaries drops below a certain threshold and **follicles no longer respond to usual stimulations**. Though a small number of follicles at that stage are still present in ovaries, they no longer respond to the usual hormonal stimuli, don't get recruited out of resting stage, don't grow and mature and, therefore, **no longer produce the hormone, estradiol (E2).** It is E2 that in a so-called feed-back mechanism, by nature a very frequently used method to control biological processes hormonally, during younger reproductive years **inhibits the secretion of follicle stimulating hormone (FSH) from the pituitary gland**. Once follicles cease to produce E2, nothing is any longer holding back FSH, and **FSH levels will, therefore, rise**. Once those go **above 40mIU/mL, an FSH level is considered "menopausal."**

Concomitantly the menstrual cycle ceases and women become "amenorrheic." Women reach so-called physiological (or normal) menopause at the average age of 51 years, defined by FSH above 40.0 mIU/mL (though it can exceed 100.00mIU/mL) and amenorrhea for at least 6 months. If menopause strikes between ages 40 and 50, it is called **"early menopause."** We here, however, are addressing **menopause that happens before age 40 years**, a condition with several different names, from **"premature menopause"** to "**premature ovarian failure (POF)"** and, most recently, "**primary ovarian insufficiency" (POI)** or **"premature ovarian insufficiency" (also POF).**

Why ages 40 and 50 years, respectively, differentiate between those various entities/names is unclear and there is really no logic in differentiating between menopause at age 39 and age 41; but current professional consensus does, even though **premature ovarian aging (POA), by some also called "occult primary ovarian insufficiency" (oPOI)** is, of course, a continuous precursor process of which POF/POI is only the last station to be reached.

The literature suggests that ca. 10% of all women, independent of race and ethnicity, suffer from POA/oPOI but only 1% (10% of all POA/oPOI patients) reach the end-stage of POF/POI.[1]

Paradoxically, 50 years ago, if a woman experienced POF/POI, the diagnosis was often not as tragic as it is today because women started having children at much younger ages. Even if they experienced POF/POI in their late 20s or early 30s, there was a good chance they already had children. Nowadays, often as teens, women initiate hormonal contraceptives and stay on them uninterrupted into their mid- to late-30s. At that age for the first-time considering conceiving, the shock is substantial when they discover that, **under the cover of contraceptive use, they quietly had developed POF/POI.**[2]

continued from page 5

Receiving a diagnosis of POF/POI

As noted earlier, the process of **premature ovarian aging** affects ca. 10% of all women and, unfortunately, is clinically quiet. Its first signs are often menstrual irregularities, in women on hormonal contraceptives often completely covered up by the creation of artificial cycles. CHR[2] and others, therefore, have **advocated that young women, every 2-3 years, go off hormonal contraceptives for a few months and have their ovarian reserve reevaluated**.[3] The CHR and several of its investigators, indeed, were awarded **a U.S. patent for an algorithm which allows for an early POA/oPOI diagnosis**, - in most cases long before POF/POI is reached. Though as of this point in time, there is no known treatment available to arrest the process of POA/oPOI, early diagnosis at least **offers the options of fertility preservation** through egg or embryo cryopreservation **or of having children at younger ages than was originally planned**.

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Once a diagnosis of POF/POI is reached, options are, however, more limited. This **does not necessarily mean that all options with use of own eggs must be ruled out.** As always, much depends on the age of the patient at time of diagnosis: **the younger she is and the shorter the time is the patient has been in menopause, the better the chances are for still being able to squeeze out a few eggs and embryos that may result in pregnancy.** The CHR also offers a clinical trial for young women with POF/POI in which the patient's own so-called **platelet-rich plasma (PRP)** is injected into her ovaries. This registered trial, running under the title PRP I (trial number NCT03542708), is still recruiting a handful of new patients but will soon be closing enrollment after the originally predicted number of participating patients is reached.

Other factors that may influence chances of treatment with autologous oocytes are **the underlying etiology of a patient's POF/POI.** For example, if the POF/POI is iatrogenic (i.e., caused by medical interventions, like surgical removal of ovaries, chemo- or radiation therapy), a patient's own ovaries may, simply, no longer be capable to produce eggs; **if the process is likely immune or genetic, there may still be a chance.** Two rules apply, however, to every diagnosis of POF/POI: **(i) Seek out special expertise because most fertility specialist will consider only third-party egg donation as an option**; and **(ii) don't waste any time because, if there is still an option with autologous eggs, it usually will not last very long.**

Finally, we also want to point out that CHR investigators several years ago reported on **a new clinical presentation that mimics POF/POI in its clinical picture** but really does not reflect primary (i.e., in the ovary-caused) ovarian insufficiency (POI) but **a form of secondary ovarian insufficiency (SOI) with much better prognosis than POF/POI.**[4] SOI is caused by adrenal glands becoming insufficient in their androgen (male hormone) production. Under normal circumstances, approximately half of all androgens in a female come from the adrenal glands (the other half comes from ovaries). If the adrenals become insufficient (**usually believed to be an autoimmune condition**) and a woman's androgen levels drop to significant degrees, maturation of ovarian follicles may come to a standstill because ovaries need normal androgen levels for follicles to grow and for their eggs to mature. If that process is halted for lack of androgens, follicles don't grow and, like in menopause, do not produce E2. Without E2 previously noted feed-back to FSH does not happen, and FSH again start climbing. **The end result is a hormonal picture very similar to POF/POI,** - abnormally **high FSH and very low E2**. No wonder, therefore, that **this form of SOI is frequently misdiagnosed as POF/POI.** CHR's investigators recently also reported in a just submitted paper two cases of **corticosteroid-induced SOI**, where long-term steroid use suppressed ACTH secretion which, in turn, suppressed adrenal androgen production, causing SOI. Discontinuation of glucosteroids normalized the ovarian function of both women. Considering how many women are on long-term steroid treatments, there must be a substantial number of women with SOI out there who may not even know that they have this diagnosis.

Since this form of ovarian insufficiency is not caused by lack of follicle in ovaries, it is very easily remedied: All that needs to be done is to substitute the missing androgens from the adrenal glands with oral

androgens or in the latter case of ACTH suppression, by stopping corticosteroid treatments. Once that is done, ovaries quickly kick in and **some women will even conceive spontaneously**. **Though the diagnosis of SOI is rare, it occurs often enough to be seen at the CHR on a pretty regular basis**. Patients who are lucky enough to have **come to the CHR with a diagnosis of POF/POI and to leave with a diagnosis of SOI** often feel like **they have won the lottery, - and in a way, they have!**

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patient testimonial.

"

Dr. Barad is kind, compassionate, and warm. He's also scientific and knowledgable. He took time to explain things to me, address concerns, and alter the program when needed. I felt a sense of calm every time I met with him--whether it was for a check on where I was in my cycle or for an actual transfer. I'm sixth months pregnant, and I owe it all to the wonderful doctors, nurses, and staff at CHR. When I first visited them, I was completely green at the world of IVF. I knew I was at an advanced age for conceiving my first child, so I went to them immediately when I made the decision to try. I hadn't looked on blogs or read books or talked to a million friends about the process. What I found at CHR was a group of people who were willing to hold my hand and be there for me every step of the way.

What happens to IVF if Roe v. Wade is really overturned by the Supreme Court?

By Norbert Gleicher, MD
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The US Supreme Court building in Washington, D.C.

As this commentary is written, it is only four days after the Supreme Court was embarrassed by an unprecedented leak, suggesting that in announcing a final decision in the *Dobbs v. Jackson* case in a few weeks, the court, likely, will overturn *Roe v. Wade*. Without addressing the callousness of this leak (with the leaker as of this moment still unidentified) and without wishing to even come close to the central issue whether *Roe v. Wade* is constitutional or not (this is a medical and not a legal newsletter), the reaction the "infertility community" offered on the Internet in recent days in response to this affair was surprising enough to spur this month's column.

First a few general comments: Even if *Roe v. Wade* will, indeed, be overturned (and since the leak involved an early February draft of a potential opinion, the final document may still significantly differ), **this does not mean that as of that moment abortions will be prohibited in NYC or anywhere else in the U.S.** All such a decision by the U.S. Supreme Court would mean is that the court found that the subject of "abortions," even though it may have other connotations as well, under the constitution as a health issue is not for the federal government to supervise but should be the responsibility of individual states.

The liberal icon and former Supreme Courts Associate Judge, **Ruth Bader-Ginsburg**, indeed, shared this opinion and opined in public that the Supreme Court likely erred in its *Roe v. Wade* opinion in declaring the right to have an abortion a federal issue. She, indeed, saw the court's 50-year-old decision as the principal reason why the nation in all these years has been unable to find a consensus on this controversial subject. Since there are significant differences based on geography (i.e., the voters in different states have different opinions on this subject), she argued that finding a mutually acceptable solution for such **a divisive subject like abortions (which splits the U.S. population into two roughly equal-size opinion blocks**) may be better handled on the local state than federal level.

Even if the final written decision of the court should be exactly what the leaked version suggested, all this decision would mean is that **the abortion issue moves from being a national to being a local state issue.** In other words, the constitutional principle that as much decision making as possible in the union of states should be at the local

level (i.e., closest to voters) would be followed. Every one of the 50 states plus U.S. territories, based on local political processes, would then have to decide whether they want to permit abortions and, if so, under what limitations (if any).

This is, indeed, how abortions were performed in the U.S. before *Roe v. Wade* because New York already then was a bastion of liberalism and had a generous abortion law long before Roe v. Wade came into being. New York, indeed, became one of only a relatively small number of states which evolved as a **destination for abortion tourism**. Whatever other states may decide based on their local populations' wishes, the citizens of New York can be assured that this state will, likely, establish even more generous laws, should that become necessary. This will, likely, also apply to most other states, though restrictions as to how long into a normally progressing pregnancy an abortion can be performed may very well vary between states. Such restrictions, indeed, have majority support throughout the nation because **it is difficult to find even hypothetical scenarios where pregnancy terminations of normally progressing pregnancies would be indicated in, for example, the third trimester of pregnancy.** And there may, indeed, also be a small number of states where most citizens oppose abortions and, in these states, abortions will not be available until opinions change. Neighboring states will, however, be only too happy to offer those services.

"it is difficult to find even hypothetical scenarios where pregnancy terminations of normally progressing pregnancies would be indicated in, for example, the third trimester of pregnancy"

The infertility community, both patients and providers, are, of course a special interest group when it comes to the abortion issue. As a lifelong supporter of "choice" for women when it comes to all their medical decisions, **supporting a woman's choice to terminate a pregnancy must be included.** At the same time, **there, of course, is a psychological barrier to be overcome when daily fighting for every egg and embryo in attempts to help women to conceive.** Infertility patients must experience similar psychological strains when considering this issue. Add to this that **some extremists on the "pro-life" side of the argument have also remained hostile to birth control and especially to in vitro fertilization (IVF), as a fertility treatment,** it is not surprising that **the infertility community clearly overreacted to the leak** from the Supreme Court; and, in a way, **who can blame them?**

In certain aspects, IVF has, indeed, mirrored the abortion issue, though not necessarily in a positive way. While considering *Roe v. Wade*, the federal government, in Democrat as well as Republican administrations, has maintained the status quo regarding abortions, while **both parties have shown little similar sympathy for the practice of IVF**. Federal health insurance plans, from Medicaid, over Medicare and, with very few exceptions also military health plans, exclude to this day IVF coverage. To this day almost all federal research funding, again under both Democrat and Republican administrations, has almost completely excluded (by federal law) all funding of IVF-related research.

Insurance matters are generally under state control. That has led to a patchwork of insurance mandates, with only 15 states mandating some form of IVF insurance coverage as part of a general health insurance plan or in association with obstetrical coverage (they, of course, cannot mandate the federal government from offering IVF insurance through its various health plans). But even in states with mandates, there exist usually many loopholes through which companies can escape these mandates in providing health care to their employees. Consequently, as a recent ***ACOG* Bulletin** reported, only ca. 27% of companies with over 500 employees offer some form of IVF insurance to their employees. As of 2015, that percentage was almost the same at 24%. In other words, **IVF insurance is still the exception in the U.S.** because smaller firms, likely, offer even less coverage than larger companies.

At the same time, **IVF has over the last 40 years matured into the most frequently performed infertility treatment** (it, on a sidenote, started in the U.S. before the *Roe v. Wade* decision) and it will continue as the most important infertility treatment unchanged even in case the Supreme Court returns abortion decisions to the states. Interestingly, IVF is likely the most intensely regulated medical treatment in the U.S. It is regulated by the federal government (through the *FDA* which regularly inspects all IVF centers) and state departments of health in all 50 states do the same. And, on a further sidenote, the **New York State Department of Health** has in many ways more stringent rules than even the *FDA*. In other words, state departments of health in various states should have no problems instituting and overseeing abortion rules; and like IVF rules, they will somewhat vary between states.

Reading the many concerns expressed on the Internet that a possible Supreme Court decision to overturn *Roe v. Wade* would also cause repercussions on IVF practice, therefore, appear unlikely, - not the least, however, because Democrats and Republicans, alike, have been anything but kind to the IVF field from the very beginning. Things, therefore, cannot get much worse than they already have been for decades.

All of this appears especially peculiar at a time when practically all Western nations suffer from insufficient population growth and not even achieve replacement levels of births. **One shining exception is the country of Israel;** and a big reason is that the government not only does not discriminate against IVF but generously subsidizes the procedure by covering the costs for almost unlimited IVF cycle numbers until a mother has had three children.

Whatever, therefore, happens to *Roe v. Wade*, the IVF field should not experience adverse consequences. It, indeed, appears high time to end the almost complete exclusion of IVF from federal funding. But since the IVF field in over 40 years has mostly been self-sufficient, it now has the advantage of having little to lose. At least this one time, this may be an advantage!

Increasing numbers of Fertility Doctors **revealed** as not only providers of fertility services

NYC in the 1980s (pictured) was one of the few urban areas that had so-called infertility specialists

Up until the late 1970s, there were no **frozen donor sperm banks** anywhere in the U.S. They only came about in the very late 1970s and early 1980s because of the rapidly growing **AIDS crisis** which, of course, was especially daring in New York City. There was also no IVF in those days (the first IVF baby was born in the U.K. in July 1978). Donor sperm in those days was used for one purpose only, in mostly **intravaginal,** and later, **intrauterine inseminations (IUIs).** There was also almost no **subspecialty of reproductive endocrinology and infertility** in existence. There were a handful of gynecologists in NYC and in other major urban areas who presented themselves as **"infertility specialists;"** but there was almost nothing they offered that general OB/GYNs had not also offered, including IUIs, - many IUIs.

Because **ICSI (intracytoplasmic sperm injection)** in association with IVF was still a pipe dream, **male infertility** in those days was almost as big a problem as **female infertility** but some female infertility at least had (poor) treatment options: **Clogged tubes could be operated;** and those were the days when on the female side the fertility field was, therefore, dominated by so-called **micro-surgeons**. But if there was little or no sperm on the male side, donor IUIs were the only treatment. And donor IUIs in those days, therefore, were also big business, organized in ways today probably considered somewhat absurd; but in those days the process was working surprisingly efficiently and, most importantly, safely (that is, until the AIDS epidemic changed everything).

Who were the best sperm donors? Medical students and residents, of course, and with medical students and residencies in those days still mostly male, - hospitals offered large pools of great donor candidates. Residency programs had their internal organization, with senior residents getting priority over juniors and students, and being responsible for organizational supervision of the donor pool as well as rare cases when specific donor selection criteria had to be fulfilled, like, for example, a red-head donor was requested by one of the doctor offices. At the time, these programs made sense: many doctor offices, indeed, marketed the fact that ***"all of their donors were medical students or residents."*** These were the days before the top of the class went to Wall Street or, later, to start-ups. In those days **the physician sperm donor was still considered the "creme-de-la-creme."** *How times have changed!*

Between 9:00 am and noon, you often could see taxis lined up at hospital exits waiting for students and residents rushing out with brown paper bags in their hands that obfuscated the sperm samples they had just produced in their on-call rooms. The few female residents knew that during those hours, on call rooms were not to be entered without first knocking. Receiving a piece of paper with the address of the designated doctor's office, the taxi drivers loved these jobs which did not require the turning on of their meters and guaranteed them a nice cash payment at delivery, when a staff person was already awaiting the brown paper bag at the pavement with cash in-hand.

The system worked so well that specimens usually arrived at the doctor's office still warm. The process was anonymous because neither doctors

nor patients ever knew which resident had been the donor. In addition, all documentations were destroyed. Since mostly married residents in those days were considered "safe," infectious disease screening of sperm donors was also not practiced yet, - that is until first cases of AIDS were reported following IUIs, - and the whole system, literally overnight, shut down.

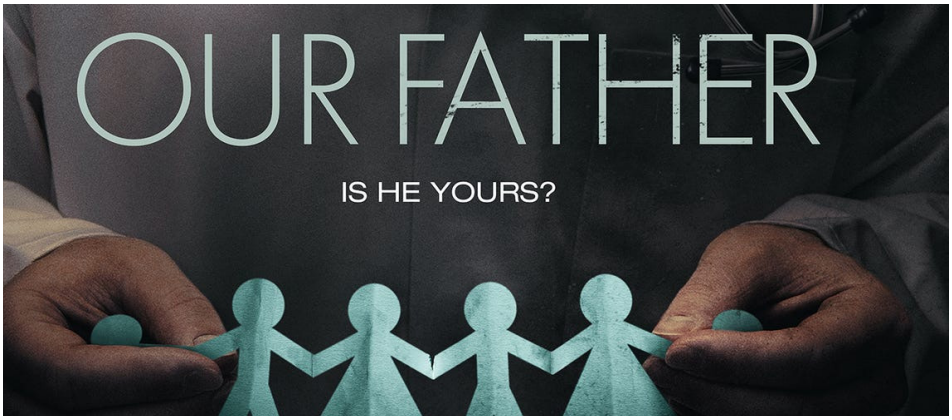
Why all this detail? Because all this detail will help in understanding how **Donald Cline, MD,** a respected general OB/GYN in Indianapolis, IN, could have become the genetic father of at least 94 children, conceived through IUIs in his office. And, yes, he, of course, was not the only one and he, most certainly, was not the first to make headlines. But with **Netflix's *Our Father*, a 1h 37m – long documentary**, having premiered on May 11, he is presented as something of a posterchild for the misconduct of an apparently surprisingly large number of male OB/GYNs who lacked all insight into the depth of depravity they ended up representing ethically as well as morally.

But he was by no means the only one. A series of disclosures in recent years, indeed, would suggest that a surprising number of OB/GYNs in those days considered it appropriate to use their own semen. Whether **Morris Wortman, MD,** in Rochester, NY, who in a lawsuit filed by one so conceived woman was accused of having used his own sperm, while representing to her mother he was using medical students' semen,[1] **or Boyd Coates III, MD** from Vermont who in a Florida court recently was told to pay $5.25m in damages to one of his patients who also had been advised that her donor was a medical student.[2] In a 2020 article **Rosie McCall** pointed out that in those years fertility doctors using their own sperm proved to be a rather widespread problem.[3] Moreover, the habit was not only restricted to the U.S. She, for example, pointed out that a Dutch fertility doctor fathered at least 49 children in this way. Until the recent Cline documentary on Netflix, the most "prominent" U.S. physician in this group of fertility doctors accused of using their own semen was unquestionably **Cecil B. Jacobson, MD,** who is suspected to have fathered more than 70 children and was already on May 8, 1992, given a 5-year jail sentence federal court for 52 counts of fraud and perjury because he not only impregnated women with his own semen but he also lied to his patients by telling them they were pregnant when in reality they were not, - and he knew it.

Because of increasing utilization of **genomic testing,** like **23andme** significant numbers of additional cases are becoming public almost daily. For example, a New Jersey woman found out that her doctor, **Martin Greenberg, MD,** was the genetic father of her daughter only after her daughter underwent 23andme testing. The mother's treatments were received in New York City.[5] The article describing the case quotes a lawyer claiming that his law firm alone represented **over 1000 people who brought claims against physicians who allegedly used their own sperm during IUIs**. At least some of these cases have been settled quietly without ever having been made public.

Why did they all do it? The Netflix documentary and media analyses of Dr. Cline[6] portrayed him as an "*evil Christian-Cultist Doctor who secretly fathered 94 children*," possibly "*to procreate as much as possible in order to swell the ranks of God's disciples*." Though Cline, was likely indeed a religious zealot, evidence that his religious beliefs motivated him toward inseminating his patients with own rather than medical student sperm, and then lie about it, is unconvincing. A much more likely explanation for his behavior can be deducted from the background information with which we introduced this article. IUIs in those years were routine procedures in many general OB/GYN offices. Donors were not formally selected by physicians or patients. Neither party, indeed, knew who the random volunteer medical students or resident was who provided the specimen. The informal nature in which donors for IUIs were recruited, therefore, relatively easily lent itself to the conclusion, "***if they, why not me?***"

Add to this that by becoming the sperm donor, those docs no longer had to procure semen from real donors (in those day procurement of donor semen was a responsibility of the medical office, while, nowadays, patients themselves must procure their specimens from sperm banks). Saving in addition on transportation costs, knowing how stingy some doctors can



Netflix's documentary on Donald Cline, MD

be, even only borderline sociopathic personalities, unable to perceive the gravity of their transgression and unable to channel their patients' anxieties about undergoing IUIs with anonymous semen, simply jumped on the "economic opportunity." As some of the already decided court cases clearly demonstrated, none of the accused physicians perceived himself doing something unethical or acting in immoral ways. To the contrary, many, in not unfamiliar egomania in medicine, considered themselves to be premium sperm donors and saw themselves as doing their patients a favor in allowing them to achieve motherhood with use of their sperm.

That many, if not most, of those physicians were sociopaths was well demonstrated by Cecil B. Jacobson, MD, **the first of the pack to be discovered and convicted**. When on March 5, 1992, convicted by a jury, his response was not a plea for forgiveness but the following statement: "*I'm in shock. I really am. I spent my life trying to help women have children. If I felt I was a criminal or broke the law, I would never have done it.*"[7] This was **the same physician, in his days considered a leading specialist in the field, who injected his female patients with human chorionic gonadotropin (hCG) and then claimed they were pregnant because they, of course, had false-positive pregnancy tests from these injections.**

In short, whether Donald Cline, MD was member of a Christian "cult," is not the issue. The real issue is that, **like all professions, medicine on occasion produces some rotten apples among physicians**, because of personality disorders incapable of empathy and of differentiating between ethical and unethical behavior. It is, therefore, the field's responsibility to find and expose these physicians as early as possible because they, often, are simply incapable of judging themselves. As here described cases so well demonstrate, discovery through the court system usually comes already too late, as damages have already occurred and, as all of these cases so amply demonstrate, can be substantial.

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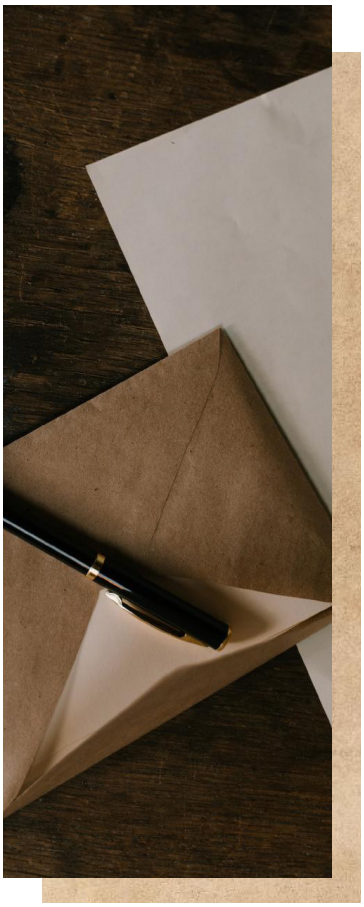

"patient testimonial.

Dr. Gleicher took time to personally address our many questions and apprehensions, putting us at ease that, while our hopes and prior experiences were low, that he WOULD succeed. We found him to be accessible and approachable, besides the obvious, extremely knowledgeable expert in his field. Having the benefit of perspective of multiple clinics and experiences (and outcomes!), we unabashedly recommend CHR to ANYBODY facing this stressful and agonizing process, and wish them all the best in making their dreams come true. We welcomed our little girl into the world and are forever grateful to the exceptional team at CHR that made it possible.

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.

How important is physical health for fertility?

Evolution favors physical health and it, therefore, should not surprise that, in female as well as male fertility, physical health is important. Likely the most obvious example is **obesity**. Both in women and men, **obesity is associated not only with increasing prevalence of infertility but also with lower success rates for all fertility treatments**.[1,2] Good physical health is also a prerequisite for women who wish to go through pregnancy because **pregnancy stresses every part of and every organ in the body**. Many, indeed, perceive pregnancy as a universal stress-test for the whole body. This is the principal reason why professional guidelines in infertility practice suggest that **women above age 45** who wish to conceive have a more extensive pre-IVF cycle work-up than younger women. A good example is **diabetes mellitus**: women with **borderline diabetes** and/or **insulin resistance** during pregnancy often become diabetic (so-called **"gestational diabetes"**). Or women with **borderline hypertension** can become **hypertensive**.

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1. Best D, Bhattacharya S. *Horm Mol Biol Clin Investig* 2015;24(1):5-10
2. Kahn et al., *Curr Opin Urol* 2017;27(5):441-445

Have you heard about INVOcell?

If you have not heard about INVOcell, here is your chance. Its manufacturer advertises it as, "*the first and only FDA-cleared and CE-certified medical device for fertility treatment through intravaginal culture (IVC).*" Now in the U.S. distributed by Ferring Pharmaceuticals USA, it is further described, *"as an innovative approach where a woman's body acts as a natural incubator for fertilization*."

Since many readers very likely will not understand what that means, here is the explanation: INVOcell is a mechanical device that allows natural fertilization of an egg by a spermatozoon in its **inner chamber** which, combined with a so-called **culture device** and a **retention device**, sits in a woman's vagina. What this means in practical terms is that, once eggs are retrieved and semen is obtained from the partner during a regular IVF cycle, instead of achieving fertilization in the lab using an incubator, **the gametes are placed into the inner chamber of the device and the combined device is placed into a woman's vagina**, where it is allowed to sit uninterrupted for on average 3-5 days. The device is then removed and delivered to the embryology laboratory where **the inner chamber is opened** and the number of so-created embryos is determined and, from there on, regular IVF practice takes over.

So, what is then the proposed rationale for carrying around a mobile incubator in the vagina rather than leaving the process of fertilization and embryo development in its traditional home, - the embryo laboratory?

Frankly, we have no idea; but the company promoting this product claims a **"deeper personal connection"** (we assume between potential future mother and her embryos??), **"access for more families"** (we here presume an argument of lower costs??) and, of course, **"reduced lab procedures."**

We are more than skeptical! While maybe an option in geographic regions of the world that lack standard IVF services, the logic of such an IVF approach in the U.S., with the abundance of IVF centers this and other developed nations nowadays enjoy, makes little sense to us. It appears telling that **the website of INVOcell does not provide any IVF cycle outcome data utilizing their product, nor does it offer cost-comparisons with routine IVF.**[1] In this context it

is important to reiterate that when costs for IVF services are compared, this should not be done on a per-cycle basis but **should be based on costs per healthy live birth.** In other words, it does not help if a cycle is "cheaper," when it takes more cycles to have a baby.

REFERENCES

1. https://www.invocell.com

What happens when a genetic parent is HIV-positive and needs a gestational carrier (surrogate) to carry the pregnancy?

This is not only an important question but also a well-timed question, considering we are approaching **Pride Month** in June and considering **the broad swath of family building options the CHR is offering to the LGBTQ+ community and is constantly attempting to expand**. Here is some background: Whenever gametes and/or embryos are used in attempting pregnancy in a third-party (i.e., after semen, egg, or embryo donations **but also in surrogacy situations**), donors of gametes or embryos, under *FDA* and *New York State Department of Health (NYSDH)* rules, **must be tested beforehand for several infectious diseases, including HIV**. Positive results then preclude gametes and/or embryos from the positive individual to be used in establishing a pregnancy in a third-party recipient.

Consider, therefore, the following circumstance, which the CHR recently has encountered on several occasions: **A gay married male couple presents with the desire to start a family**. The couple produced embryos with eggs from an, in accordance with *FDA* and NYSDH, carefully selected young anonymous egg donor. The semen, however, came **from a for years HIV-positive male** who, under treatment, for many years **constantly demonstrated undetectable viral HIV loads**. The couple's desire was to use a gestational carrier to establish a pregnancy with these embryos. **Under current rules, these embryos in New York State are, however, not eligible for transfer into a surrogate.**

What then is there to do?

Researching various options, the CHR discovered a laboratory in Massachusetts that offers a highly sensitive assay for the detection of HIV virus in semen. If the laboratory does not detect virus, it freezes the semen sample, certifies that it is "***free of HIV virus***" and ships it cryopreserved to the referring IVF center. In many states this suffices for use of a semen sample or of embryos produced with semen of the individual whose semen was tested by the lab. Not so, however, in New York State. Here, **the *NYSDH* reserves the right of review**: i.e., the IVF center must submit **a letter with a request for "exception,"** including the Massachusetts test. The anticipation then is that the *NYSDH* will grant such an "exception" in writing; and only then can semen from an HIV-positive male be used to produce embryos for potential transfer into a gestational carrier.

Any such transfer, of course, also requires consent from the gestational carrier and such consent must be obtained in writing with full transparency.

As this rather detailed answer to this question well demonstrates, **CHR's highly individualized treatment approach to every patient, of course, also extends to the needs of the LGBTQ+ community**. Whatever can be done, will be done, even if it requires special efforts.

What does CHOLINE do in fertility supplements?

Choline supplementation in pregnancy (and, therefore, during infertility treatments) has become a very actively discussed subject on the Internet. Moreover, choline **is increasingly added to better quality prenatal vitamins**. It is an important nutrient reported to support lipid metabolism and liver health and helps the brain to control memory and mood. Because we get most choline through our nutrition, supplementation is **especially recommended for vegetarians and pregnant women.** Research suggests that maternal choline levels may also affect offspring: Good levels in their mothers have been suggested to improve the attention of newborns and may reduce the risk of cleft lip defects, hypospadias in males and cardiac defects in both sexes **The CHR, therefore, now suggests that patients take prenatal vitamins that contain choline. CONFLICT STATEMENT: CHR staff own shares in OVATERRA, a company that produces a choline-containing prenatal vitamin, "*Advanced Prenatal*."**

RECENT PUBLICATIONS from *the CHR*

We are pleased to offer brief summaries of over the last month published papers with CHR investigators as authors. We will gladly provide you with reprints if you contact us at social@thechr.com.

Gleicher N, Barad DH, Patrizio P, Orvieto R. We have reached a dead end for preimplantation genetic testing for aneuploidy. *Hum Reprod 2022. Deac052. Doi: 10.1093/humrep/deac/052; Online ahead of print.*

This commentary was initiated by two papers which at the end of 2021 to considerable attention appeared in *The New England Journal of Medicine*. The first, a large multicenter prospective trial of PGT-A from China;[1] and the second a detailed commentary on the increasing clinical utilization of PGT-A, especially in the U.S., despite absence of any clinical utility. The Chinese study, indeed, concluded that **non-performance of PGT-A was non-inferior to performance of PGT-A.** In more simple language, PGT-A did NOT improve IVF outcomes.[1] The very excellent commentary in the same issue of the journal by prominent PGT-A experts from The Netherlands and the U.S. reemphasized this point and concluded that, consequently, **there were no good reasons left to continue routine clinical utilization of PGT-A** and suggested that PGT-A be only utilized under experimental protocols.[2]

Both articles, however, missed important points, which provided the impetus for the manuscript in *Human Reproduction* by CHR's investigators and U.S. as well as Israeli colleagues; The first manuscript with slightly corrected analysis of the same Chinese data set demonstrated that, not only was there no difference in IVF outcomes between use and non-use for PGT-A (as the study had suggested), but **non-use actually produced significantly better cumulative pregnancy rates.** In other words, PGT-A not only failed to improve IVF outcomes but actually reduced pregnancy chances. This has been an argument made by CHR's investigators and colleagues from the Netherlands for over a decade.[3,4] This paper, therefore, was written and published with the intent of reemphasizing the fact that PGT-A not only does not offer benefits but, **instead of improving IVF outcomes, harms the outcome potential of IVF patients** and, especially, of IVF patients with lower ovarian reserve and, therefore, few eggs and embryos.

REFERENCES
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2. Mastenbroek et al., *N Engl J Med* 2021; 385(22):2096-2000
3. Gleicher et al., *Fertil Steril* 2008;89(4):780-7888
4. Mastenbroek et al. *N Engl J Med* 2007;357(1):9-17

Roy S, Sinha N, Huang B, Cline-Fedewa H, Gleicher N, Wang J, Sen A. Jumonji Domain-containing Protein-3 (JMMd3/Kdm6b) is critical for normal ovarian function and female fertility. *Endocrinology 2022; 163(5):bqac047. Doi: 10.1210/endocr/bqac047*

CHR's Medical Director and Chief Scientist, **Norbert Gleicher, MD,** is listed as co-author of this manuscript because of a many years-long collaboration with **Aritro Sen, PhD,** and his laboratory that has resulted in many important papers, this one included, in which the CHR contributed some of the required biological samples for the study. Sen was the lead author in the original androgen receptor knock-out study in mice that for the first time well demonstrated the important androgen effects on follicle maturation and egg quality.[1] This study appeared in the literature a few years after Gleicher and his colleague **David Barad, MD, MS,** the CHR's Clinical Director of IVF, for the first time observed and reported the effects of DHEA supplementation in women with low functional ovarian reserve (LFOR).[2] CHR's investigators have since published 36 papers involving DHEA supplementation in infertile women. A collaboration evolved between the two labs, with Sen for several years also becoming a Visiting Scientist at the CHR. This collaboration offered the ability to go from observations in humans to experiments in mice and back and, consequently, unique opportunities arose for improving the understanding of androgen effects on ovaries.

The here reported study highlighted **the critical role of JMJD3 (or KDM6b),** a Jumonji domain-containing histone demethylase in nuclear-mitochondrial genome coordination **essential for maintenance of ovarian function and, therefore, female fertility** and also points out its **potential role in ovarian aging,** as this demethylase decreases with advancing age in mice as well as humans.

REFERENCES
1. Sen A, Hammes SR.. *Mol Endocrinol* 2010;249&0:1393-1403
2. Barad DH, Gleicher N. *Fertil Steril* 2005;84(3):756

Barad DH, Albertini DF, Molinari E, Gleicher N. IVF outcomes of embryos with abnormal PGT-A biopsy previously refused transfer: a prospective cohort study. *Hum Reprod 2022 https://doi.org/10.1093/hum rep/deac063; Online ahead of print.*

When first published electronically, this study attracted immediate media attention, including an article in *The New York Times*[1] and in several other daily newspapers. An article in *Scientific America* is expected soon. CHR's investigators in this article attempted to address the large number of so-called **chromosomal "abnormal" embryos, currently cryopreserved but refused transfers by an overwhelming majority of IVF centers**. Physicians at the CHR have been transferring such "abnormal" embryos selectively since 2014 and reported first healthy births from such embryos in 2015.[2]

In recent years increasing numbers of patients who after IVF cycles at other IVF centers had produced only "abnormal" embryos that were refused transfer and, therefore, were not even given a chance of pregnancy, **moved their "abnormal" embryo to the CHR**. The now published papers reported on cycle outcomes for the first 50 consecutive such patients and, unsurprisingly for the CHR, but likely quite surprising for the rest of the world, **clinical outcomes were excellent, especially considering the advanced age of the patients 41.35 ± 3.98 years and their overall poor prognosis for other reasons**. **Among those 50 transfers, pregnancy, miscarriage, and live birth rates per cycle start were, respectively, 33.3%, 19.3%, and 14%. Per patient those rates were even better at 38%, 22.0%, and 16.0%. Two pregnancy losses, however occurred following amniocenteses, with both likely preventable and demonstrating chromosomal-normal pregnancies. Live birth rates, otherwise, would have been even higher and miscarriage rates lower.**

Considering **these amazing outcomes**, the media attention this paper received cannot surprise, especially since the in this paper reported **50 patients/couples, still, have over half of their allegedly "abnormal" embryos cryopreserved.** In other words, **they, likely, can still at least double up on in this paper reported live birth rate.** If one then furthermore considers how many thousands and thousands of such allegedly "abnormal" embryos are still cryopreserved in the U.S. and elsewhere in the world, and refused transfer, conclusions for IVF centers become quite obvious (and that does not even consider even much larger numbers of allegedly abnormal embryos that over the years have been simply discarded): **START SELECTIVELY TRANSFERRING CHROMOSOMAL ABNORMAL EMBRYOS,** and if you, as a center, are not willing to do so, at least release the embryos and refer your patients to centers that are willing to do such transfers. Fortunately, their number is increasing.

REFERENCES
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2. Barad et al., *Hum Reprod* 2022; https://doi.org/10.1093/humrep/deac063; *Pubmed ahead of print*.

NEWS RELEVANT TO REPRODUCTIVE MEDICINE IN THE LITERATURE

Likely in compensation to the previous month's huge bounty of interesting articles in news media and science as well as medical literatures, interesting articles for reproductive medicine last month were rather sparse. Below we present what we, nevertheless, found interesting.

General Medical News

The relevance of obesity in inflammatory diseases

Increasing data in the medical literature in recent years well established that inflammatory diseases **like,** for example, **atopy and asthma**, present with **more severe clinical phenotypes in obese than non-obese individuals and are also more treatment resistant.** Concomitantly, it also has become apparent that obesity and associated metabolic diseases can influence the immune system. Now came a large group of U.S. – based investigators from several universities; they attempted to elucidate, using two mouse models of atopic dermatitis, how immune responses differ in obesity and absence of obesity.[1]

Atopic dermatitis is (by the way, like pregnancy) usually associated with a **classical type 2 T-helper cell (T_H2) response.** This response in obese animals was, however, diverted into a **much more malignant T_H17 inflammation.** This reprograming of the immune response was also associated with distinctively **different clinical responses to biological therapies against T_H2 responses**: as anticipated, they worked well in lean mice but **actually exacerbated disease in obese mice**. Further single cell molecular investigations in the animals revealed **decreased PPAR-gamma** (nuclear receptor peroxisome proliferator-activated receptor-gamma) **in T_H2 cells from obese mice**. Conditional ablation of PPAR-gamma in T cells reaffirmed its importance in focusing the *in vivo* T_H response toward the desired T_H2 status, while preventing aberrant inflammations like above noted T_H17 response. Further confirming the importance of PPAR-gamma, treatment of obese mice with **a small-molecule PPAR-gamma agonist reduced T_H17 pathology and reconstituted responses anti-T_H2 biologics**. The authors concluded that this study revealed not only the biology how obesity adversely affects inflammatory diseases but, "also offers a new precision medicine approach to target the immune dysregulation caused by obesity."

This is a fascinating paper because an anti-inflammatory **T_H2 immune response must also dominate in pregnancy to allow for normal pregnancy to progress**. A so-called inflammatory T_H1 response, for example, has been associated with pregnancy pathologies, including miscarriages, as first suggested by the much too early deceased **Thomas G. Wegman, PhD**.[2] In this paper **reported PPAR-gamma associated findings, therefore, now urgently call for investigations in normal and abnormal pregnancies.**

REFERENCES
1. Bapat et al. *Nature* 2022;604:337-342
2. Wegman et al., *Immunol Today* 1993;14(7):353-356

News in Clinical Reproductive Medicine

Interesting obstetrical news

A word about guidelines

In an interesting editorial in the "Gray Journal" with co-author **Wayne R. Cohen, MD**, **Emanuel A. Friedman, MD,** the "father" of **the Friedman Curve of labor**, asked, whether current labor management guidelines from *ACOG/SMFM* are really evidence-based?[1] That Friedman, already for years in retirement, would have to ask this question because he apparently received no response to many inquiries from those at the *ACOG* and the *SMFM* who updated current guidelines using labor data produced by statistical remodeling of earlier data (mostly generated by Friedman and associates), - yet without further clinical validations, appears troubling, as **this newsletter has repeatedly pointed out the value as well as dangers of modelling studies in medicine**. One just must look at some of the absurd models that received huge media attention in the early days of the Covid-19 pandemic. They turned out to be off in predicted mortality rates by hundreds of percentage points.

> Like so many other aspects of life in recent years, guidelines increasingly appear driven by politics rather than "evidence."

Though we strongly sympathized with the arguments made by Friedman and Cohen in their article, the principal reason why we chose this editorial for presentation, is the much broader topic of **professional guidelines in general.** Like so many other aspects of life in recent years, guidelines increasingly appear driven by politics rather than "evidence." And by politics, we do not mean left versus right or Democrats versus Republicans but the fact that, like in national politics, differences of opinions in medicine are no longer resolved through the conduct of appropriately designed and controlled studies but by **strategic political alignments between likeminded physicians, often supported by industry,** in **a pursuit of becoming opinion leaders,** not by generating new evidence-based data but by controlling editorial boards and professional organizations. We will in the future return to this subject in more depth but found it remarkable that the father of modern obstetrics in this country had to come out of retirement to pen an editorial to express his concern about how practice in obstetrics is guided into new directions without convincing evidence. In reproductive medicine, we, of course, have now for decades seen this happening.

Hypertension in pregnancy

Wherever one looked over the last two month, there was an article about hypertension in pregnancy. What had made the subject suddenly "vogue" was unclear because there had not been any substantial progress or new finding on the subject. Probably the most interesting article appeared in *The New England Journal of Medicine* and came from the **Chronic Hypertension and Pregnancy (CHAP) Consortium** involving many U.S. universities.[2] We would argue, unsurprisingly, the study concluded that in women with **mild chronic hypertension** , maintaining blood pressures below 140/90 mm Hg resulted in better obstetrical outcomes than non-treatment until patients were severely hypertensive and did not result in more cases of small for gestational age offspring.

In the same journal British investigators offered a comprehensive review article on **preeclampsia**,[3] which we only recommend because there hasn't been a comprehensive review article on this subject in years in the literature. Unsurprisingly, there is not much new to report on the subject but, **astonishingly, the article discussed preeclampsia practically without reference to the immune system.**

Obstetrics is not spared article retractions

Medscape recently reported that the *European Journal of Obstetrics & Gynecology and Reproductive Biology (EJOG)* had to retract a "*clinically influential 2016 paper*," titled, "**Antenatal corticosteroid administration before elective caesarean section at term to prevent neonatal respiratory morbidity: a randomized controlled trial,"** authored by a group of investigators at *Cairo University*, with lead author **Adel Nasa, MD**.

Which allows us to bring into the picture a colleague, **Ben Mol, MD,** originally from the Netherland but more recently hyperactive mostly from Monash, Australia, who for many years has been an honest **"truth-seeker"** in the OB/GYN field and, in the process, unsurprisingly, was not always the most popular among colleagues. In looking above noted manuscript, he noticed that the female/male ratio in

over 1200 newborns was 59/41, - an obviously impossible finding. By 2021, he submitted an article to *EJOG*, pointing out this and other incongruities in the manuscript. Following standard practice, *EJOG* requested explanations and the original dataset but received no answer from the authors. The article, therefore, was retracted "at the request of the Editor-in-Chief."[4]

Once again, there is a purpose why we feature this news item and that is the indisputable fact that there are large numbers of "fake news" papers accepted not only in reproductive medicine journals but in medical journals in all specialties. We do not envy the editors who, often based on only circumstantial evidence, must make decisions to retract papers. Considering a completely implausible way to analyze data which bunched fresh and frozen-thawed IVF cycles together, we, however, could at least suggest one recent paper in the IVF field that deserves Dr. Mol's scrutiny.[5]

We are not doing well in obstetrical outcomes in the U.S.

Maternal mortality in women 40 and older reached 107.9 deaths/100,000 live birth in 2020. This represents a 43% increase over 2019. In women under the age of 25 the rate was 13.8/100,000. Overall maternal mortality surged by almost 20%.[6] We, consequently, are **not doing well with older women having babies,** while older women represent the age groups growing proportionally most rapidly

> "Increasing numbers of infertility treatments in older women, therefore, unquestionably contribute to the increasing mortality."

in conceiving, and often having to resort to infertility treatments. **Increasing numbers of infertility treatments in older women, therefore, unquestionably contribute to the increasing mortality.**

Minorities also do not do well: A recent paper in *JAMA* looked at advanced pregnancy outcomes with **gestational diabetes** by race and ethnicity.[7] Between 2014 and 2020 the **frequency of multiple adverse pregnancy outcomes significantly increased** in women with gestational diabetes and **differences to the disfavor of Black and Hispanic women continued.**

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2. Tita AT, et al. *N Engl J Med* 2022 386(19):1781-1792
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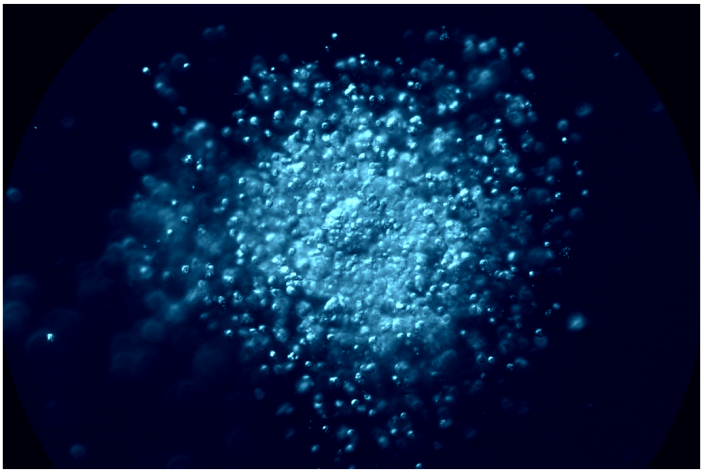
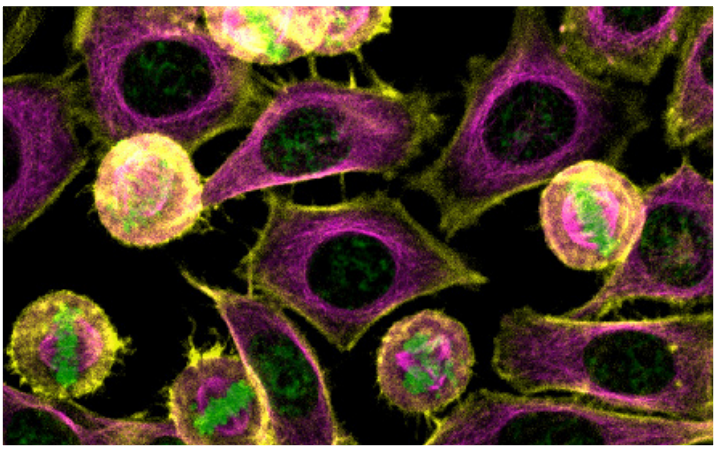
4. https://www.medscape.com/

Dr. Albertini's Photo Gallery

Photos prepared by David Albertini, Ph.D.



This is an image of a human oocyte taken in the embryology laboratory at the CHR. It shows just what the embryologists are looking for after the doctors suction each of a patient's follicles the day after receiving an ovulation trigger injection. The oocyte is seen in the center of a mass of cells known as cumulus cells, named because the first time scientists discovered these structures, they resembled clouds of the cumulus variety. Before performing ICSI on mature oocytes, these surrounding cells are gently removed so as not to disturb the potential of the oocyte to develop normally after it is fertilized.



A field of human cells grown outside the body (in vitro) is shown where many actively dividing cells appear round and yellowish and the cells that are not dividing are flattened and magenta colored. Here at the CHR, research is going on to determine just what are the molecular and cellular factors that cause cells to divide or not. These are important and clinically relevant studies because we know that similar forces causing these cells to divide are required in the oocytes and embryos collected in an IVF/ICSI cycle. In this picture you can see them in action as the green chromosomes are highlighted and positioned on the magenta spindle.

Are we losing donor anonymity in the U.S.?

Various media sources also reported on a proposed Colorado law that would eliminate confidentiality for sperm and egg donors. Countries, like the U.K., that followed such a route saw a precipitous decline in donations.

This new law which passed the state legislature through a bipartisan bill, would give offspring the right to learn the identity of their sperm and egg donor at age 18. They, however, already earlier would be given access to a donor's anonymized medical information. Fertility clinics are mandated to update contacts with their donors and medical records every 3 years. Moreover, infertility clinics would be charged with ensuring that not more than 25 families conceive from a single donor, with sperm and egg donors allowed to donate only six times. Minimum donor age would be 21. The bill is scheduled to go into effect as of January 1, 2025.

As **Mary Chris Jaklevic** reports in Medscape, New York State allegedly has a bill underway that would require IVF clinics to verify the medical, educational and criminal histories of donors and allow donors access to this information.[1]

REFERENCE

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How outdated are the Rotterdam Criteria for the PCOS?

For decades PCOS (the polycystic ovary syndrome) is, as the term "syndrome" indicates, not a single disease but an amalgam of 4 conditions, allegedly sharing important enough common denominators to keep them in one common basket. Based on **Rotterdam Criteria**, these individual conditions for all these years are described as phenotypes A, B, C, and D. CHR's investigators have now for several years been making the point that PCOS would be better explained as 2 distinct conditions, with one encompassing phenotypes A, B, and C (**genomic, likely, a mostly metabolic conditions** since women are at significant risk for the **metabolic syndrome**) and the D-phenotype (genomic likely an autoimmune/inflammatory condition) since it by age 35 is in ca. 85% associated with evidence of a hyperactive immune system. There, of course, are additional highly significant differences between these 2 conditions but here is not the time to discuss them further.

Now **Marcelle I. Cedars, MD,** one of the most prominent academic voices in reproductive medicine published a brief editorial opinion in *Fertility & Sterility* in which she is making the absolutely correct point that Rotterdam Criteria, "*have not helped us either care for women or design research*."[1] CHR investigators have currently a much more detailed manuscript our for review in which they, similarly to Cedar, propose **a reassessment of Rotterdam Criteria if our understanding of PCOS is to, finally, make some relevant progress.**

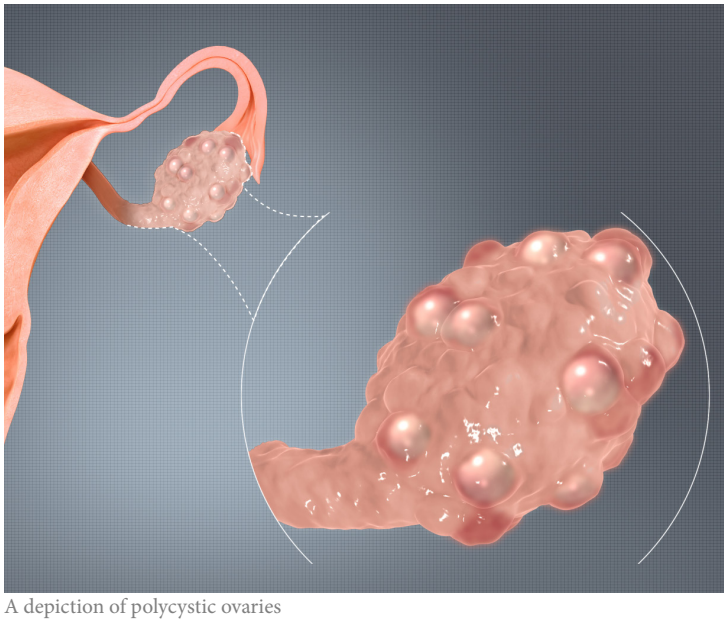
REFERENCE

1. Cedars MI. *Fertil Steril* 2022;117(4):696-697

Can treatment-resistant follicles be activated?

Mostly Japanese investigators (with one U.S. contributor) in 2013 hoped to demonstrate that ovarian tissue, removed by biopsy from the ovary, *in vitro* then exposed to mechanical fragmentation and, therefore, supposedly **interruption of the Hippo pathway**, while also bathing the biopsy specimen in phosphatase and **tensin homolog (PTEN) inhibitors** and **Akt-stimulants,** would promote follicle growth, induced follicle activation in previously treatment-resistant follicles.[1] Biopsies were then reimplanted into ovaries in the hope that this treatment would lead to pregnancies. Though sporadic pregnancies have been reported, **the treatment was obviously too invasive for the little return in pregnancies that was received** and has not been heard of in a long time.

But one question was left unanswered: **how effective is potential in vitro mechanical fragmentation of ovarian tissue on its own in causing follicle activation?** Spanish and U.S. investigators from *IVI/RMA-NJ* now reported an interesting study of women with poor ovarian response who underwent a controlled randomized study in which during laparoscopy an ovarian biopsy was performed, with the removed tissue being fragmented and immediately during the surgery returned into small "pockets" created as receptacles for the fragments. The authors claimed that, though **IVF outcomes were not affected, antral follicle counts appeared to have increased, while AMH and FSH did not improve**.



A depiction of polycystic ovaries

This study involved only 34 patients. **This is not large enough a group of patients to demonstrate outcome differences in any randomized IVF study**, - even if patients are good prognosis patients. With poor prognosis patients, where expected pregnancy chances are much lower, the patient numbers must be even larger. **That the authors would publish such a study, and that a respected medical journal would accept it is, of course, astonishing but not surprising** considering the history of the journal and considering that the journal's previous editor-in-chief is the study's senior author.

We, however, found the study, nevertheless "interesting" because, considering how invasive a surgically performed ovarian biopsy is, there are less invasive ways to test whether activating Hippo may reactivate resistant follicles, and **the CHR has such a prospectively randomized study, indeed, running**. This is the center's registered PRP III study, in which patients are randomized to injection with the PRP plasma fraction and a placebo fraction from the patients' own blood. Since the way how the CHR injects PRP into ovaries involves multiple mini-injections under the capsule into each ovary**, there must be a mechanical effect on the Hippo pathway**. Should there be activation following PRP, without this randomization, it again would be impossible to tell whether the effect was caused by the PRP or Hippo activation. It, however, will likely take at least another year to accumulate the number of patients needed to have an answer.

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1. Diaz-Garcia C, et al., *Fertil Steril* 2022;117(4):747-754

Still, neither federal government nor most companies offer IVF coverage as part of their general health plans; this is how the CHR can help

Except for veterans who are infertile because of injuries, the federal government does not provide insurance coverage for infertility services, including IVF for any of its insurance plans, **Medicare, Medicaid,** and **Veterans Administration.** And private employers only add IVF coverage very slowly to the health plans they offer their employees. In 2015 only 24% of corporations with over 500 employees offered IVF coverage. By now **the number is up to only 27%,** according a recent *ACOG BULLETIN* on May 5, 2022. And one must furthermore assume that IVF coverage is offered even more sparingly in smaller corporations.

THE CHR, THEREFORE, WITH STARTING DATE JULY 1, 2022, WILL OFFER EMPLOYERS A SIGNIFICANTLY DISCOUNTED FEE SCHEDULE FOR INFERTILTY SERVICES THEY ARE WILLING TO COVER AT LEAST PARTIALLY. IN ORDER TO MAKE THIS PROGRAM ATTRACTIVE FOR EVEN SMALL EMPLOYERS, THEY WILL BE ABLE TO CHOOSE THE PERCENTAGE OF CO-PAYMENT THEIR EMPLOYYES WILL BE RESPONSIBLE FOR. Interested corporate representatives (as of this point only in the larger New York tristate area) are welcome to contact the CHR's COO, Ms. Jolanta Tapper at +1 212-994-4400/Ext 4406 or via e-mail at **jtapper@thechr.com**. **If your company does not offer IVF coverage, tell your HR department that CHR's services for corporate entities are unmatched in quality and cost structure.**

COVID-19

What causes "severe" Covid-19?

In a recent article **Smiriti Mallapaty** in *Nature* reviewed data from papers already published and still at preprint (unreviewed) stages, which all point toward the conclusion that by SARS-CoV-2-infected immune cells may hold clues why some patients develop severe Covid, while most have only mild disease. Primarily **implicated are monocytes in blood** and **macrophages in lungs**. Both studies also confirm what so-far has been only suspected, - namely that **immune cells do get infected**.

In the first already published study,[2] Boston investigators noted that **6% of monocytes** were undergoing **pyroptosis,** a form of inflammation-associated cell death, which is an unusually high number. On closer examination, these cells then were found to be infected by the virus which, as the researchers hypothesized, activated i**nflammasomes** which trigger cell death. In looking at **macrophages in the lung,** they also found that a fraction of these cells was infected

> "Both studies also confirm what so-far has been only suspected, namely that immune cells do get infected."

by the virus and also demonstrated inflammasomes. Cells from the lung's epithelium did not demonstrate infections.

The second study, still to undergo peer review, offered similar results:[3] This group of investigators from *Yale University* confirmed that the SARS CoV-2 virus could infect and replicate in human and mouse macrophages, and macrophages demonstrated the same inflammatory response, as described by the Boston group.

Many questions, however, remain to be answered; among those, how much do here described observation contribute to "severe" Covid-19 and how could these observations be used in developing new treatments against "severe" Covid-19.

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