As, almost without spring, summer appears to have arrived, we are presenting here the last regularly scheduled VOICE of the academic year 2015/2016. During July and August, the VOICE usually goes on hiatus, unless, of course, important events require immediate communication.

In such cases we, in the past, have published shorter issues of this newsletter also during the summer months, and will do so again should such needs arise this year. Under the assumption of an undisturbed summer break, we, however, want to wish all of our readers a wonderful summer, and hope to welcome you back as interested readers of CHR’s newsletter in September for the new academic year.

Of course, CHR’s clinical activities continue uninterrupted during the summer months. Indeed, July and August in recent years have been clinically very busy, as many patients, especially teachers and academics, frequently choose to pursue IVF cycles during their summer breaks.

Academically the year has broken all previous records, as not even having reached the half way point of the year, CHR investigators already saw 10 peer reviewed papers appear in print, while an additional seven have already been accepted for publication. 2016, therefore, unquestionably will become yet another record year in publications for CHR, confirming the steady growth of the center’s research efforts.

For a number of reasons, the new academic year, starting in September, promises to be even busier than in the past:

- Sometime in October, we hope to move the center’s IVF unit from the fourth floor into the ground floor of the new building, which, of course, will require collaboration by all staff in a highly complex week of transition.
- Because of many invited lectures at various European meetings, some of CHR’s physicians and scientists, especially CHR’s Medical Director and Chief Scientist, Norbert Gleicher, MD, in addition have this year a very heavy fall travel schedule.
- CHR investigators submitted 23 abstracts to this year’s Annual Meeting of the Society for Reproductive Medicine (ASRM), this year in Salt Lake City, Utah. Though how many of the 23 will be accepted is still undetermined, the number will unquestionably be large enough to require attendance by many, if not most, of CHR’s physicians and scientists.
- Finally, CHR is a major sponsor of a big scientific meeting that will be taking place in New York City between November 17 and 20, welcoming not only a large faculty of renowned investigators and clinical experts as speakers but also a worldwide audience, as already received registrations from over 15 countries well demonstrate. (See the announcement on pages 2-3.)

Four Important CHR Publications

No less than four new CHR publications appeared during May in print. All four, we feel, deserve a brief discussion in these pages because they have the potential of significantly affecting clinical practice. Two among those studies demonstrate the expanding breadth of CHR’s clinical research, which in recent years increasingly crossed borders into general medical endocrinology, here addressing adrenal and thyroid glands. The other two publications involve the flawed concept of embryo banking and more emerging evidence against indiscriminate use of single embryo transfer (eSET).
cycles (FETs) in the last decade. In our opinion, embryo banking cycles are advocated by some colleagues for mostly all the wrong reasons.

Here is why: A leading argument in favor of embryo banking has been the assertion that the endometrium can be better prepared in FETs and, therefore, pregnancy rates will be better when all embryos are cryopreserved and only at a later date transferred in a thaw cycle. Studies on which these claims are based, in our opinion, however, have been using inappropriate statistical methodologies, which greatly exaggerated outcome successes of such banking cycles.

In addition, CHR’s investigators, based on careful review of the literature and CHR’s own outcome experience over many years, have reached the conclusion that, even though cryopreservation of gametes (sperm and eggs) and embryos has greatly improved over the last decade, any form of cryopreservation to at least minor degrees negatively affects IVF outcomes. To believe that cryopreservation does not at all have negative outcome effects, biologically simply does not make sense.

When IVF cycle outcomes are compared, a principal question that always arises is, what are the controls? Many colleagues, who have advocated for embryo banking based on the claim of better outcomes with FETs than fresh embryos, simply had poor IVF outcomes in fresh IVF cycles. Their FET cycles, therefore, looked relatively better in comparison. Considering their relatively poor outcomes with fresh cycles, they may, indeed, be well advised in transferring their patients in FET rather than fresh cycles.

It would be, however, a disservice to patients to accept outcome reports from such IVF centers as representative. CHR, therefore, is convinced that in IVF programs with good embryology laboratories, with very few exceptions, “fresh” always will beat out “frozen.” As we recently reported in these pages following a publication by CHR investigators in the prestigious medical journal JAMA, this was once again demonstrated when national outcome data for donor egg cycles demonstrated small, but statistically significantly better live birth rates with use of fresh rather than frozen donor eggs (Kushnir et al., JAMA 2015;314:623-4).

Then there is yet another major reasons why patients should stay away from embryo banking: Not only are outcome data greatly misrepresented in association with embryo banking, as noted above, but claims of lower costs for embryo banking based on fewer embryo transfers also do not hold up to scrutiny because many cryopreserved embryos do not survive thawing. Indeed, the poorer the embryo quality, the poorer will embryo survival be. Yet, as CHR investigators approximately a year ago demonstrated based on national IVF data, poor prognosis patients (older women and/or patients with low functional ovarian reserve, LFOR) are in the US the majority who undergo embryo banking. Though they can least afford to lose embryos, they will end up with the smallest number of surviving embryos, and often do not even make it to embryo transfer. Patients who do not reach embryo transfer until very recently did not have to be included in IVF centers’ national IVF outcome reports. As CHR investigators in the above mentioned study demonstrated last year, a small number of U.S. IVF centers took advantage of this reporting loophole and excluded their poor prognosis patients disproportionately from the federal reporting requirements in this way. By doing so, they artificially inflated their outcome statistics for the remaining good prognosis patients, which allowed them to disproportionately increase their market shares of IVF cycles (Kushnir et al., 2015;104:1435-41).

As a preliminary investigation by CHR investigators of the recently greatly improved national reporting system demonstrated, even utilizing this improved outcome reporting, a significant number of mostly poor prognosis cycles go, likely, still unreported, thereby still strongly exaggerating IVF results for some of the nation’s best known IVF centers.

In a recent publication (Kushnir et al., Effect of embryo banking on US national assisted reproductive technology live birth rates. PLoS ONE 2016 DOI:10.1371/journal.pone.054620, May 9, 2016), CHR investigators reported that, during the last available reporting year (2013), utilization of embryo banking with advancing female age in the U.S. further increased, strongly suggesting a potential age selection bias in performing embryo banking. Moreover, as such practice artificially inflated IVF outcomes for IVF centers that actively pursued this clinical approach, this study now demonstrated that
this effect had become so large that it even, especially among older women, inflated success rates on a national level.

Adrenal-ovarian interaction

In another study published during May, CHR investigators expanded on a theme that in recent years has attracted increasing attention at the center: the relationship between adrenal glands and ovaries in infertile women. Androgens (male hormones) in women are derived from ovaries and adrenal glands, approximately half and half. If women demonstrate androgen abnormalities, whether high or low, therefore, it can be caused by adrenals and/or ovaries.

Adrenal gland and zona reticularis

Adrenal cortex consists of three layers: Zona glomerulosa, zona fasciulata and zona reticularis. Zona reticularis, the innermost layer of the adrenal cortex, converts cholesterol into androgen precursors, including DHEA. Image from Wikimedia Commons, by OpenStax College under Creative Commons license.

CHR’s research interest in the effects of androgen hormones on follicle maturation and ovarian function is well known, and has been repeatedly addressed in these pages over the years. Indeed, CHR has been instrumental in explaining the importance of good androgen levels (especially of testosterone) for normal female fertility to the medical specialty of reproductive endocrinology and infertility all over the world. For example, already in 2013 CHR investigators reported that all conditions, characterized by LFOR, whether due to advanced female age or premature ovarian aging (POA), were characterized by low androgen levels (Gleicher et al., Hum Reprod 2013;28:1084-91). In the same study these investigators also noted for the first time that ovarian and adrenal function may relate; i.e., that low androgen may also be associated with relatively low cortisol levels, a hormone exclusively produced only by the adrenal glands.

More recently, earlier this year, the same group of investigators expanded on these observations and for the first time demonstrated that precursors of female sex hormones, and especially peripheral dehydroepiandrosterone (DHEA) levels, were reflective of cortisol and, therefore, adrenal function (Gleicher et al., J Steroid Biochem and Molec Biol 2016;158:82-89), thus further strengthening evidence that ovarian and adrenal functions relate.

Expanding further on this theme (Gleicher et al., The importance of adrenal hypoandrogenism in infertile women with low functional ovarian reserve: a case study of association with adrenal insufficiency. Reprod Biol Endocrinol 2016;14:23) this group of CHR investigators even further defined the relationship between ovaries and adrenal gland, actually demonstrating a certain degree of control the adrenal glands can exert over the ovaries via androgen production. Since the ovaries are dependent on good testosterone levels for normal function, if adrenals cut off androgen production, ovarian follicular development can be diminished or, in most severe cases, even stop. As a consequence, ovaries produce less or no estradiol and less or no anti-Müllerian hormone (AMH), which makes the pituitary gland produce more follicle stimulating hormone (FSH). As FSH rises and AMH falls, a clinical picture arises, suggestive of what is called primary ovarian insufficiency (POI), and with most severe cases outright ovarian failure (or “early menopause”).

The general assumption in such patients is that their ovaries have failed, when in reality their ovaries just shut down because they did not receive high enough testosterone levels. The correct differential diagnosis between these two forms of ovarian insufficiency is most important because in cases of true POI, the likelihood of successful pregnancy with use of the patient’s own eggs is very remote. If the cause of the ovarian shut down is, however, insufficient androgen production by the adrenal, in other words, if the cause is secondary ovarian insufficiency (SOI) due to primary adrenal androgen insufficiency, then just raising testosterone levels will, in contrast, allow ovaries to kick back in, and restart the arrested follicle maturation process. Estradiol production will resume, AMH will rise and FSH will fall, and lo and behold, patients will with considerable likelihood be able to conceive with use of their own eggs. SOI due to...
adrenal insufficiency was never before reported. 

Because of the increasingly obvious interdependence of adrenal glands and ovaries, the authors of this paper in addition concluded that infertile women with low androgen levels should always be investigated in their adrenal function, while the rare patient with known adrenal insufficiency (Addison’s disease) should always be investigated in her ovarian function. This paper, therefore, has not only relevance to female infertility but to female endocrinology in general.

We have pointed out on a number of occasions that immune and endocrine systems are so intertwined that they might be considered one and the same. Many of the most important genes controlling ovarian function also have important immune functions. To continue the general theme of how immune and endocrine systems interphase, CHR investigators last month published yet another study in which they investigated the interplay between thyroid gland and female fertility.

**Thyroid disease and infertility**

The thyroid gland is, of course, a very important endocrine organ, providing via production of thyroid hormone important metabolic fuel for the body. Like all endocrine glands, the thyroid can develop diseases, the most frequent being hypothyroidism (under-function of the gland). The cause of hypothyroidism in most cases is an attack of the immune system on the thyroid gland, a process called organ-specific autoimmunity or in this case autoimmune thyroiditis (also called Hashimoto’s thyroiditis). Autoimmunity against the thyroid gland can also lead to hyperthyroidism (over-function of the gland), also called Grave’s disease which is much less common.

**Thyroid system**

Thyroid gland produces thyroid hormones (T3 and T4) that regulate how quickly the body uses various energy sources, protein synthesis and the body’s sensitivity to other hormones T3 and T4 regulate the growth and rate of function of the other organs in the body. Public domain image from Wikimedia Commons.

Combined autoimmune diseases of the thyroid are the most commonly diagnosed autoimmune disease in women during reproductive years, and autoimmune diseases, in general, affect women (with very few exceptions) approximately 7 times as frequently as men.

Thyroid dysfunction has for decades been known to be associated with menstrual irregularities, anovulation (failure to ovulate) and female infertility. Whether functional ovarian reserve (FOR) is directly associated with either thyroid function or thyroid autoimmunity, however, has remained under dispute.

Investigators at CHR, therefore, addressed this question in a recently published study (Weghofer et al., What affects functional ovarian reserve, thyroid function or thyroid autoimmunity? Reprod Biol Endocrinol 2016;14:26). This study demonstrated that good control of thyroid function (i.e., of thyroid stimulating hormone, TSH) was more important than suppression of thyroid antibodies (i.e. of thyroid autoimmunity) in attempts to improve FOR. Patients receiving fertility treatments at CHR, therefore, will now understand why CHR’s physicians place so much emphasis on appropriate TSH levels before IVF cycle start.

**New information about eSET**

Steady readers of the VOICE have known over the years that CHR disagrees with the increasing push toward almost universal elective single embryo transfer (eSET) in IVF, which initially started in Europe but since has crossed the Atlantic, and in recent years has gained increasing favor here in the U.S. The reasons for our disagreement with eSET being a preferred treatment approach for most infertility patients have been published in great detail in a good number of publications. We, therefore, do not want to be too repetitive here. Only so much as a quick summary:

- Proponents of eSET are trying to avoid twin pregnancies, which they believe carry greater risks and costs than singleton pregnancies. Transfer of only one embryo, of course, avoids almost all twin pregnancies.
- eSET in comparison to 2-embryo transfers (2ET), however, significantly reduces clinical pregnancy and live birth chances in IVF. Proponents of eSET consider these decreases more than... eSET in IVF started in Europe but has since crossed the Atlantic”

Continued reading on Page 5
compensated by the above noted lower outcome risks for singletons, especially since two consecutive eSETs (one fresh and one frozen) result in similar clinical pregnancy and live birth rates than a 2ET.

- We have argued that proponents of eSET are mistaken in claiming higher outcome risks and costs for twin over singleton pregnancies because their conclusions were incorrectly based on comparisons of outcomes between 2 twins and 1 singleton, while correct statistical comparisons have to be matched for outcomes (i.e. 2 children). If this is done and outcomes are compared between 2 twins and 2 consecutive singletons, twins no longer demonstrate significantly increased clinical outcome risks and costs.

- This means that eSET reduces pregnancy chances without compensatory gains and, therefore, should not be used, unless patients do not wish to conceive twins and/or have medical contraindications to twin deliveries.

- This argument applies even more to intermediate- and especially poor-prognosis patients because eSET is usually combined with extended embryo culture to blastocyst stage, which in poor prognosis patients, by itself, reduces pregnancy and live birth chances.

- Finally, the Dutch investigators Helmerhorst et al already reported in 2004 that treatment outcomes after IVF and after spontaneous conception could not be assumed to be the same for either singleton or twin births (BMJ 2004; 328:261). After reviewing the literature up to that point, they concluded that twins born after IVF demonstrated approximately 40% lower outcome risks than spontaneously conceived twins, while in singletons the opposite was true: IVF singletons demonstrated higher outcome risk that spontaneously conceived twins. Since the higher twin risks alleged by proponents of eSET were based on spontaneously conceived twins, these data overestimated twin risks after IVF, therefore, by ca. 50%.

Since obstetrical practice patterns have changed over the last decade, the recently published study by CHR investigators set out to determine whether the data reported by Helmerhorst et al in 2004 were still valid [Gleicher et al., Risks of spontaneously and IVF-conceived singleton and twin pregnancies differ, requiring reassessment of statistical premises favoring elective single embryo transfer (eSET) Reprod Biol Endocrinol 2016;14:25]).

By reviewing all appropriate studies published since then, CHR’s investigators confirmed the 2004 Dutch report. More specifically, the CHR manuscript determined that severe outcome risks are approximately 50% lower for IVF than spontaneous twins, while milder perinatal outcome risks are exaggerated by approximately 25% if data are taken from spontaneously conceived twins. These data not only confirmed the work by Helmerhorst et al but also reemphasizes the fact that IVF twins do not appear to generate increased outcome risks in comparison to IVF singletons if comparisons are made in statistically appropriate fashion. More than ever, CHR is, therefore, convinced that currently widely propagated eSET policies are not in the best interest of most patients undergoing IVF and unnecessarily reduce IVF pregnancy and live birth rates.

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For the full Conference program, registration, and abstract submission, visit the official Conference website: http://frm.cme-congresses.com/
A first glimpse into early human embryo development and related news

Last month, two research teams, one at New York’s Rockefeller University (Laboratory of Stem Cell Biology and Molecular Embryology, headed by Ali Brivanlou, PhD, MD) and the other at Cambridge University in the UK (Laboratory of Mammalian Development and Stem Cell Biology, headed by Magdalena Zernicka-Goetz, PhD), reported in separate manuscripts in Nature and Nature Cell Biology, respectively, successful culture of human embryos for 13 days in vitro, observing the earliest stages of self-organization. These in vitro cultures, remarkably, succeeded without any maternal contribution, establishing the apparent independence of early human embryonic development.

This, of course, raises significant new questions about our current understanding of embryo implantation during IVF. Indeed, these experiments are further evidence for how little is known about human embryo implantation, though independence from the uterus for implantation and early human development after implantation should not necessarily surprise, considering the obvious independence of abdominal and tubal pregnancies in clinical practice.

Both studies were widely discussed in lay media as well as editorial pages of leading scientific journals, like Science and Nature, and not only because of the very obvious scientific excellence of both papers. Both studies were stopped after 13 days of embryo culture because current international conventions allow in vitro embryo culture only up to day 14. Somewhat unexpected success in doing so now raises the question whether the tolerable culture period for human embryos should not be extended to allow for further groundbreaking research.

The figure above demonstrates one of these in vitro cultured embryos from the Brivanlou Laboratory at Rockefeller University at early stages of implantation, stained with various tissue markers which identify different cell types within the embryo by color. The cell aggregate at the bottom of the embryo represents the inner cell mass, from which the fetus arises, while the circular sphere represents the trophectoderm, from which the placenta arises.

It is the trophectoderm from which six cells on average are removed during embryo biopsy when preimplantation genetic screening (PGS) is performed.

CHR is very proud to have developed a close research working relationship with Prof. Brivanlou and his lab at Rockefeller University over the last year and a half. Their study was, indeed, for the first time presented within a public forum by Alessia Deglincerti, PhD, the paper’s first author, on March 15, at CHR GrandRounds.

Prof. Brivanlou also serves as one of four Conference Chairmen of the upcoming Annual 2016 Conference of The Foundation for Reproductive Medicine - Translational Reproductive Biology and Clinical Reproductive Endocrinology, which will take place in November in New York City. His lab will, in

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Special Honor for CHR’s Medical Director and Chief Scientist, Norbert Gleicher, MD

It may not be widely known that CHR’s Medical Director and Chief Scientist, Norbert Gleicher, MD (right), started his medical career at Vienna University School of Medicine in Vienna, Austria. After three preclinical years, he then transferred for the clinical years to Tel Aviv University’s Sackler School of Medicine in Israel, where he graduated before coming to Mount Sinai Hospital Medical Center in New York City for residency in Obstetrics and Gynecology and a fellowship in Immunology.

We are now pleased to report that the Medical University of Vienna awarded him a professorship in the Department of Obstetrics and Gynecology “in recognition of his collaborative accomplishments with the department.” Dr. Gleicher, thus, currently holds professorships at Rockefeller University in New York City, likely the world’s leading research university, housing the largest number of living Nobel Prize Laureates, and just this month reported to top the worldwide global ranking of institutional scientific impact, and the Medical University of Vienna, one of the world’s oldest, and up to World War II one of the premier medical schools in the world, with historical alumni and professors like Sigmund Freud and 6 Nobel Prize Laureates in medicine and physiology.

Please join us in congratulating him on this honor and accomplishment!

First glimpse: Continued from Page 7

addition, conduct a workshop on embryo implantation, discussing the in vitro model of human embryo implantation utilized in both studies, and initially developed for mouse studies by Prof. Magdalena Zernicka-Goetz’s laboratory at Cambridge University.

Finally, we are also very pleased to announce that Prof. Magdalena Zernicka-Goetz, herself, has accepted the invitation of the four Conference Chairmen to give the Annual “Breaking News” Lecture, which is the opening plenary lecture at the November conference. She in that lecture will present another seminal study from her laboratory, recently published in Nature Communications: Bolton et al., Mouse model of chromosome mosaicism reveals lineage-specific depletion of aneuploid cells and normal development potential (2016;7:11165).

This work was chosen for this presentation because of its highly significant relevance for currently ongoing discussion about the clinical utility of PGS in human IVF. We hope you all will attend!

-Magdalena Zernicka-Goetz

Mitochondria Study

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