SCIENCE Magazine reports on CHR research

In its March 24, 2017 issue, the highly prestigious SCIENCE Magazine dedicated a full-length article to one of CHR’s recently initiated research projects, which we previously described in these pages. SCIENCE is one of the highest ranked scientific journals in the world. It publishes science-related news and original research articles in all areas of science, and to be published in this journal is considered a major accomplishment in any scientist’s career. For SCIENCE to dedicate a full-length article to a CHR project, therefore, must be viewed as a real accomplishment for CHR’s research efforts.

The project in detail described in the article, written by accomplished SCIENCE writer Mitch Leslie, involves the selected administration of Influenza vaccine to women prior to IVF. CHR investigators hypothesized that such vaccinations may induce pathways within a woman’s immune system that improve chances of conception by enhancing the woman’s immune system’s tolerance of an implanting fetus.

Since every fetus is half paternally derived, it for the mother’s immune system is a so-called semi-allograft. This means her immune system should see the implanting embryo like a mini-organ transplant from her partner and, therefore, reject it. But in normal pregnancy, if the woman has a normally functioning immune system, she should see the embryo like any foreign object and thus should accept it.

The political tussle around Obamacare: Impact on IVF

As medical providers, we are usually trying to stay away from outright political topics to maintain political neutrality. But what recently has been going on around continuation, modification or outright repeal of Obamacare (a.k.a., Patient Protection and Affordable Care Act, ACA) has been so blatantly ridiculous that we can no longer escape the need to address a few relevant issues to the provision of fertility services.

Let’s start with the good news: Fortunately, Obamacare has not had much impact on fertility services because, except in states where state laws mandate in vitro fertilization (IVF) coverage, there never was any impact at all. Obamacare, for example, never affected longstanding Congressional prohibitions to pay for IVF services under Medicaid and Medicare. A recent congressional allowance to spend federal money on IVF in the Veterans Administration affected only veterans with infertility caused by injuries received in combat.

The bad news is that we are entering a period of increasing uncertainty, which, indeed, in the end may negatively affect currently existing medical coverage, especially in states which mandate that private insurance companies cover IVF as part of their coverage portfolio.

Recent Republican attempts to repeal Obamacare and concomitantly replace it with a new plan, the American Health Care Act (AHCA), jokingly referred to by some as Trumpcare, Ryancare, or the Greatest Health Plan Ever), recently failed bitterly (though attempts at resurrection are underway at time of this writing), not the least because for some Republicans

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it did not offer immediate reductions in insurance premium costs, for others it did not provide enough cost reductions for the national budget in coming years. Democrats did not even consider the AHCA worth consideration because maintenance of President Obama’s single most important legacy, Obamacare, was worth any effort, even if it in the end meant killing the already terminally thick patient, called Obamacare.

Unable to reach a majority in Congress, President Trump agreed to withdrawal of the proposal, leaving the country with Obamacare, which everybody agrees is already in the fangs of a death spiral, with costs increasing far more quickly than even the most pessimistic forecasts, while insurance companies are still losing money and, therefore, increasingly are withdrawing from the business of covering people under Obamacare.

All, of course, as always comes down to money: Insurance companies want to make profits; Congress wants to save money because the country is already close to $20 trillion in debt; but patients want maximal coverage, and neither political party nor the president have the guts of levelling with the public that there, simply, is no health care system in the world that can offer unlimited high quality health care at decreasing cost.

There are good reasons why even relatively good national health care systems in Canada, the U.K. and elsewhere are limiting access, causing often lengthy waiting periods for non-emergent medical care, and, ultimately, restrict care where such care is believed not to be warranted.

Returning to IVF, there are good reasons (at least the Swedes believe so) why Sweden, likely a country with one of the most progressive views about national health care, offers IVF coverage in a national health care benefit package, but does so only up to female age 40. Sweden’s health care economists, simply, concluded that the return in pregnancy and delivery rates achieved in women above age 40 no longer warrants coverage since society will be better served by using these funds for other forms of health care.

In other words, health care systems all over the world have taught us that unrestricted fee-for-service health care systems cannot be tamed within preset budgets. The only way to control health care costs is to set not-to-exceed boundaries for health care costs, and squeeze national health care into these boundaries, which, of course, is only possible through various forms of rationing. Republicans, Democrats and the president can, therefore, promise anything they want to promise; to believe that any one or all three parties together, suddenly, will find a way to squeeze all demanded medical care into a diminishing cost structure is unrealistic. **We, therefore, better get ready for rationing of medical care one way or the other, whatever the final health care system will be that follows Obamacare.**

The really bad news is that, as progressive countries like Sweden so well demonstrate, female fertility services and especially IVF are always at the top of the unneeded/unwanted list. Canada’s largest province, Ontario, just learned that again very recently. Only a few years ago, the progressive province (in Canada health care systems are determined by individual provinces) offered significant IVF coverage. It was rescinded last year because of excessive costs. It seems likely to us that, whatever new national system will, finally, be approved by a majority in Congress, it will remove most, if not all, insurance mandates. Together with mandates to cover obstetrical care, drug addiction, psychiatric conditions and other currently mandated services under various laws, we are deeply concerned that insurance mandates for infertility services, including IVF, will disappear. If our pessimistic outlook proofs to be warranted, then already rather limited insurance coverage for fertility services will in the not-too-distant future further shrink.

This is one prediction where we would not mind being wrong! ●

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Increasing restrictions for infertility services by insurance companies

Because infertility has not been considered a “disease” for the longest time, and by many institutions till today, private insurance coverage of infertility services has been a challenge since the advent of IVF. As private insurance is only mandated to cover disease states, this distinction was legal grounds for refusing the coverage of infertility treatments. Further support came from the federal government also refusing coverage under federal health insurance programs, Medicaid and Medicare.

All of this started to change in the 1990s when a small number of states, starting with Massachusetts and Illinois, passed laws that mandated the coverage of infertility services, including IVF, under standard health plans. While extent of coverage varied between states, these state laws offered for the first-time access to IVF to broad swaths of the population. In parallel, infertility was by the courts recognized as a disability, setting the stage for the legal argument that withholding insurance coverage for infertility represented a breach of the Americans with Disability Act. Employers and private insurance companies, therefore, started offering infertility coverage, though at different levels, with some covering only diagnostics, others offering lower levels of treatments up to IVF and a small minority offering a comprehensive package including 3-4 IVF cycles.

But as IVF coverage seemingly increased, insurance companies also started interfering in the practice of IVF by mandating which patients could or could not be treated (some insurance companies, for example, restricted treatment based on age and/or FSH levels) and how patients had to be treated (for example, before a patient could be offered IVF, a patient had to have failed 3 IUI cycles).

These practice restrictions, as insurance companies uniformly have been representing to public and treating physicians, were based on “best scientific evidence,” usually collected by paid medical consultants and, therefore, were claimed to be motivated only by a desire for best patient care. That they may be motivated by containing costs to the insurance companies, is usually strenuously denied.

The control insurance companies exercise over IVF practice has over the years constantly increased. We recently witnessed one of the most bizarre cases ever, when a major insurance company approved a patient’s IVF cycle but refused coverage for the proposed use of intracytoplasmic sperm injection (ICSI), which represents just a minute fraction of total IVF cycle costs. The patient appealed the decision and the insurance company set up a “peer-to-peer” telephone conference between a CHR physician and a medical director at the insurance company.

This medical director turned out to be anything but a “peer.” He was not a fertility specialist, not even an Obstetrician-Gynecologist. When the CHR physician explained the rational for ICSI, that the male demonstrated sub-fertile sperm morphology at 7% Kruger criteria and that maximal fertilization was essential since the 45-year-old female patient, likely, would produce only very few eggs, the medical director’s only response was that, based on “best evidence” the company allows (i.e., pays for) ICSI only once sperm morphology is in infertile range, below 4% Kruger criteria. CHR’s physician’s retort that this may make sense in a young woman but does not in a 45-year-old woman, fell on deaf ears.

What makes this case so extraordinary and such a good example for the stupidity of the system, is the willingness of the insurance company to risk the whole IVF cycle (if fertilization fails) at a cost of thousands of dollars, to save a few hundred by refusing to pay for ICSI. Moreover, think about all the costs the insurance company incurs in administrating all this bureaucratic morass, including the hiring of medical directors who prefer to shuffle papers to practicing medicine.

Because of practice restrictions like this (which we, as in this case, simply, consider bad medicine), and the increasing administrative overhead required from physician providers to manage the demands of many insurance companies (nobody, for example, paid CHR for all the time staff dedicated to this appeals process), CHR, already a good number of years ago, discontinued relationships with most insurance

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immune system, she will not reject the fetus because her immune system will have developed adequate tolerance.

In women with inadequate tolerance development, the immune system, however, will see the implanting embryo as “foreign” and attack it. Consequences of inadequate tolerance are, therefore, failure to implant (so-called implantation failure) and increased miscarriage risk.

CHR investigators hope to be able to demonstrate that, especially in women with a history of implantation failure and recurrent pregnancy loss, administration of Influenza vaccination before IVF cycles improves outcomes by improving tolerance. They are also attempting to identify the specific immune pathways that may relate to tolerance development, since their definition could also have major importance for other areas of medicine, like autoimmune diseases and, of course, organ transplantation.

This study is open to all CHR patients undergoing IVF, including donor egg recipient cycles. We, however, also encourage women with histories of implantation failure and repeated pregnancy loss, currently not in treatment at CHR, to consider entry into this registered study (actually, 2 studies are registered, one in infertility patients using their own eggs and one in patients using donor eggs), and welcome referrals from colleagues.

Since CHR’s investigators are anxious to complete this study as rapidly as possible, they are currently also looking for collaborating IVF programs, which would be interested in joining the study. Interested parties are requested to contact David H. Barad MD, MS, CHR’s Director of Clinical ART at dbarad@thechr.com.

Mitochondria Study
DO YOU CARRY A MITOCHONDRIAL DISEASE OR KNOW SOMEBODY WHO DOES?

If you do, please call us at 212-994-4400 for a free consultation in person, by phone or via Skype. CHR is searching for a way to prevent inheritance of these awful diseases in collaboration with colleagues at the famous Salk Institute for Biological Studies in La Jolla, CA. You may be able to help us find a way to prevent mitochondrial diseases in children!

Contact us to learn more about the study: http://kaywa.me/43Mdn
Monthly Case Report: Transferring “aneuploid” embryos or starting another fresh IVF cycle?

In this section, we report brief case summaries we believe may be educational for patients and colleagues. We invite colleagues to participate in this monthly feature by contributing interesting cases. Submitted cases should be described in not more than 500 words, and suggested treatment and outcome should not exceed 250 words. If accepted for publication in the VOICE, CHR will add a commentary. If you think that you may have an interesting case to report, please contact this newsletter’s editor, Yu Kizawa, at ykizawa@thechr.com.

Case: A 34-year-old G0 patient presented for initial consultation after 3 consecutive IVF cycle failures at another regional IVF center. The indication for IVF was a severe case of male infertility, with less than 5 million total sperm. The patient produced good oocyte numbers in all 3 IVF cycles (n=8-12), with a majority being mature. Good fertilization (>60%) was accomplished in all cycles, utilizing intracytoplasmic sperm injection (ICSI), and a total of 10 blastocyst stage embryos (4, 3 and 3) were cryopreserved after trophectoderm biopsy for PGS. In each of the 3 IVF cycles, PGS, however, revealed no euploid embryos. The patient, therefore, had no embryo transfer in any of her cycles. She, however, had 9 allegedly chromosomally abnormal, and 1 embryo that failed to give a reading result, cryopreserved.

She presented to CHR with the principal question whether her cryopreserved, allegedly “aneuploid,” embryos could be transferred at CHR since the IVF center where those embryos had been generated refused to do so.

Review of her medical record further revealed a BMI of 24, an FSH of 8.6mIU/mL and an AMH of 1.1ng/mL. Her testosterone levels were in normal midrange but her SHBG was mildly elevated at 128nmol/L. All remaining labs were within normal ranges. Among her 9 cryopreserved “aneuploid” embryos, 3 were chaotic, 4 monosomic and 2 trisomic (likely lethal).

Analysis: This was a young woman, presumed to demonstrate infertility due to a severe male factor. She, however, demonstrates mildly elevated age-specific FSH and mildly low age-specific AMH and, therefore, also carried a diagnosis of mild premature ovarian aging (POA), also called occult primary ovarian insufficiency (oPOI). Though her testosterone levels were in range, her relatively high SHBG suggested that, considering her hormone receptor memory, they actually may have been a little low. Male infertility remained the most likely primary cause of this couple’s infertility. We, however, felt that her POA/oPOI could also contribute to the couple’s infertility by negatively affecting egg quality.

The couple was advised that under an experimental consent protocol CHR would feel comfortable transferring her 4 monosomic, 2 trisomic and 1 undetermined embryos. We recommended against transfer of the 3 chaotic embryos because in our center’s preliminary experience, we failed to establish pregnancies. In contrast, transfers of monosomic and trisomic embryos resulted in chromosomally normal pregnancies in almost 50% of transfers. We also discussed with the couple whether to transfer their aneuploid embryos or keep them frozen for future potential use, and the decision was to proceed with another fresh IVF cycle.

Resolution: Since the couple was desirous of 3 or more children, they decided to keep their cryopreserved allegedly “aneuploid” embryos “on reserve,” and to pursue another fresh IVF cycle. The female, therefore, was pre-supplemented with DHEA and CoQ10, following the center’s standard protocol for women with POA. As expected, her SHBG under DHEA supplementation declined to 69.0 nmol/L, confirming our suspicion that she, likely, had been mildly hypo-androgenic despite apparently normal testosterone levels.

In a subsequent IVF cycle, she produced a record 14 oocytes, of which 9 fertilized and 6 reached day-3. Two embryos were transferred on day-3 without PGS, and the patient conceived a singleton pregnancy, resulting in a normal vaginal delivery at term. The couple currently still has 4 day-3 embryos cryopreserved from their most recent cycle at CHR plus 10 blastocyst stage embryos from 3 prior PGS cycles elsewhere.

Conclusions: This case illustrates a few often-overlooked facts: (i) Even when an obvious cause of infertility is identified, a second significant cause may co-exist. (ii) FSH and AMH levels must be assessed in age-specific fashion if women with mild POA are to be correctly diagnosed. (iii) Women with POA, likely, will conceive quicker with day-3 than with days-5/6 transfers. (iv) Currently PGS, in CHR’s opinion, is unable to determine accurately whether an embryo is chromosomally normal or not. PGS should, therefore, be avoided.
Malicious Internet attack against CHR’s website

CHR’s webmaster who, among other responsibilities, is charged with maintaining the security of our website, informed us approximately two months ago that CHR’s website has been under a highly organized, apparently well-financed and professionally very competently executed malicious attack since the summer of 2016, with the apparent goal of driving down the organic traffic to our website. As of this point, CHR’s webmaster was able to free the website off many malicious links used as part of the attack, and our attorneys are ready to attack back! It, surely, also would be very interesting to find out who is behind all of this.

These kinds of attacks are not inexpensive, and one wonders who might be willing to spend the money? It is hard to believe that a competitor would do this; but who else but a competitor might even consider such a thing? If it is a competitor, then we take it as a compliment because, boy do we have to be good for somebody to be threatend enough to go that far!

The Internet has become important for most medical providers since patients increasingly select their physicians via Google or other search engines. Search Engine Optimization (SEO) is, therefore, critical in establishing top ranking for key words a medical provider wants to attract. To rank competitively for important key words, which usually means on the first page, is, therefore, of great importance and, nowadays, much more difficult than only 2-3 years ago. Because proactive steps to rank highly have become increasingly difficult and are also more and more expensive, a new type of SEO has emerged in recent years, the so-called “negative SEO.”

Saying something very important about the morality of our society, recent research, indeed, suggests that most companies, when approached, agreed to use of negative SEOs on their direct competitors in hope of damaging their Google listing and, thereby, improving their own.

All of that, of course, surprised us but, even more surprising was the recognition that, apparently, a whole industry of agencies willing to perform these negative SEOs has arisen over a very short time-period, taking “playing dirty” to a new level. The thought that a medical competitor may go that far is highly disturbing to us.

A negative SEO can involve hacking a website (so far apparently not the case), building up to thousands of spammy links to a website (allegedly discovered), copying content and distributing it all over the Internet (under investigation). Posting links between the website and negative key words (allegedly discovered), creating false social profiles in attempts to ruin reputations online (under investigation) and removing good backlinks from website (allegedly discovered).

Google rankings can also be damaged by so-called “Google Bowling,” which means that the attack exploits certain Google algorithms used for ranking purposes. So, for example, Google, in attempts to reflect best content, searches all the time for “fake” content that is only placed for gains in ranking. A negative SEO attack may be carried out by buying a large quantity of low quality links directed at a competitor’s website, making it look like this website is artificially trying to improve ranking. In successful negative SEOs, this will result in a Google manual or algorithmic penalty, requiring link audits and subsequent link cleanup prior to forgiveness by Google.

Another way to harm a website is by devaluating the site’s content by, for example, duplicating it and disseminating it all over the web.

We are now in the process of “cleaning up” but, at the same time, must be vigilant about repeat attempts to damage CHR’s Google ranking because somebody out there has it in for us! The thought that somebody considers CHR enough of a competitor to unleash such a cyberattack is, indeed, in a perverse way a compliment, but it is also extremely disturbing as a statement of character!

-Steven E. Fallopini, MD

Staying Connected

New informational material on treatments or news coverage on fertility breakthroughs, the best way to stay up to date on CHR’s activities is via our social media channels. Follow us, and never miss important news!