Looking Forward to an Exciting 2016

We welcome all of our readers to the year 2016, hoping you experienced a wonderful Holiday Season. CHR is for a number of different reasons looking forward to an exiting year: First of all, we expect to, finally, complete our center’s expansion. Those who have visited the center in recent months may have noticed that significant progress is being made, but much still remains to be done.

Another major event we are looking forward to is an international scientific conference the Foundation for Reproductive Medicine (FRM) is organizing in November of this year here in New York City (with co-

Emerging Subjects of Interest in IVF

Since CHR’s Medical Director and Chief Scientist, Norbert Gleicher, MD, will in March be giving a number of invited lectures in Australia, he was asked to submit in advance brief summaries of his talks for the audience. We thought they would make interesting material for the VOICE. So, here they are:

Should we stop transferring fresh embryos?

This subject in principle addresses the question of whether fresh embryo transfers should be abandoned in favor of uniform embryo banking and subsequent frozen-thawed embryo transfers. Some investigators, indeed, have started proposing such an approach for IVF, which they suggest improves clinical pregnancy and especially live birth rates.

Their argument is based on two hypotheses: (i) that in stimulated IVF cycles, where we are transferring fresh embryos, we are transferring embryos into “compromised” (i.e., out of phase) endometrial cavities; and (ii) that by transferring thawed embryos into either natural or artificial cycles, we improve synchronization of embryo development and endometrium.

We suggest that both of these underlying assumptions, as of this point, are unproven. Moreover, we suggest that this proposed approach ignores a rather well-established fact of basic reproductive biology, namely that any form of cryopreservation to some degree negatively affects pregnancy and live birth chances. For example, claims of equivalency between fresh and cryopreserved donor oocytes were recently refuted (Kushnir et al., JAMA 2015;314:623-4).

Premature acceptance of the premise of abandoning fresh embryo transfers, and introduction of such a clinical approach into routine IVF would only, once more, raise the specter of introducing a potentially harmful modification of routine IVF practice, which can negatively affect cycle outcomes for at least some patient populations.

Acceptance of such untested practice patterns into routine IVF practice has accelerated over the last decade, and has negatively affected IVF outcomes all around the world. As further discussed later, a good example is the concept of mild ovarian stimulation (“mini-IVF”), which has become the dominant IVF protocol in Japan over the last decade. As a consequence, Japanese national IVF live birth rates (if calculated properly with reference point cycle start) have plummeted by approximately two-thirds over a decade, while total number of IVF cycles performed in

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the country has tripled. Japan, thus, barely succeeded over the last 10 years to maintain overall live birth rates with IVF but had to triple IVF cycle starts; hardly what we would call a successful strategy, either clinically or economically!

Like the concept of “mini-IVF,” abandonment of fresh embryo transfers relies on embryo cryopreservation (i.e., embryo banking). As we have reported (Kushnir et al, Fertil Steril 2013;100:736-41), embryo banking leads to significant distortions in IVF outcome reporting, significantly exaggerating clinical pregnancy and live birth rates. The reason is that outcomes after embryo banking are usually reported with reference point embryo transfer. Such reporting is, however, biased since pregnancy and live birth rates are reported only for patients who reach embryo transfer. Outcomes, therefore, reflect only the best prognosis patients; yet, the interpretation of so published data in the literature is allowed to be expanded to general populations. Outcome evaluations applicable to general IVF populations have to be performed based on “intent to treat,” which means with reference point cycle start rather than embryo transfer, as is further discussed in the section on embryo selection.

Is there one ideal ovarian stimulation protocol for women with low functional ovarian reserve (LFOR)?

Since there is considerable confusion about the terminology that describes a woman’s functional ovarian reserve (FOR), it is essential to start discussing this topic by defining the terminology. FOR is defined as the so-called small growing follicle pool between primary follicles (immediately after recruitment) and small preantral follicles. It is this pool of follicles that in the end determines how many follicles are likely to respond to ovarian stimulation and how many oocytes will be retrieved in an IVF cycle. At least at younger ages, it is best described by anti-Müllerian hormone (AMH) values. If AMH values are very low, AMH, however, loses its ability to predict ovarian response to stimulation, and FSH becomes a better predictive tool.

FOR declines with advancing age and, therefore, is not stable. This means that ovaries will increasingly poorly respond to ovarian stimulation as women get older. This phenomenon is also called increasing ovarian resistance to stimulation. Besides age, FOR can also be diminished by diseases affecting ovarian function at younger ages. In such cases FOR declines and ovarian resistance to stimulation increases already at unusually young ages, a condition we have given the clinical term premature ovarian aging (POA), and others have called occult primary ovarian insufficiency (oPOI). Here, younger women demonstrate the same clinical presentation (phenotype) as usually only seen in older women, including falling AMH and rising FSH levels, which is why we have given this condition the term POA.

While physiological ovarian aging (i.e., aging because of advancing age) and POA have much in common, there are also significant differences. Those include that the chance of pregnancy per oocyte/embryo at young ages is much higher. Therefore, younger women need fewer embryos to achieve pregnancy, and overall pregnancy rates, even with identical FOR, will be higher in younger women. Another difference lies in the fact that increasing gonadotropin dosages in younger women will be more effective in raising oocyte numbers than in older women.

Whether the cause of low FOR is POA or physiological aging, low FOR, interestingly, is almost always associated with relatively low androgen and elevated SHBG (sex hormone binding globulin) levels. Good testosterone levels are, however, now recognized as essential for normal follicle development at above noted small growing follicle stages because at those stages testosterone, acting via the androgen receptor on granulosa cells, synergistically enhances FSH effects on follicles. We, therefore, raise androgen levels in women with low FOR by pre-supplementing usually with DHEA, but sometimes, when DHEA is not effective, with testosterone directly.

Only recently described in the literature by CHR investigators (Wu et al., J Endocrinol 2015;100:736-41) was the observation that in women with low FOR,
Here we have previously expressed our opinions on newly developed human gene editing technologies. These technologies have great promise in reproductive medicine, yet also require careful consideration before any clinical application. Especially the use of germline editing (i.e., “crossing the germline”) has been subject to heated disputes in the scientific literature, with some prominent investigators advocating a complete moratorium on any such research, while in our opinion cooler heads proposed a temporary moratorium on clinical use (especially in reproductive medicine where such treatment effects would be passed onto future generations) until further basic research establishes the techniques as effective and safe.

Last December, The National Academy of Sciences, Engineering and Medicine hosted an International Summit on Human Gene Editing in Washington, D.C., which offered widely varying opinions on the subject but reached a rather reasonable consensus, very much along the lines we from the beginning have been advocating here at CHR. The Organization Committee for the Summit was composed of experts from the U.S. Canada, the U.K., Germany and importantly, China.

China’s participation in the consensus opinion was considered essential because the only study so far published on the use of gene editing technology in human embryos came from China. The international scientific community, therefore, was fearful that Chinese scientists may pursue human germline editing prematurely. The following summarizes almost verbatim the principal conclusions that were reached:

Basic and Preclinical Research:
Intensive basic and preclinical research is clearly needed and should proceed, subject to appropriate legal and ethical rules and oversight, on (i) technologies for editing genetic sequences in human cells; (ii) the potential benefits and risks of proposed clinical uses; and (iii) understanding the biology of human embryos and germline cells. If, in the process of research, early human embryos or germline cells undergo editing, the modified cells should not be used to establish a pregnancy.

Clinical Use Involving Somatic Cells:
Many promising and valuable clinical applications of gene editing are directed at altering genetic sequences only in somatic cells, that is, cells whose genomes are not transmitted to next generations. Examples proposed include genes for sickle cell disease, or for improving the ability of immune cells to target cancer cells. There is a need to understand involved risks, such as inaccuracies in editing, and the potential benefits of each proposed genetic modification. Because such clinical uses are intended to affect only the individuals who receive them, they can be appropriately and rigorously evaluated within existing and evolving regulatory frameworks for gene therapy, and regulators can weigh risks and potential benefits in appropriate clinical trials and therapies.

Clinical Use Involving Germline Editing:
Most relevant to our field, gene editing in principle might also be used to make genetic alterations in gametes and early embryos, which then will be carried by all of the cells of the resulting child and will be passed on to subsequent generations as part of the human gene pool. Proposed examples range from avoidance of severe inherited diseases to “enhancement” of human capabilities. Such modifications of human genomes might include introduction of naturally occurring variants or totally new novel genetic changes thought to be beneficial.

Such editing imposes many important issues, including: (i) risks of inaccurate editing (off-target mutations) and incomplete editing of cells of early-stage embryos (resulting in mosaicism); (ii) difficulty of predicting harmful effects that genetic changes may have under the wide range of circumstances experienced by the human population, including interactions with other genetic variants and with the environment; (iii) the obligation to consider implications for both the individual and the future generations who will carry the genetic alterations; (iv) the fact that, once introduced into the human population, genetic alterations would be difficult to remove, and would not remain within any single community or country; (v) the possibility that permanent genetic enhancements to subsets of the population could exacerbate social inequities or be used coercively; and (vi) the moral and ethical considerations in purposefully altering human evolution using this technology.
It would be irresponsible to proceed with any use of germline editing unless and until: (i) the relevance and efficacy issues have been resolved based on appropriate understanding of balancing of risks, potential benefits and alternatives, and (ii) there is broad social consensus about the appropriateness of the proposed application. Moreover, any clinical use should proceed only under appropriate regulatory oversight. At present, these criteria have not been met for any proposed clinical use: the safety issues have not yet been adequately explored; the cases of most compelling benefit are limited; and many nations have legislative or regulatory bans on germline modification. However, as scientific knowledge advances and social views evolve, the clinical use of germline editing should be revisited on a regular basis.

Need for an Ongoing Forum:
While each nation ultimately has the authority to regulate activities under its jurisdiction, the human genome is shared among all nations. The international community should strive to establish norms concerning acceptable uses of human germline editing, and to harmonize regulations in order to discourage unacceptable activities while advancing human health and welfare.

By publishing the Summit’s principal conclusions, we hope to contribute to the ensuing discussion among scientists and patients. As we also previously noted in these pages, in the U.S. the Food and Drug Administration (FDA) has assumed the role of regulatory body for germline editing. This became apparent when the FDA disallowed any experiments involving 3-parent IVF, and basically announced that it would not address the issue until the Institute of Medicine would complete a review of the subject, a process which started with formation of a new committee in January of 2015, and was expected to take ca. 18 months.

Even if the Institute issues a report by the summer of 2016, considering the many political sensitivities involved, it appears unlikely that the FDA will reach any significant conclusions before the November 2016 elections, which will bring a new administration to power in Washington. We, therefore, see nothing but further delays in the near future, and research in the U.S. in this arena, unfortunately, falling further behind the U.K. and Asia.

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!

The collaboration with the Salk group, headed by Prof. Juan Carlos Izpisua Belmonte, the Roger Guillemin Chair at the Salk’s Gene Expression Laboratory, was established early last year, but actual research project had to be put on hold.

The Salk investigators are on the forefront of genetic editing, which has significant potential in eliminating genetic diseases and help infertile women conceive. CHR is looking forward to a long and fruitful collaborative effort between the two institutions, now that the study can finally proceed.

CHR in the Media

After seeing a drop in the number of patients pursuing IVF cycles leading up to the 2008 financial crisis, Norbert Gleicher, MD, CHR’s Medical Director and Chief Scientist, observed that a drop in IVF cycle activities may be a predictor of coming economic troubles. It seemed only natural that people become hesitant to have children when they feel economic uncertainty ahead.

In early December, New York Post’s economic columnist, John Crudele wrote an editorial piece, quoting Dr. Gleicher extensively, on the possibility that there may be economic problems on the horizon given the recent drop in fertility treatments in a number of IVF centers.

We hope that we are wrong, but considering the most recent news from China, IVF cycle activities may, indeed, prove to be a predictor of economic trends.
ovarian stimulation leads to premature luteinization of follicles. This means that in women with low FOR (as we now know, whether low FOR is due to age or POA) follicles “mature” biologically much quicker than in women with normal FOR. Women with low FOR, therefore, have to have egg retrievals when their follicles are much smaller, in order to get best quality oocytes and best pregnancy and live birth outcomes.

Women with DOR, therefore, require highly individualized protocols in IVF to maximize their obviously limited outcome chances. There is no one ideal stimulation protocol, which is why we, at CHR, place so much emphasis on individualized IVF protocols for most patients.

Should every embryo now undergo PGS?

CHR’s opinions about PGS are, of course, well known to readers of these pages. We, therefore, will be brief in addressing this topic here once more.

Preimplantation genetic screening (PGS) in association with trophectoderm biopsy at blastocyst stage is very rapidly spreading into routine IVF practice all around the world. As we will demonstrate, unfortunately, the utilization of this procedure in routine IVF, likely, does more harm than good.

The concept of PGS has been proposed for almost 20 years, and is based on the hypothesis that a large degree of the inefficiency of IVF is the consequence of transfer of aneuploid (chromosomally abnormal) embryos. Since it is believed that most aneuploid embryos do not implant, and among those few that do, most will be miscarried, proponents of PGS have argued that transfer of only euploid (chromosomally normal) embryos will improve pregnancy and live birth rates and reduce miscarriage rates with IVF.

Unfortunately, in over 15 years of IVF practice, this hypothesis has never been proven. To the contrary, no prospective study of PGS has ever been able, if statistically correctly analyzed, to demonstrate any outcome benefits from PGS. Indeed, some studies demonstrated distinct reductions in IVF pregnancy rates in selected patient populations following PGS, mostly affecting poor-prognosis patients. This, of course, includes older women; yet, older women, because they demonstrate the highest aneuploidy rates, are the primary targets for interventions with PGS, as recent ESHRE statistics once again confirmed.

Above, we partially addressed the statistical mistakes widely made in IVF outcome assessments, if patient selection is not properly considered. We will expand on this further below when discussing the subject of embryo selection. These concerns, of course, also apply to PGS, which in its current usage requires embryo culture to blastocyst stage, which, of course, is a patient selection technology.

Here, we, however, want to concentrate on the recent evidence which quite clearly demonstrates that the biological concept of PGS is flawed, disqualifying PGS in most patients as a clinically useful procedure.

Assuming, as PGS proponents suggest, that selection of euploid embryos prior to embryo transfer can, indeed, affect IVF outcomes (though we do not recommend reaching such a conclusion as of this moment), the PGS procedure would be valuable if through a single trophectoderm biopsy at blastocyst stage (as PGS is now widely performed) it can reliably distinguish whether an embryo is euploid or aneuploid.

What would the procedure’s value be, however, if PGS could not distinguish by single biopsy between normal and abnormal embryos?

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The drawing demonstrates a day-5/6 blastocyst stage embryo with inner cell mass and trophoblast delineated. The area of trophoblast showing the 3 circles as potential areas of biopsy, represents the so-called trophectoderm. Because abnormal cell lines at early embryo stages are often segregated into the trophectoderm, biopsies from that region of the embryo often do not reflect the chromosomal status of the inner cell mass, from which the embryo arises, causing a so-called false-positive biopsy. Such embryos are usually discarded by IVF centers, not being aware that they would give rise to normal pregnancies.

And this is where the principal problem with PGS lies:

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Recent data have demonstrated beyond reasonable doubt that mosaicism in trophectoderm is so frequent (some data suggest a rate as high as approximately 50%) that a single trophectoderm biopsy simply cannot determine whether an embryo is really euploid or not. Recognizing this fact, a number of centers, ours included, have started to transfer so-called “aneuploid” embryos, and over 10 completely normal pregnancies/deliveries have so far been reported from such transfers in the literature with surprisingly high implantation, pregnancy and live birth rates considering the patient populations undergoing these embryo transfers.

Is there really a value in embryo selection?

Since in vitro fertilization (IVF) cycles are on purpose hyper-stimulated with gonadotropins in most cases, they usually produce multiple embryos. To select among those the best for embryo transfer into the uterus has been a goal of IVF laboratories since the beginning of IVF. This process is called embryo selection.

Practically all embryology laboratories select embryos by morphological criteria at cleavage stage (day-3 after fertilization), which used to be the day of embryo transfer in most IVF centers. A more functional embryo selection evolved, however, with the increasing utilization of longer embryo culture to blastocyst stage (days-5/6 after fertilization), with the claim being that longer embryo culture selects out the “best” embryos with the highest pregnancy potential.

Blastocyst-stage embryo culture has become increasingly popular in the last decade. Indeed, increasing numbers of IVF centers during this period converted their programs completely from cleavage-to blastocyst-stage transfers. This development was further enhanced based on the secondary embryo selection processes that were introduced in recent years, which are co-dependent on blastocyst-stage embryo transfer, such as preimplantation genetic screening (PGS) and closed incubation systems with time-lapse imaging (CIS/TLI).

The concept of embryo selection is largely futile, and for selected patient populations may, indeed, be harmful by reducing their pregnancy and live birth chances in association with IVF.

Our opinion is based on the physiology of human reproduction as well as clinical realities associated with embryo selection. In considering the physiology of human reproduction, it is widely accepted that embryo quality is primarily dependent on oocyte quality. The ultimately retrieved oocyte is, of course, the result of months of maturation within a follicle environment that is influenced by a multitude of factors. While individual follicles may mature differently, it is generally accepted that within one follicle cohort, though oocyte maturity may vary, environmental conditions are likely rather similar.

It, therefore, appears unlikely to us that individual follicles, which for months have been maturing together within a given ovarian environment, at the very end of this long cohabitation process may still be individually influenceable to significant degrees by our current clinical interventions. In other words, it appears much more likely that by the time we intervene in the follicle maturation process in the so-called gonadotropin-sensitive period of folliculogenesis (the last 2 weeks of follicle maturation), the ultimate fate of follicle and egg is already largely determined. Attempts at influencing...
egg quality (and, embryo quality), consequently, would have to take place at much earlier stages of follicle and egg development.

This conclusion is further supported by a recent study from our center, which demonstrated that in good prognosis patients, who on day-3 after fertilization have a large number of good quality embryos, selection of embryos by oocyte quality parameters actually better correlated with pregnancy outcome than selection by standard morphological embryo parameters (Lazzaroni-Tealdi et al., PLoS ONE 2015;10:e0143632).

The strongest arguments against effectiveness of current methods of embryo selection, however, are based on clinical observations. They mostly center on false outcome claims for blastocyst-stage embryo culture and, therefore, also apply to co-dependent secondary embryo selection methods, like PGS and CIS/TLI.

The principal criticism stems from the fact that alleged outcome advantages of blastocyst-stage embryo transfer have been misleading. Most IVF centers that switched their practice from cleavage- to blastocyst-stage embryo transfer did so under the assumption that this would improve the programs clinical pregnancy and live birth rates. This is, however, an incorrect assumption!

As two meta-analyses in the COCHRANE library demonstrate (Cochrane Database Syst Rev 2007;17:CD002118 and 2012;7:CD002118), if one looks at the cumulative pregnancy rate achieved from a single IVF cycle follicle/oocyte cohort, cleavage-stage embryo transfer will always achieve significantly more clinical pregnancies and live births than blastocyst-stage embryos in all patient populations. The reason is simple: Some embryos, which do not survive longer embryo culture to blastocyst-stage, if transferred on day-3, will still result in completely normal live births. Extended embryo culture to blastocyst stage, therefore, results in loss of embryos with normal pregnancy potential.

Patients who are most negatively affected by blastocyst-stage embryo transfers are women with relatively few embryos (i.e., poor-prognosis patients like older women or women with low functional ovarian reserve at younger ages) because they may end up with simply no transferable embryos. Good-prognosis patients, who usually produce larger numbers of embryos, even after losing some, will still have enough for transfer and, indeed, may have selected out their “best” embryos by culturing to blastocyst stage. The two meta-analyses, therefore, suggest that they marginally improve their immediate IVF outcomes.

Good-prognosis patients (representing ca. 20% of women on average), thus, marginally benefit from blastocyst stage transfers, though still lose cumulative pregnancy chances; average-prognosis patients (approximately 60%) experience no benefit; and poor-prognosis patients (also ca. 20%), indeed, have outcome chances from IVF reduced with long-term culture. One, therefore, really has to wonder whether blastocyst-stage culture is worth the effort.

How come this information is not widely known?

The answer is simple: Proponents of blastocyst-stage transfer report their outcomes with reference point embryo transfer. Consequently, patients who do not reach embryo transfer are never included in outcome reports. Even though outcomes reported this way, therefore, only include relatively good-prognosis patients, their outcomes are, however, erroneously applied to all IVF patients, a statistical error, unfortunately committed only too often in recent years in the introduction of new procedures to IVF, including PGS and CIS/TLI.

What effects did new treatments introduced to IVF over the last decade have on IVF outcomes?

IVF practices over the last 10 years have radically changed in many countries. Our investigation revealed that international IVF practices are characterized by highly significant outcome differences between regions. Time-associations suggest that some failures to improve live birth rates coincided with introduction of specific new assisted reproductive technology (ART) practices over the last decade.
world was even more pronounced than in fresh cycles. Moreover, it accelerated after 2009. These observations, however, have to be considered with caution since they coincide with increasing utilization of embryo banking in the U.S., which distorts ART outcome reporting, as previously noted.

Australia and New Zealand improved embryo cryopreservation outcomes along with increased utilization of embryo banking, now matching reported live birth rates following fresh embryo transfer in that region. This observation, however, also has to be viewed with caution and should not be interpreted (as incorrectly stated in the literature in some publications) as supportive evidence for embryo cryopreservation and delayed transfer in a subsequent thaw cycles.

Fresh live birth rates in Australia and New Zealand are significantly inferior to those reported elsewhere in the world. The fact that frozen/thawed cycles have similar outcomes in these regions of the world, therefore, cannot be viewed as evidence that fresh embryo transfers should be abandoned. The real question to be asked, instead, should be why fresh IVF outcomes are so low in Australia and New Zealand to begin with.

Here reported outcome trends, therefore, suggest that some newly introduced ART practices may have negatively affected IVF outcomes. Since the desire for establishment of pregnancy leads every infertility patient’s wish list, some newly introduced treatments may, therefore, also be inconsistent with patient desires. New IVF-associated clinical practices should be introduced to general clinical practice more cautiously.

Why are randomized controlled trials (RCTs) are rare in infertility, and what can we do about it?

(This presentation is largely based on a recently published editorial, Reprod Sci 2016;23:6-10, where further detail can be found.)

The proper utilization of randomized controlled trials (RCTs) has been controversial for decades. The subject in recent years has become even more controversial, as more authorities have started to criticize excesses brought on by evidence-based medicine.

There is, of course, little dispute about the fact that modern medicine should be "evidence-based." Where the controversy starts is how appropriate evidence should be collected. As we in detail describe in above cited editorial, this controversy affects all areas of medicine but may be particularly relevant to reproductive medicine and infertility because, in contrast to many other areas in medicine, we receive comparatively little research support. Indeed, in the U.S., the federal government is prohibited by a law of Congress from supporting any research associated with in vitro fertilization (IVF).

In addition, like only few other areas in medicine (oncology, cardiology, etc.), the treatment of infertility in older women and in younger women with prematurely declining functional ovarian reserve is time-sensitive. Patients, therefore, often do not have the reproductive time left to risk randomization to placebo in RCTs.

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Both of these factors contribute to RCTs being relatively rare in reproductive medicine, and explain why their utilization will also remain so for the foreseeable future, despite laments from some vocal academic voices who believe that practically all clinical practice should be based on RCTs. For the purpose of this presentation, we will refer to them as the “purists.” “Realists,” in contrast, are of the opinion that utilization of RCTs should be carefully chosen because (i) their utilization to determine all medical practices is unrealistic; (ii) RCTs are expensive, and require significantly more resources than other study formats; and (iii) time restraints often do not allow RCTs.

The recent Ebola outbreak in Africa, indeed, led some of the most prominent ethicists to conclude that in situations with significant time constrains, the utilization of RCTs may be unethical when medical evidence can be developed with quicker studies of lower evidence levels (Am J Bioeth 2015;15:4-10).

All of this, of course, does not in any way deny that RCTs represent the gold standard in developing clinical evidence. Sometimes, however, lower levels of evidence are preferable to no evidence at all. The absolute insistence on RCTs for evidence development by some purist journal editors is, therefore, counterproductive, and does not serve the field well.

The editorial process of peer-reviewed journals, therefore, has at times led clinical practice into rather circuitous, and self-defeating ways, claiming preference for complete absence of evidence over presence of lower levels of evidence, even when proposed treatments were inexpensive and exposed patients to no significant risks. Yet, paradoxically, we have witnessed during the same time period the widespread introduction of very costly and risk-loaded changes to IVF practice with full support of the editorial “establishment” without any demand for prior RCTs.

Examples for such practice changes include the introduction of elective single embryo transfer (eSET), mild ovarian stimulation (“mini-IVF”), blastocyst-stage embryo transfer, preimplantation genetic diagnosis (PGS) and closed incubation systems with time-lapse imaging (CIS/TLI), while rather minor modifications to practice are often outright rejected from consideration if documented only by lower levels of evidence.

Which brings us to another distortion in the current utilization of RCTs, also discussed in above referenced editorial and in a more recent invited “mini-commentary” in the British Journal of Obstetrics & Gynecology (in press). Because RCTs are so highly regarded in clinical medicine as the ultimate arbiters, they can become highly misleading if improperly conducted, as when they are statistically underpowered or when patient selection is biased. Unfortunately, underpowered RCTs abound in reproductive medicine because properly powered studies require large patient populations, and are often unaffordable. If not recognized as such, false-negative results in underpowered RCTs can, however, be highly misleading. Utilization of other study formats, which depend on smaller study populations and are less costly, therefore, may often be preferable, even if of lower evidence levels.

Another often missed deviation from proper RCT design is what have come to call “phantom RCTs.” Those are RCTs of usually controversial subjects, such as endometrial scratching for implantation failure. Instead of investigating the procedure in patients with presumed implantation failure, a phantom RCT investigates the procedure in regular IVF patients with no suspicion of implantation failure.

This represents the equivalence of an RCT investigating the effectiveness of aspirin on headache in patients who do not suffer from headache. In other words, it is a “phantom study” because the disease entity it pretends to investigate is not represented in the study population.

Just as aspirin can show no effectiveness in patients without headaches, endometrial scratching can show no effectiveness in women who do not suffer from an implantation problem. Yet, even the editor of Human Reproduction recently got fooled (Hum Reprod 2014;29:2355) when, indeed, lauding such a phantom study of endometrial scratching (Hum Reprod 2014;29:2474-81).

Because IVF centers can use all of their patients, studies in general IVF populations are easier and quicker to perform and less costly than studies that require selection of small subgroups of patients with very specific problems. Such studies may, indeed, serve a useful purpose, as long as readers are made aware of the fact that the study is not conducted in the original target population. Unfortunately, however, this caveat is only rarely clearly pointed out in such phantom studies, sometimes also overlooked by editors and, ultimately, leaving readers with false conclusions.

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...false-negative results from underpowered RCTs can be highly misleading
The Conference will take place at the Grand Hyatt Hotel between November 17 and 20. On Thursday, November 17, four pre-Conference workshops will be offered, covering two basic science and two clinical themes, chaired by authorities on the subjects. The regular Conference program will commence on Friday, November 18 in the morning and will go through Sunday, November 20 at mid-day.

Considering the prominence of announced faculty and timing as well as location of the conference to the pre-Christmas season in New York City, we are expecting a good-size audience of basic scientists and clinicians from all over the world. A limited number of hotel rooms at very favorable rates has been reserved at the Grand Hyatt Hotel, where the conference will take place. Registration for the conference is already open at www.reg.co.il/cmecgnyc. Because seating is limited, we recommend early registration. Since discounted hotel rooms are even more limited, and since hotel reservations during the pre-Christmas period in New York City are usually difficult to obtain and costly, we suggest even earlier room reservations at the hotel via the registration link above.

Exciting new year: Continued from Page 1

A large invited faculty of leading basic scientists and clinicians from all over the world will offer a comprehensive review of newest basic science and clinical developments, relevant to infertility practice. More importantly, the Conference will bring together basic science and clinical expertise to foster new collaborations, with the purpose of enhancing the speed of development of new translational treatments for clinical practice, and will present structured reviews of clinical paradigm changes, either already underway or on the verge of being introduced into clinical practice. A substantial Young Investigator Award of $5,000 serves as inducement for young investigators to submit their research abstracts for presentation.

IN FOCUS

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

Peering deep inside the inner workings of human genes is a mission taken very seriously by the CHR research enterprise. Here, we show the organization of DNA within a nucleus from a human granulosa cell (white). Granulosa cells are retrieved along with oocytes during patient treatments and provide an important source of living ovarian cells that CHR scientists use to explore the roots of ovarian aging, PCOS and other factors that compromise fertility. In red, the nucleus can be seen embedded within a rich network of actin fibers that are now believed to position our nuclear genes.

Emerging subjects: Continued from Page 9

In summary, reproductive medicine and infertility require a logical reassessment of need and utilization of RCTs, with the understanding that RCTs represent a rarely available and costly resource, which should be reserved for investigations of high risk and high cost treatments. For all other treatments, investigations utilizing lower evidence level study designs should be considered adequate, as long as potential shortcomings to conclusions drawn are clearly noted.

-The CHR

Fighting for every egg and embryo!

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