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December 23, 1999

Mark A. Damario, M.D.
Section of Reproductive
Endocrinology

Dockets Management Branch (HFA-305)
Food and Drug Administration
5360 Fishers Lane Room 1061
Rockville, MD 20852

RE: Docket #97N-484S, Suitability Determination for Donors of Human Cellular and Tissue-Based Products

As Director of the Mayo Clinic Assisted Reproductive Technologies Program, I am writing you with regards to issues related to the use of frozen and quarantined embryos in oocyte donation. The reason that I am writing is due to the fact that I believe that our program may be the only in the United States that has actually tried to maintain an anonymous oocyte donation program primarily based on embryo cryopreservation which offers embryo quarantining as an option.

Initially, this program developed along these lines for multiple reasons. First, we had developed a high level of competency in embryo cryopreservation, specifically at the pronuclear stage, that actually allowed clinical outcomes that approached those that were achieving with fresh embryos. With our cryopreservation method, we were routinely attaining embryo thaw survival rates >90% and frozen embryo implantation rates that were only approximately 5% less than we were achieving with fresh embryos. Secondly, we faced a unique situation in Rochester, a moderate-sized midwestern city with no local colleges or universities and one of the world's largest medical centers. The obvious fact that the employees of the medical center would likely serve as our primary source of oocyte donors made us concerned that we might not have an infallible ability to protect the donor-recipient anonymity arrangement under all circumstances utilizing fresh synchronized cycles. Lastly, we were concerned about the potential of infectious risks. In addition to initial screens for hepatitis B, hepatitis C, HIV and syphilis, we instituted repeat HIV screening just prior to each oocyte retrieval. As all the oocytes were primarily frozen as zygotes, this allowed time for this latter HIV result to be reviewed prior to either contacting or beginning treatment of the recipients. We then offered the option of a further six month quarantine to every recipient couple. Some (relatively few) chose to further quarantine, whereas others (the majority) did not. We did not feel that it was absolutely mandatory that we quarantine for six months in all cases based on the fact that we were not aware of any documented cases of infectious disease transmission through oocyte donation. Since many of these couples were anxious to proceed with treatment, we felt that we could allow them to make an informed choice.

Since this program was instituted in 1995, its clinical efficacy has actually exceeded our expectations. In addition, we have found it to be remarkably efficient. Donor-recipient synchronization, which is a significantly time-consuming task with fresh embryo transfer approaches is vastly simplified with embryo cryopreservation. All of our recipients undergo a programmed hormonal protocol, with all

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transfers occurring on Thursday mornings. This degree of predictability of treatment seems to be very appreciated by our patients, particularly those that travel over long distances. Through the monitoring of "presumed" uterine receptivity through ultrasounds performed during the course of treatment and the time to alter management to possibly extend estrogen therapy, we have not found a need to perform preliminary "mock hormonal treatment cycles" (thereby saving time and costs for recipients). We have almost exclusively (99%) used the recipient husband's previously cryopreserved sperm in each instance. Therefore, both recipient partners are not aware of the actual day that their donor undergoes oocyte retrieval. In our system, as mentioned earlier, we feel that this helps to safeguard patient confidentiality.

Throughout the history of the program, we have achieved embryo thaw survival rates of 92-93%, implantation rates of 27-29% and clinical pregnancy rates per transfer of 48-53%. However, simply focusing on these numbers alone will still not permit you to fully appreciate the potential of this treatment. That is because we have achieved these outcomes by thawing only the precise number of embryos intended for transfer (customarily three) and thereby conserving all the remaining embryos for potential additional transfer attempts. We have never split oocytes amongst recipients. Therefore, our recipients have had a mean number of 11 pronuclear oocytes frozen per oocyte donation. With this system, the average recipient has at least three potential transfer attempts. We believe that this provides two further substantial advantages: 1) a cumulative chance for a recipient delivery per oocyte donation that exceeds 70%, and 2) a considerable potential for secondary, and even tertiary, deliveries from the same oocyte donation (while preserving donor oocytes and limiting recipient costs in the process). Due to the potential for secondary deliveries, we believe that our approach will actually prove to be very cost-efficient.

Our program has recently published our preliminary results from this program in *Fertility & Sterility*. I enclosed a copy of a reprint from this article for further review. In addition, we have presently completed 148 transfers to date utilizing this approach and have accomplished 74 clinical pregnancies (maintaining a clinical pregnancy rate per transfer of 50.0%).

Although we presented results from this program both in Europe (European Society of Human Reproduction and Embryology Annual Meeting, 1998) and the United States (The American Society for Reproductive Medicine Annual Meeting, 1999), it seems that our program received very little attention and was delegated to poster presentations at both meetings. This saddened us secondary to the fact that besides the novelty of the program, we had felt that we were demonstrating a new level of efficacy and efficiency with embryo cryopreservation.

We have debated many times whether we should simply mandate embryo quarantining. Since we had found ourselves uniquely faced with the issue, we were forced to examine it carefully. Our experience with oocyte donation, as is similar to most U.S. ART clinics, is that this treatment has evolved primarily into a therapeutic modality for older women. These women seem to always be particularly anxious to get pregnant. Despite informing them that delaying transfer to allow six months of embryo quarantining would have a negligible effect on their potential outcome, we have found very few recipients that were willing to delay treatment for this amount of time. Because of this, at one point, we had consulted several Mayo colleagues in the areas of infectious disease, laboratory medicine as well as blood banking. In addition, we carefully reviewed the history behind the "six month quarantine" policy decision with regards to donor sperm. It initially struck us that this policy was not necessarily evidence-based. In 1988, it was established based on the "limited information available at the time" on the "window period" of HIV seroconversion. A question that we raised was whether the development of

further second and third-generation antibody assays which were now available further refines the "window period" of seroconversion for HIV as well as other potential infectious agents. I received several opinions that perhaps 3 months of embryo quarantining might be appropriate. We felt that this could potentially be advantageous because it might be more appealing to a significantly higher fraction of our recipients. Ultimately, we could not come to any conclusions about either deciding on a specific quarantine interval or even fully agree whether we even needed to quarantine at all. Therefore, we simply continued to offer embryo quarantining as an option. We continued to discuss this issue fully with all of our recipients and allowed them to make an informed choice.

Due to the unique nature of our anonymous oocyte donation program at the Mayo Clinic, I wanted to forward this information. My overall view is that due to the lack of documented infectious transmissions through oocyte donation, mandatory quarantining may not be entirely warranted at the present time. I would also have to say, however, that simply due to the fact that no one really knows for certain what infectious risks, if any, there are, we simply should not be prepared to dismiss this potential risk entirely at this point. In addition, we have found that oocyte donation performed primarily through the use of embryo cryopreservation is highly efficient and effective.

Sincerely,

A handwritten signature in cursive script that reads "Mark A. Damario".

Mark A. Damario, M.D.

MAD/jmq

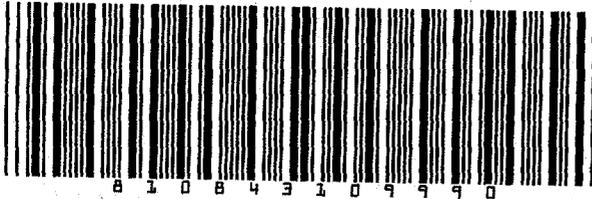
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