We are again very pleased to present in this issue of the UPDATE last year’s IVF pregnancy rates at CHR. Indeed, we are excited about the opportunity, as they show considerable further progress, demonstrating well how effective CHR’s “fighting for every egg and embryo” has become.

We encourage you not only to look at the numbers but take the time to read the footnoted because they, at CHR, are probably much more important than at any other IVF program in the world.

What makes CHR’s pregnancy rates so remarkable is the patient population in which these rates were achieved. As noted in the footnotes, there, likely, is no IVF program in the world with less favorably selected patients than CHR. The overwhelming number of patients contacting CHR for advice and treatment has previously been in treatment at other fertility centers, and has failed. In addition, they probably represent the oldest patient population any center is serving!

Please remember that the rates reported here, as in past years, represent ongoing pregnancy rates, signed out into obstetrical care. Delivery rates are, of course, not yet available for the year 2011, and will, as always, be reported to and through the national CDC and SART databases. Clinical pregnancy rates are reported with reference point embryo transfer (pregnancy rate/embryo transfer) and not cycle start, meaning that only patients who reach embryo transfer are counted.

Delivery rates can be anticipated to be somewhat lower than ongoing pregnancy rates, since additional pregnancy losses can be expected. As we repeatedly reported, including in peer-reviewed medical journals, CHR’s miscarriage rate is unusually low, especially considering the center’s very adversely selected patient population, a finding attributable to CHR’s use of DHEA supplementation in all women with diminished ovarian reserve (DOR), whether young or older. If pregnancy rates are calculated per cycle start, they, of course, also would be lower.

As in past years, we wish to point out that comparisons of clinical pregnancy rates between IVF centers may not be meaningful because patient characteristics and treatment approaches greatly vary between individual IVF centers. This is probably nowhere more obvious than at CHR, where a very large majority of patients, independent of their age, suffer from severely diminished ovarian reserve (DOR). Yet, this fact renders CHR’s 2011 outcome data especially remarkable.

Let’s look at a little more detail: Only 6% of IVF cycles were performed in women under age 30, 22.2% in women between 30-35 years, 25.0% at ages 36-39, 28.7% in women between 40-43 and a full 18% in women of age 44 or older (up to age 49).

Considering that over 90% of CHR’s patients by objective parameters demonstrate DOR, clinical pregnancy rates in the high 30% range up to, and inclusive of, age 40 years; a pregnancy rate of 25.0% at age 41; pregnancy rates around 15.0% at ages 42 and 43; and a pregnancy rate in excess of 10% in women ages 44-49; is almost incredible!

Without comparing CHR’s pregnancy rates to other centers,
above noted data demonstrate quite obviously that, likely, no other IVF center in the world serves a more adversely selected patient population; yet, CHR’s pregnancy rates, at all ages, nevertheless, are highly competitive! What we, however, are even more proud of is that our center’s pregnancy rates continue to improve at a time when European IVF data suggest that, in general IVF populations, pregnancy rates have plateaued (for CHR commentary on this point, please see our website: www.centerforhumanreprod.com/news_eu_ivf_success_rate.html) And CHR accomplished all of this with continuously low cycle cancellation rates and, due to DHEA supplementation in women with DOR, with very low miscarriage rates.

**ECO-IVF Cycles (Low-intensity IVF, also called “Mini-IVF” at other centers)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pregnancy Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Pregnancy Rate</td>
<td>0</td>
</tr>
</tbody>
</table>

Reflecting CHR’s cautious attitude towards Eco-IVF (“Mini-IVF”), 2011 cycles were too few for a valid statistical assessment. Indeed, CHR performed only one such cycle in 2011.

**Frozen-Thawed Cycles (FETs)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pregnancy Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Pregnancy Rate</td>
<td>42.3</td>
</tr>
</tbody>
</table>

Here, too, CHR demonstrates a dramatic improvement in clinical pregnancy rate (42.3%), likely, reflective of overall improvement in embryo quality. As a program improves, more embryos of better quality are generated, leading to better fresh IVF cycle pregnancy rates, more embryos available for cryopreservation, better quality of frozen embryos and, therefore, overall, also in better frozen-thawed cycle pregnancy rates, as observed here.

**Donor-Recipient (Egg Donation) Cycles**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pregnancy Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Pregnancy Rate</td>
<td>45.0</td>
</tr>
</tbody>
</table>

At first glance, one may conclude that pregnancy rates in donor egg cycles at CHR have decreased over the last two years from a peak in the mid-60% in 2009 to ca. 45.0% in 2011. On more careful analysis, however, this conclusion is proven wrong because standard donor egg cycles, indeed, still demonstrated pregnancy rates around 60.0% in 2011. The decline observed here is due to important new developments in the center’s egg donation program: (i) An increasing number of patients chose to use so-called “directed” (open) egg donors, often family members or friends, who frequently do not fit the strict criteria of donor selection, which characterize CHR’s own egg donor pool. (ii) A rapidly increasing number of patients, receiving donor eggs, also request preimplantation genetic diagnosis (PGD), a procedure that requires embryo biopsy, which, to a mild degree, negatively affects pregnancy chances of biopsied embryos.

In summary, 2011 was another great year at CHR!

**Are women really born with all of their eggs?**

We on a number of previous occasions discussed in these pages the brewing controversy within the field of reproductive physiology whether women were born will all of their eggs, or, are constantly producing additional, fresh eggs.

This is a very important issue because current dogma holds that women are born with all the eggs they will ever have at their disposition, and constantly lose eggs as they age. Indeed, the current definition of “ovarian aging” is based on remaining eggs/follicles in women’s ovaries, a number, which, of course, is believed to constantly decline as eggs are “used up.”

Jonathan L. Tilly, Ph.D., head of the Vincent Center for Reproductive Biology, Massachusetts General Hospital of Harvard Medical School, Boston, Massachusetts, initiated the controversy a few years ago, when he and his group for the first time claimed to have demonstrated stem cells in mouse ovaries, which could give rise to new eggs.

Because other investigators were largely unable to replicate their work, the concept failed to gain traction in the field, even though research in other organs, which previously were also believed not to regenerate themselves (i.e., the brain and the heart), discovered organ-specific stem cells, suggestive of regenerative processes.

Tilly and associates, however, did not give up, and, in cooperation with investigators from Saitama Medical University in Saitama, Japan, just published an exciting new paper in the prestigious science journal *Nature Medicine* (doi:10.1038/nm.2669; advance online publication), in which they present convincing evidence for the presence of stem cells in mouse as well as human ovaries, which can produce oocytes (eggs).

If confirmed, this finding offers exciting new expectations and potential promises for reproductive physiology in general, and, of course, the treatment of female infertility. Since the study undoubtedly will receive considerable media exposure, we would also like to raise some points of caution to prevent excessive expectations:

- This study, indeed, appears to demonstrate that, like mice, the ovaries of young women contain specific stem cells that can give rise to oocytes (eggs). Presence of such cells, however, does not automatically mean that these cells actively produce fresh oocytes. Whether they do still needs to be determined. It is also possible that women are, simply, born with these stem cells, like women are born with very immature eggs in very immature follicles, the so-called primordial follicles. Like some of these primordial follicles are never recruited into maturation, these stem cells may never be initiated to produce eggs.
Alternatively, they, of course, may; and if this were the case, then our current understanding of ovarian aging would have to be reassessed because current dogma holds that everything starts with recruitment of primordial follicles from an existing pool of such follicles from birth into a many months-long follicle maturation process.

- Detection of stem cells in ovaries of young women does not necessarily mean that such stem cells can also be found in ovaries of older women. We were told that, since this paper was submitted for publication, the Tilly group also found evidence of these stem cells in older women. That, of course, is encouraging on the one hand but could also be viewed to suggest that women may be born with these stem cells, and they just linger, without ever really producing eggs.

In a more optimistic interpretation of this study’s results, one can, however, also conclude that presence of these stem cells opens tremendous new opportunities for research and potential clinical applications in women with aging ovaries. Dr. Tilly and co-workers are to be congratulated on an outstanding achievement!

Another cautionary word about use of untested clinical methods

We are much less enthusiastic, however, about what we see going on in current clinical practice around us and, therefore, want, once more, sound a word of caution:

We previously noted our concerns about the excessive use of so-called “Mini-IVF” (Low-intensity IVF) in these pages (available at www.centerforhumanreprod.com/about_chrupdate_1110.html), and also voiced these concerns in an invited “Commentary” in a leading medical journal of our specialty (Gleicher et al., Low-intensity IVF: real progress? Reproductive Biomedicine Online 2011;23:274-8). Since then, we, in the same medical journal, also published a case-control study on the subject, confirming our concerns (Gleicher et al., A case-control pilot study of low intensity IVF in good prognosis patients. Reprod Biomed On line; doi:10.1016/j.rbmo.2011.12.011; advance online publication).

Taking our own advice very much to heart, above noted 2011 outcome statistics for IVF demonstrate the very small number of such cycles performed at CHR.

But now, we, increasingly, also are seeing a related phenomenon, the use of so-called natural cycle IVF. In such cycles patients receive absolutely no ovarian stimulation, and are really left to the mercy of their own natural cycles. Since these cycles are mostly utilized in women with severely diminished ovarian reserve (DOR), natural cycles, very obviously, rarely are really “good” cycles.

The literature, indeed, mostly reports rather dismal pregnancy rates in such natural cycle IVF. Since DOR patients usually have little time to lose, we strongly caution from wasting time on a treatment that, over and over again, has been shown rather ineffective.

And then another word on preimplantation genetic screening (PGS) to improve pregnancy chances with IVF: Only recently we noted in these pages that a new generation of tests has been introduced into practice, which, for the first time, allow for the chromosomal evaluation of all chromosomes in an embryo. In this sense, these new techniques, unquestionably, represent progress. Yet, PGS has with earlier techniques not only proven to be ineffective in improving IVF pregnancy chances but, actually, was shown to reduce those, especially in older women. Authoritative bodies here in the U.S. and overseas, therefore, have published categorical statements that PGS should not be used as a way to raise IVF pregnancy rates.

Yet, colleagues, increasingly, are doing exactly that! Even worse, they are doing it without advising their patients that the application of these new techniques is “experimental,” and, therefore, should not be offered without prior review and approval by an Institutional Review Board (IRB) and without appropriate informed consents.

This is, indeed, what “Mini IVF,” natural cycle IVF and PGS all have in common: all three are unproven IVF side-shows, offered to an uninformed public as “established treatments,” when all three have never been established as effective, and, indeed, much evidence points towards the opposite.

We thought this is worth noting one more time!

- The CHR

“Fighting for every egg and embryo!”