AUGUST 2012

Best Practices in
IVF Nursing
NEWSLETTER SERIES

Ovarian reserve: Explaining the tests, interpreting the results

Shannon Gwartney is interviewed by Carol Lesser, Editor of this newsletter series

EDITOR'S NOTE

Predicting pregnancy potential: Never say never

Carol B. Lesser, MSN, RNC, NP

In vitro fertilization (IVF) is an assisted reproductive technology (ART) technique initially developed to help women with tubal disease in uniting egg and sperm. Several years after this breakthrough, through serendipity and against expert prognostication, it was observed that injecting less-able sperm into eggs yielded excellent fertilization rates. Thus began the era of IVF with intracytoplasmic sperm injection to treat male factor infertility, and countless couples now had an alternative to donor sperm for procreation.

As time passed and experience with IVF techniques accrued internationally, maternal age became recognized as a powerful indicator of fertility potential. In addition, we discovered that a woman's age has a significant role in egg and embryo quantity and quality, as well as pregnancy potential. What seems elementary now was not evident in the early days of IVF.

Several key reproductive endocrinologists deserve our respect and gratitude for observing this age-related phenomenon. They helped us understand why women of similar ages and backgrounds would have such disparate cycle experience and outcome. They helped focus our attention on precycle fertility measurements that would explain why some couples had multiple oocytes and embryos while others struggled to produce even a single egg or embryo. They helped us predict who would require higher doses and more elaborate combinations of fertility drugs to provide optimal support for a cycle.

These reproductive medicine giants not only accurately described the impact of age on fertility, but also quickly developed tools to help us quantify what we now refer to as "ovarian reserve."

Today, IVF nurses understand the importance of maternal age as a determinant in ART outcome. Part of our daily responsibilities is explaining to our patients what the various infertility tests measure and interpreting the results for them. For example, what is the difference between a day 3 follicle-stimulating hormone (FSH) level, an antral follicle count (AFC), an anti-Müllerian hormone (AMH) level, and a clomiphene citrate challenge test (CCCT)? What do the levels mean, and how can you predict outcomes for patients when test results seem to contradict each other? Is 1 test better than another?

IVF nurses convey these test results to the patient so that she can understand them and use them to consider her best treatment options. This is a complex task because, as helpful as these tests are, we still lack the perfect biologic test that can always predict an individual's fertility fate. The best we can do is describe trends and speak in generalities; while this provides perspective and probabilities for success, it is imperfect. The nurse's role is often to share this reality and help balance the patient's hopefulness with a realistic sense of her chances for success, while understanding the tests' limitations and the patient's need for useful information.

To cope with this challenge, IVF nurses look at multiple variables, not a single laboratory result. We have all met the exception to the rule on more than 1 occasion. She may be the older patient with an elevated FSH level, multiple failed IVF attempts, with a 1% chance of pregnancy, and a history

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This supplement is supported by Watson.

EDITOR'S NOTE *continued*

screams for the need for other ways of family building. She then conceives naturally or with treatment despite her dismal history and our negative predictions. We learn the hard way to "never say never," while maintaining humility when it comes to predicting pregnancy potential. Nature remains in charge, and as long as a woman ovulates, she will have a chance, albeit remote, for pregnancy.

When patients are well informed and well cared for, they will usually "forgive" us if they are not successful. However, patients who have been told they will never get pregnant with their own eggs may not be so forgiving if nature cooperates despite their poor prognosis. We all learn from experience, and despite the limitations of these tests, we rely on them to guide our patients, keeping in mind that there are always exceptions to the rule.

When counseling patients, it's important to be aware that while poor ovarian reserve testing can tell us who may not be the best candidate for ART, it cannot always predict who may or may not conceive with her own eggs. This is especially true when a younger patient presents with abnormal levels. Although elevated FSH levels, elevated AFCs, and decreased AMH levels indicate decreased ovarian reserve, age is also a powerful predictor of ultimate success.

To simplify: age and obstetrical history describe relative oocyte quality, and ovarian reserve testing describes the relative quantity of eggs that remain and how responsive one will be to ovulation induction medications. As nurses, we educate our patients and guide them through challenging decision making.

In this issue's interview with nurse practitioner Shannon Gwartney, RN, MSN, we explore the methods available for testing ovarian reserve, how to interpret test results, and using results to help patients make treatment decisions. Shannon provides her suggestions for how to best share the meaning of test results with patients and helping them to balance hopefulness with realistic expectations.

Ovarian reserve: Explaining the tests, interpreting the results

An interview with Shannon Gwartney by Carol Lesser

Shannon Gwartney, RN, MSN

Ms Lesser: Shannon, please describe your role regarding interpreting and explaining ovarian reserve test results for your patients.

Ms Gwartney: When I see a patient for their initial ultrasound evaluation for ovarian reserve testing, I explain in detail what the tests are that are being performed and provide them with information on the results we are looking for. The information that patients are receiving at this visit can be overwhelming and confusing on top of the anxiety they often feel during this information gathering stage, so we provide patients with as much written material on the tests and interpretation of the results as possible. When I call a patient with their test results, I review the findings and explain what they mean in relation to their ovarian reserve. If the results are different than expected, they will be advised to return for a discussion with their physician to revise their treatment plan and discuss the results further.

Ms Lesser: Which tests are preferred in your ART center for assessing ovarian reserve?

Ms Gwartney: Our standard workup includes transvaginal ultrasound to assess basal antral follicle (BAF) count and estradiol, FSH, and AMH levels. We perform the ultrasound and estradiol and FSH level tests on cycle day 1, 2, or 3. AMH level can be obtained at any time during a woman's cycle, but is typically done at the same time as the estradiol and FSH blood draw. We perform a CCCT on all women age 35 years and older.

Ms Lesser: Please explain the reason behind checking day 3 FSH levels, in terms that your patients can understand.

Ms Gwartney: FSH is a hormone produced by the pituitary gland. It acts upon the ovary to stimulate oocyte growth, which then leads to ovulation. FSH levels are going to be at their lowest level early in a woman's cycle. Multiple studies have shown that women with an abnormally high FSH level on day 3 have a decreased chance of conceiving. FSH will rise in response to decreased egg quality, quantity, or a combination of both. The evaluation of FSH helps to determine the appropriate treatment plan, medication dose, and helps us to advise women on their individual success rates with a given treatment.

Ms Lesser: In your center, are levels checked on cycle day 3 exclusively, or is there a range? Do you always

check FSH with an estradiol level? If so, why? Can you tell us how you explain an elevated estradiol level and low-to-normal FSH level to your patients?

Ms Gwartney: We will check FSH on cycle day 1, 2, or 3, although cycle day 3 is preferred. We always check estradiol along with FSH because an elevated estradiol level will artificially suppress the FSH level. Estradiol may be elevated at the beginning of the cycle due to an estrogen producing ovarian cyst or as a result of diminished ovarian reserve. If a patient has an elevated estradiol and low-to-normal FSH level, I will explain to them that the FSH results are likely being artificially suppressed and we would have them return on day 1, 2, or 3 of their next cycle to reassess the levels. We always perform a vaginal ultrasound when assessing estradiol and FSH levels to screen for an estrogen-producing cyst.

Women who have abnormal FSH levels on day 3 or day 10 are considered to have diminished ovarian reserve and tend to have a poorer response to gonadotropin ovarian stimulation and decreased pregnancy rates.

Ms Lesser: Do you check BAF counts? If so, is this done at a specific time in the cycle? What results do you ideally like to see?

Ms Gwartney: We evaluate BAF count on cycle day 1, 2, or 3, along with estradiol and FSH levels. A variety of factors can influence BAF count including age, polycystic ovarian syndrome, or recent use of hormonal birth control. On average, we would like to see at least 10 total BAFs.

Ms Lesser: Do your physicians use the BAF count to determine the starting gonadotropin dose? If the BAF is very high, as we see in our younger patients and oocyte donors, do your physicians lower the starting gonadotropin dose or watch for signs of ovarian hyperstimulation syndrome (OHSS)?

Ms Gwartney: Our physicians use the BAF count, FSH and AMH levels, and patient's age to determine the optimal starting gonadotropin dose. If, based upon the results, we feel that the patient is at risk for OHSS, we would lower the starting dose and closely monitor their response during the stimulation cycle, lowering the dose further if needed. We have also been using more antagonist protocols in patients with a high BAF count, which allows us to use a Lupron trigger instead of human chorionic gonadotropin to decrease the risk of OHSS.

Ms Lesser: Do you use AMH levels to assess ovarian reserve? Can you explain what AMH measures and why this test is gaining in popularity internationally as a helpful ovarian reserve assessment tool?

Ms Gwartney: We include the measurement of AMH as part of the basic fertility work up. AMH is a hormone produced by the granulosa cells in ovarian follicles. It is first made in primary follicles after they advance from the primordial follicle stage. At this stage, the follicles are too small to be seen by ultrasound. The production of AMH is highest in the preantral and small antral stage of follicle development, in follicles that are less than 4 mm. As the follicles grow, AMH production decreases and eventually stops. Almost no AMH is produced in follicles larger than 8 mm. AMH levels are believed to reflect a woman's remaining egg supply. The level of AMH remains relatively constant; therefore it can be measured at any time during a woman's cycle. As women age, their pool of remaining preantral follicles decreases, thus leading to low AMH levels. Women with many follicles, such as women with polycystic ovaries, have high AMH levels. High AMH levels do not necessarily correlate with better egg quality, but women with higher AMH levels tend to have a better response to ovarian stimulation and tend to have higher numbers of eggs retrieved. The interpretation of AMH levels has yet to be clarified and agreed upon by the experts, but in our clinic, we like to see AMH levels greater than 1.0 ng/ml.

Ms Lesser: In some mandated states, such as Massachusetts, certain insurance carriers require a normal CCCT before coverage will be granted for ART. Do you use the CCCT? As if speaking to your patients, can you explain why the test was promoted and what the desired FSH levels are on day 3 and day 10? Why is the day 10 FSH level preferably lower than the day 3 level? What does it mean if it is not?

Ms Gwartney: Oregon is not a mandated state, but in our clinic we typically perform the CCCT in women age 35 years and older. The test is used to uncover patients who have a high FSH level, which may not be detected simply with a day 3 FSH measurement. Women who have abnormal FSH levels on day 3 or day 10 are considered to have diminished ovarian reserve and tend to have a poorer response to gonadotropin ovarian stimulation and decreased pregnancy rates. In our lab, normal FSH levels are less than 13. FSH levels of 13 to 15 are considered borderline, and levels greater than 15 are abnormal. The day 10 FSH is a reflection of the ovary's ability to overcome the effects of the clomiphene blocking the estrogen receptors, and it correlates well with ovarian responsiveness to gonadotropins and overall clinical outcome. A high day 10 level would suggest decreased ovarian reserve and decreased pregnancy rate.

Ms Lesser: How do you counsel your patient when ovarian reserve test results seemingly contradict each other?

Ms Gwartney: We take all of the results together to develop an overall picture of the patient's ovarian reserve. If 1 test result were to come back very different from the rest, we would not likely put as much weight on the 1 test, but would rather look at other factors such as patient's age, previous pregnancy history, and any history of response to ovarian stimulation to counsel the patient appropriately.

Ms Lesser: Does your center discourage and deny IVF if test results indicate decreased ovarian reserve? Are there exceptions? How is this decided?

Ms Gwartney: We have protocols in place that have been agreed upon by all of our providers for patients who are found to have severely decreased ovarian reserve as evidenced by abnormal FSH levels, very low BAF count, or very low AMH levels. This is based upon the low rate of pregnancy in relation to the high cost of treatment, both emotionally and financially. We do make exceptions for extenuating circumstances. Patients who do not meet criteria to move forward with IVF can be presented to the other providers at our weekly IVF meetings where we discuss upcoming IVF cycles. If agreed upon by the other providers, the patient may proceed with IVF or be offered mini-IVF if the providers feel that the oocyte yield will be similar with mini-IVF as with high dose gonadotropin stimulation. The patients are counseled extensively by their physician regarding their decreased success rate.

We take all of the results together to develop an overall picture of the patient's ovarian reserve.

Ms Lesser: Does your center advocate any adjunct treatments to improve ovarian reserve?

Ms Gwartney: To date, there is not a large amount of research-based evidence to support the effectiveness of adjunct treatments to improve ovarian reserve. We have occasionally used DHEA, CoQ10, and omnitrope growth hormone in select IVF patients to try to improve ovarian responsiveness to stimulation with mixed results.

Ms Lesser: In closing, I want to thank Shannon for sharing her experience and passion for caring for patients who are facing the challenge of trying to conceive in their later reproductive years. We know her patients benefit from her expertise, and we are grateful she has shared her experience with us.

There is an increased awareness of the role of declining mitochondrial function as we age and its impact on egg quality. This is an exciting time to be involved with patients who present with ovarian insufficiency and decreased ovarian reserve. Treatments are being developed that hope to positively impact and improve mitochondrial function and ovarian potential for these patients. This next decade will likely provide us with new tools and treatments to help our patients as they progress through the course of normal reproductive aging as we seek to improve the competency of their oocytes. We expect, at the same time, to improve and refine our tests that measure ovarian reserve so we can better counsel and treat our patients.

DISCLOSURES

Carol B. Lesser, MSN, RNC, NP, reports that she has served as a consultant and on the Speakers Bureau for Watson Pharmaceuticals. She received compensation from Watson for her participation in preparing this newsletter.

Shannon Gwartney, RN, MSN, received compensation from Watson for her participation in preparing this newsletter. She reports that she has no other commercial or financial relationships from any sources.

Comments or questions for Carol Lesser? Email your thoughts to SRMnurses@QHC.com

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