The year has not even yet reached half point, and, already, 12 peer-reviewed CHR publications have been published per PubMed [http://1.usa.gov/17m3sIn]. That is one more than in all of 2012, already a highly productive year for CHR. We, therefore, when it comes to scientific publications, are definitely looking forward to another record year as well.

Like the high acceptance rate of CHR abstracts at ASRM reflects on their quality, diversity of topics, increasing numbers of CHR-based authors and quality of journals where CHR’s work is published are almost equally remarkable. CHR is truly evolving into a research center of major international importance in reproductive medicine.

Amongst papers published so far this year, many deserve notice. But limited by space on these pages, we want to concentrate on three because we consider those of special importance, and because we previously promised in these pages to review them in more detail, once formal publication allowed that. Not coincidentally, the three chosen papers all appeared in very prestigious journals:


During July and August these pages usually go on hiatus. But this year, there is simply too much to write about, starting with a blowout new record of CHR abstracts accepted for presentation at the Annual Meeting of the American Society for Reproductive Medicine (ASRM) in October, this year in Boston, MA.

As we reported in the May issue, simply submitting 18 abstracts already represented a new CHR record. What, however, made this year a blowout record performance is that 17 out of 18 submitted abstracts were accepted for presentation! This is really unprecedented, and we seriously wonder whether, ever before, a single center, even amongst major academic centers, had so many abstracts accepted at a single scientific meeting.

The 3 days in Boston in October, therefore, will be busy for the CHR crew, which this year will have no choice but to attend the ASRM Meeting in full force. But what fun it is to receive so much recognition from one’s peers!

This study is of importance not only because published in the highly prestigious journal of The Endocrine Society, but because it so well demonstrates the direction CHR is trying to take in its research. While progressively expanding clinical research to the laboratory, and more specifically to the molecular level, research is not done for research’s sake only. All research at CHR has, as its primary purpose, to be “translational,” which means that it should be quickly applicable to improving clinical care.

The here-discussed paper is on a number of different levels a good example: The study was initiated to resolve an unanswered clinical question. It, however, ended up not only answering this question but at the same time also provided important additional understanding about how ovarian reserve can be more accurately assessed and about the influence of the FMR1 gene on ovarian reserve.

The principal question to be answered by the study was how measurements of the hormones FSH and AMH relate to each other. Both, supposedly, measure the so-called growing pool of follicles after recruitment, also called functional ovarian reserve (FOR). Yet, while in general correlating, not infrequently both hormones can diverge quite significantly. What these divergences clinically mean is unknown, and CHR investigators were particularly interested in one combination, which they called FSH/AMH high/high, meaning that both hormones were abnormally high.

This combination was of special interest because as FOR declines, both hormones go into opposite directions: FSH goes up and AMH goes down. A combination of FSH/AMH high/high, therefore, should really never happen. Yet, it is seen in a small number of patients, and, often, leaves physicians scrambling as to how to treat these patients.

As the study demonstrated, this combination of hormones, actually, was prognostically an excellent sign, representing
4.34-times the odds of high egg numbers and approximately 2-times the odds of pregnancy with IVF than all other FSH/AMH combinations. Yet, this observation held up only as long as the female did not carry a very specific mutation of the FMR1 gene, the so-called het-norm/low sub-genotype. If a woman carried this genotype, all advantages of the FSH/AMH combination high/high disappeared; and, indeed, oocyte yields turned negative (i.e., fewer eggs were obtained than in all other FSH/AMH combinations).

This study was not yet able to offer a final answer. As of this point, both possibilities have to be considered because a woman’s androgen production comes in similar parts from the adrenal glands, where all DHEA is produced, and from the ovaries, where the theca cells of follicles together with adrenals, and to a lesser degree with other bodily tissues, produce testosterone.

It does, however, offer preliminary evidence that, like in polycystic ovary syndrome (PCOS), where androgen production often is excessive (at least at young ages), and can be adrenal and/or ovarian in origin, low FOR may also represent a condition involving adrenals as well as ovaries. The authors of the study offer the suggestion that low FOR may, in some patients, represent the opposing physiologic extreme from PCOS:

While PCOS in some patients is characterized by hyperandrogenism and very active follicle recruitment, low FOR is characterized by hypoandrogenism and very slow follicle recruitment.

This newly developed hypothesis, in turn, then raises the question of how adrenals and ovaries control androgen levels in these two extremes, and under normal circumstances between the extremes. CHR investigators are presenting the beginning of a potential answer in an abstract at the upcoming Annual ESHRE Meeting in London in July of this year and in a paper, which was just accepted for publication, suggesting the possibility of, what they call, an androgen production factor (APF) in adrenals, which is connected to the female immune system. More on this, in the future, once both of these publications have appeared in print.

One more point has to be made, however: The recognition of the association of low androgen levels and low FOR has already greatly affected how patients with low FOR are treated at CHR. Since we now understand that DHEA supplementation works by restoring normal androgen levels in women with depleted levels, we now also understand that a patient’s androgen levels (i.e., specifically her testosterone levels) have to be reconstituted to where they used to be at younger ages. IVF cycles are, therefore, no longer automatically started with the first menses after 6 weeks of DHEA supplementation. They are only started once a patient’s total and/or free testosterone levels are back where we want them to be (the upper one-third of the normal range or even a little above the normal range).

In close to 90% of women this will be achieved within 6-8 weeks, but in a small minority of women, usually because of certain genetic predispositions, which we also started to investigate here at CHR, this will not occur. For such women resistant to DHEA supplementation, CHR is currently conducting a prospectively randomized, placebo-controlled clinical trial of direct testosterone supplementation. Because DHEA resistance is, fortunately, rare, completion of this trial will take some time. We, however, hope to have at least preliminary results ready for next year’s Annual ASRM Meeting.


Watch Dr. Gleicher discuss the findings in this article on InfertilityUniversity.com! [http://bit.ly/13aLvOL]
This paper, which so far has appeared only electronically, in the official organ of ASRM, demonstrates a very different, though also very active, area of research at CHR. CHR, for years, has been very interested in health care policy issues, which affect our field of practice. To cite only a few such subjects addressed by investigators in recent months and years: elective single embryo transfer (eSET), twin pregnancies after IVF, evidence generation in reproductive medicine, publication policies in medical journals and relevant conflicts of interest, and many more.

In this study, CHR’s investigators explored the integrity of national IVF cycle outcome reporting, which in the U.S. is mandated under federal law. A large majority of U.S. IVF centers, therefore, annually report all of their cycle outcomes to the Centers for Disease Control and Prevention (CDC), CHR included. A somewhat smaller number of centers also report on a voluntary basis to the ASRM’s daughter society, the Society for Assisted Reproduction (SART) as a condition of membership. (In full disclosure, Vitaly A. Kushnir, MD, the lead author of the study, also serves as consultant to the CDC’s section that administers the national outcome reporting system).

It was actually our colleague, Andrea Vidali, MD, who in an informal conversation a number of months ago, raised the suspicion that select IVF centers may not fully report their IVF experiences and, thereby, may consciously or not, artificially increase their reported pregnancy rates. CHR considered this important enough an issue to initiate a formal investigation.

National IVF data for the years 2005-2010, reported through CDC (818,927 cycles) and SART (812,000 cycles), formed the material for investigation. Both data sets had to be used because CDC reports only completed cycles, while SART reports initiated cycles for each center. CDC data, alone, therefore would not permit detection of “disappeared” (i.e., unreported) cycles.

As it turned out, Dr. Vidali’s suspicions were correct: Between 2005 and 2010, unreported cycles significantly increased from 3.3% to 7.4% of all cycles. More remarkably, however, by 2010, only 13 out of 341 IVF centers analyzed (3.8% of all centers) accounted for a whapping 50% of all excluded cycles. Not surprisingly, the 13 statistically defined outlier clinics reported significantly higher pregnancy rates and statistically lower cycle cancellation rates than the remaining 328 IVF centers. During the study period of 2005-2010 they increased their share of the U.S. market by a whapping 19.9%.

Further analyses strongly suggested that a large majority of “disappeared” and, therefore, unreported cycles were cycles in older women. Pregnancy chances in older women, of course, are lower. Disproportionate elimination of older patients from reporting, therefore, artificially increases reported pregnancy chances for remaining cycles. Moreover, since older women also experience higher cycle cancellation numbers, their elimination from reporting will also artificially lower a program’s cancellation rates.

Both CDC and ASRM/SART stress in their published materials that pregnancy rates in individual IVF programs cannot and should not be compared because they reflect greatly varying patient populations. The public, however, still uses these reports, especially those from CDC, for exactly this purpose. It should, therefore, not surprise that the 13 outlier clinics increased their U.S. market share over the 5-year study period by practically 20%.

Since the submission of this study, CDC and ASRM/SART published 2011 data, and here described developments further accelerated during 2011.

Though we were asked to do so, we chose not to publicly identify the 13 outlier clinics in either our published paper or here. The reason is that CHR investigators wish to present objective facts, without surmising or speculating on individual center’s motives. Those 13 outlier centers, disappointingly, however, include some of the nation’s better-known IVF programs. Since annual reports from CDC as well as ASRM are publicly available, interested parties can easily reach their own conclusions.

We are pleased to report that CDC and ASRM/SART already agreed to meet to, hopefully, find quick solutions to the problems in national IVF reporting, brought to the surface by CHR’s study. It is troubling that the national IVF reporting system was only very recently quoted by Senator Wyden (Dem., Oregon), who was its Congressional initiator, as a model for possible national reporting for other medical and surgical procedures under the Affordable Care Act (ObamaCare) (Adash EY, Wyden R. Public reporting of clinical outcomes of assisted reproductive technology programs: implications for other medical and surgical procedures. JAMA 2011;306:1135-1136).

It quite obviously is not!

So, what does all of this mean in practical terms for the patient seeking information? First, be careful in comparing pregnancy rates between IVF centers, as both CDC and ASRM/SART very clearly point out in conjunction with their reports. Second, be especially suspicious of outcome data from centers where large numbers of IVF cycle do not reach embryo transfer, either because no eggs are retrieved; embryos are cultured for too long and no embryos survive to transfer; preimplantation genetic diagnosis (PGS) is done in women with very few embryos, where the chance of all embryos being aneuploid (abnormal), of course,
Dear CHR staff:

It is hard to find the words to thank the people that made our dreams come true.

4 years after challenges, your facility found the root of the issue and brought us our sweet twins, A & J.

We are forever grateful and will serve as an incredible referral to CHR.

-B & A from New Jersey