Best Practices in
IVF Nursing
NEWSLETTER SERIES
AUGUST 2014

Endometrial Receptivity: Considering the Uterine Environment as a Contributor to IVF Success

Sue Jasulaitis is interviewed by Carol Lesser, Editor of this newsletter series

EDITOR'S NOTE

Moving Toward Higher Rates of Successful Implantation

Carol B. Lesser, MSN, RNC, NP

A failed in vitro fertilization (IVF) cycle is always a disappointment for the patient. When multiple cycles fail, patients often turn to their nurses for support and perspective.

How many times has an IVF nurse heard the following:

My embryos were highly graded and I am healthy with normal fertility testing, yet I did not get pregnant. What went wrong?

IVF nurses are educated to explain that IVF success is dependent on many factors. The genetic competency of the embryo, which is dependent on the age and biology of the woman's eggs at the time of the embryo's creation, is of primary importance.

While the morphologic appearance of the embryo and, more recently, the accumulated data from time-lapse imaging is helpful, none of our current noninvasive methods are perfect predictors of embryonic competency. We know that chromosomal normalcy or euploidy can best be determined with preimplantation comprehensive chromosomal screening (CCS). However, cost constraints and availability limit how many couples proceed with CCS. A single blastocyst has approximately a 40% chance of implantation if it has not undergone CCS. To further confound us, many ideal blastocysts are actually aneuploid. Therefore, most patients will have to complete more than one cycle to succeed.

For decades, the emphasis has been on improving oocyte and embryo quality and techniques to facilitate fertilization, like intracytoplasmic sperm injection. While success rates have improved dramatically since the early days of IVF, there is a renewed interest and focus on other contributors to success. One area receiving special attention today is the endometrium.

In previous decades, the prevailing wisdom was that the uterus contributed minimally to ongoing pregnancy rates as evidenced by women in their sixth decade of life successfully carrying pregnancies to term, as long as the embryos were created with younger gametes. This fostered a more laissez-faire attitude toward the importance of the uterine environment as a contributor to success.[1]

While at first it seemed reasonable to conclude that endometrial receptivity remained unaltered with age as long as the uterine cavity was normal and adequate endometrial thickness could be attained, this principle was challenged for the first time in a 2002 study by Toner and colleagues.[2] The study was a retrospective analysis of oocyte donation data accumulated by the Society for Assisted Reproductive Technol-

Carol B. Lesser, MSN, RNC, NP, is a Nurse Practioner at Boston IVF, Boston, MA. **Sue Jasulaitis RN, MS,** is a Clinical Research Manager at Fertility Centers of Illinois, Chicago, IL.

Disclosures
Ms Lesser discloses that she received compensation from Actavis, Inc. for her participation in the preparation of this newsletter.
Ms Jasulaitis discloses that she received compensation from Actavis, Inc. for her participation in the preparation of this newsletter.

EDITOR'S NOTE *continued*

ogy registry. For the first time, pregnancy and delivery rates appeared to decline if the recipient was older than age 45, and seemed to worsen in recipients older than age 50. However, the study was limited by its retrospective nature.

In the May 2014 issue of *Fertility and Sterility*, and consistent with Toner's earlier findings, a study by Yeh and colleagues confirmed the observation that oocyte donation to recipients older than age 45 is associated with a small but statistically significant drop in pregnancy rates. These findings support the recognition that the endometrium is an important independent variable when trying to achieve a successful pregnancy.[3]

Implantation depends on 3 fundamentals: a developmentally competent blastocyst, a receptive endometrium whose window of implantation is in midsecretory phase, and synchronicity between the blastocyst and the window of implantation.

IVF nurses understand that ensuring synchrony between the embryo and the uterus is a vital determinant of a healthy and ongoing implantation. There is a critical period after ovulation called the "window of implantation," when a viable embryo is most likely to implant. IVF protocols aim to ensure the proper timing of embryo transfer within this critical time frame. It has been estimated that 15% of failed cycles are due to a uterine receptivity problem.

While most IVF protocols raise estradiol to supraphysiologic levels, there is a concern that beyond a certain point, elevated estrogen levels may negatively affect the endometrium. This may possibly be due to a change that affects the window of implantation, causing it to close sooner than in a natural cycle. Similarly, if the progesterone level is raised in the follicular phase above a certain threshold, the endometrium may also prematurely advance and impede implantation.[4,5]

Our field has long described success with widely divergent stages of development, from the transfer of pronucleate embryos to day 7 blastocysts.[6,7] This suggests it is not the stage of development that dictates success, but rather well-timed endometrium reception.

In all transfers, the maturity of the embryo must be appropriate for the degree of endometrial advancement. Poor or failed fertilization is sometimes caused by asynchrony. This is dependent on how fast or slow the embryo is growing and its stage of development at the time of transfer, as well as the degree of endometrial advancement. Different protocols for endometrial preparation can affect outcome. While studies show equivalency with different progestins, the way these agents are used can be critical to success. When physicians try to match the endometrium to the embryo, the success rates seem to improve. Similarly, natural cycles may create a healthier environment for implantation; this may explain divergent protocols with similar success rates. We need to perfect how to use these products intelligently, so the embryo's stage of development can synchronize with the endometrium's maturation.

In summary, there is vast attention on the importance of the endometrium as a contributor to cycle success, and the suggestion that in the future we will see personalized embryo transfers that better coordinate the embryo and the endometrium.

In this issue, I will interview Sue Jasulaitis, RNC, MS, a well-known and experienced nurse and nurse educator who works at Fertility Center of Illinois (FCI). I will ask Sue about how FCI is approaching the issue of assessing and improving endometrial receptivity.

Exploring Solutions to Enhance Endometrial Function

An interview with Sue Jasulaitis by Carol Lesser

Sue Jasulaitis
RN, MS

Ms Lesser: Sue, tell us about your role at FCI and your experience in reproductive endocrine and infertility (REI) nursing, including your daily responsibilities?

Ms Jasulaitis: At FCI, I serve as the Clinical Research Manager, and am responsible for management of all US Food and Drug Administration (FDA) and investigator-initiated clinical research trials. I am also responsible for coordination of retrospective data analysis to evaluate practice protocols or new treatment interventions. I assist in protocol, abstract, and manuscript development. In addition, I lead our Continuous Quality Improvement (CQI)/Risk Management Department. In these departments, we strive to improve patient care outcomes through review of existing practice protocols and guidelines.

I have been an REI nurse for approximately 18 years, and prior to my current role I was the IVF Coordinator/

Clinical Manager for the River North IVF Center at FCI.

Ms Lesser: What do you find to be the most rewarding part of your job and why?

Ms Jasulaitis: Helping to create success from despair through advanced technology is an extremely rewarding facet of our profession. The speed at which new technology and innovation happens in this industry drives our health care professionals to remain passionate about what we do.

Ms Lesser: We want to focus on how your center approaches the issue of enhancing endometrial receptivity. For example, do you favor freeze-all cycles over fresh cycles? Please explain the rationale behind your practice and whether it is physician-dependent or a center-wide policy.

Ms Jasulaitis: As a practice, we feel assessment of endometrial receptivity is critical, and we promote a more in-depth endometrial/uterine assessment for all cases of multiple cycle failure. We also evaluate endometrial function through the endometrial receptivity array biopsy, and have performed multiple patient embryo transfers on patients that demonstrated a nonreceptive endometrium. We feel freeze-all is a viable option supported by successful frozen embryo transfer (FET) pregnancy rates and have developed many practice-wide clinical guidelines standardizing situations when a freeze-all is recommended.

As a practice, we feel assessment of endometrial receptivity is critical, and we promote a more in-depth endometrial/uterine assessment for all cases of multiple cycle failure.

Ms Lesser: Do any of your physicians offer scratch biopsies for repeated implantation failure? If so, when do you perform it and what has been your experience with this precycle intervention?

Ms Jasulaitis: Although physician-dependent, we do offer endometrial scratching. We utilize this tool not only for the recurrent implantation failure (RIF) population but also for patients with a history of unsuccessful assisted reproductive technology cycles in general. Endometrial scratching is a simple procedure in which the endometrium is disrupted to elicit endometrial repair. It is thought that this process of endometrial repair improves pregnancy rates. The procedure, similar to an endometrial biopsy, is done in the month prior to IVF stimulation and requires an informed consent from all patients. Our experience with this technique has been positive, as patients look at these procedures as another way to personalize their treatment options to maximize their cycle success.

Ms Lesser: Do you encourage CCS of blastocyst embryos before transfer? And, if so, do you vitrify the blastocysts and then transfer them in a later cycle? Do you encourage single embryo transfers for these patients?

Ms Jasulaitis: We do encourage CCS for all appropriate at-risk infertile groups (eg, advanced maternal age, recurrent pregnancy loss, recurrent implantation failure, single gene carriers). In addition, we provide CCS for all populations, and have seen an increase in CCS utilization in both domestic and international third party cases. At FCI, we work with multiple testing labs, and have the ability to receive next-day screening results. Depending on the treatment plan, we can plan for a fresh day 6 transfer or freeze the embryos while awaiting CCS results. Our recent trend is favoring embryo cryopreservation and moving away from a fresh CCS transfer. We do encourage elective single embryo transfer (eSET) on all appropriate populations, especially when we have the capacity to apply tools such as CCS for advanced embryo selection. As a practice, we strongly feel eSET is a viable option to minimize both patient and fetal risk.

Ms Lesser: When you transfer euploid vitrified blastocysts, do you prefer natural, or exogenous estrogen and progesterone-prepared endometrial linings?

Ms Jasulaitis: Our standard of care is a combination of exogenous estrogen via vaginal and transdermal routes. Choice of luteal progesterone support is, as always, physician-driven but in general we steer toward intramuscular or combo intramuscular/vaginal progesterone support for programmed FET cycles.

Ms Lesser: When you have a thin endometrium, less than 7-8 mm, what is your protocol for improving the thickness?

Ms Jasulaitis: Although patient history is key to customizing a treatment plan for a chronically thin endometrium, we traditionally add exogenous estrogen (oral, vaginal, and/or intramuscular) in both the follicular and luteal phase for both IVF and FET cycles. We utilize many additional protocols for thin uterine lining such as granulocyte colony-stimulating factor (GCSF), low dose aspirin, progesterone supplementation, and acupuncture. We will occasionally use Viagra as a treatment adjunct. We also will prescribe a stimulated FET protocol to attempt to optimize the endometrial lining. If in doubt, we have a robust embryo vitrification program in which we can freeze quality embryos and reserve them until the endometrium can be fully optimized.

Ms Lesser: For repeated implantation failure and/or recurrent pregnancy loss, do you offer Neupogen™ (Filgrastim), a recombinant form of GCSF? If so, how do you administer it? Are you part of the multicenter NT-100 clinical trial?

Ms Jasulaitis: For thin endometrium, we use Neupogen as an intrauterine infusion. For a fresh IVF cycle, intrauterine Neupogen 300 µg is given the day of or the day after human chorionic gonadotropin (hCG) trigger. For an FET protocol, intrauterine Neupogen is given the day of luteal progesterone start. In our limited experience, this procedure has resulted in a 1–2 mm increase in the endometrial lining. Anecdotally, pregnancy rates are positive with this intervention, but the numbers are too small at present to determine statistical significance.

We are pleased to be a participating clinic in the Nora NT-100 clinical trial. In this trial, daily injections of GCSF are given to determine if they will improve outcomes in the RIF population. We are equally excited for study completion so cumulative data review can determine if this protocol provides a successful intervention for this difficult population. In this trial, our experience to date has been positive.

Management of clinical research is a very specific, rule-laden activity requiring time and resources to dedicate not only to patient care but also to the many regulatory aspects of clinical research.

Ms Lesser: Do you offer either dexamethasone and/or low dose aspirin to enhance implantation? If so, how is it prescribed?

Ms Jasulaitis: Unless contraindicated, we prescribe low dose aspirin to all patients after egg retrieval and for all FET cycles. We do have a dexamethasone treatment protocol which is physician-specific. In this protocol, oral dexamethasone 0.5 mg is started the day of follicle stimulating hormone with the last dose taken the day of hCG trigger. We also use dexamethasone in conjunction with growth hormone to enhance stimulation in poor responders.

Ms Lesser: I understand that you are in charge of multiple clinical trials and ongoing research conducted by your center. How did you receive training to undertake these responsibilities?

Ms Jasulaitis: Management of clinical research is a very specific, rule-laden activity requiring time and resources to dedicate not only to patient care but also to the many regulatory aspects of clinical research. Management of clinical research programs is very similar to the multidisciplinary management of IVF third-party departments, which require proficiency in both patient care and regulatory management. Research study coordinators receive protocol-specific training from each study sponsor, as well as training in good clinical practices (GCP). In the research field, GCP is a standard of care that applies safe, fair and equitable treatment to all patients while conducting clinical trials. Aside from the sponsor-provided training, this role has evolved through personal initiative and a concerted effort from our multidisciplinary research team. For nurses that are interested in clinical research, there are many on-line courses that prepare and certify nurses to manage clinical research trials.

Ms Lesser: Do you have any other practices that you care to share that are relevant to this topic?

Ms Jasulaitis: I challenge the readers to look at their own centers. Whether large or small, you have a wealth of knowledge and clinical experience within your walls. You are the nursing leaders that drive change in your practice. Continue to investigate how you can impact the care you provide to your patients. The efforts you make today may feel small, but remember that they have a profound impact on the patients in your care. ●

References:

1. Paulson RJ, Hatch IE, Lobo RA, Sauer MV. Cumulative conception and live birth rates after oocyte donation: implications regarding endometrial receptivity. *Hum Reprod*. 1997;12(4):835–839.
2. Toner JP, Grainger DA, Frazier LM. Clinical outcomes among recipients of donated eggs: an analysis of the U.S. national experience, 1996-1998. *Fertil Steril*. 2002;78(5):1038–1045.
3. Yeh JS, Steward RG, Dude AM, Shah AA, Goldfarb JM, Muasher SJ. Pregnancy outcomes decline in recipients over age 44: an analysis of 27,959 fresh donor oocyte in vitro fertilization cycles from the Society for Assisted Reproductive Technology. Fertil Steril. 2014;101(5):1331–1336.
4. Xu B, Li Z, Zhang H, et al. Serum progesterone level effects on the outcome of in vitro fertilization in patients with different ovarian response: an analysis of more than 10,000 cycles. *Fertil Steril*. 2012;97(6):1321-1327.
5. Elnashar AM. Progesterone rise on the day of HCG administration (premature luteinization) in IVF: an overdue update. *J Assist Reprod Genet*. 2010;27(4):149-155.
6. Ahuja KK, Smith W, Tucker M, Craft I. Successful pregnancies from the transfer of pronucleate embryos in an outpatient in vitro fertilization program. *Fertil Steril*.1985;44(2):181-184.
7. Sagoskin AW, Han T, Graham JR, Levy MJ, Stillman RJ, Tucker MJ. Healthy twin delivery after day 7 blastocyst transfer coupled with assisted hatching. *Fertil Steril*. 2002;77(3):615-617.
8. Nora Therapeutics, Inc. A multi-center study to evaluate multiple doses of NT100 following IVF in women with repeated IVF failures (Thrive-IVF). NLM Identifier: NCT01864356. http://clinicaltrials.gov/ct2/show/NCT01864356.