Preserving Fertility in Rheumatologic Disease

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CHICAGO — Fertility preservation options should be presented to patients as early after the diagnosis of rheumatoid arthritis, systemic lupus erythematosus, and scleroderma as possible.

These rheumatologic diseases often strike both men and women during their childbearing years, and the diseases themselves as well as the long-term therapies used to treat them can have a negative impact on reproductive health.

"It's important to recognize that [while] many of the innovative technologies available today to treat life-threatening diseases and to provide patients with the promise of life after their disease, whether it be cancer, rheumatic disease, or other type of life-threatening condition … many of these drug treatments can be devastating in terms of reproductive health," according to Marybeth Gerrity, Ph.D., executive director of the Oncofertility Consortium at Northwestern University, Chicago.

"While many of us who treat patients with chronic diseases sometimes have a tendency to think in terms of, 'That's the least of your worries,' it's increasingly becoming a concern of survivors to look at these sorts of quality of life issues and so we need to change our mind set," she said at a symposium sponsored by the American College of Rheumatology.

In order to effect this change, it's important not only to consider the pharmacology and reproductive impact of the drugs being used to treat rheumatologic diseases, but also to have a heightened awareness of the types of standard fertility preservation options, "so you can at least have your receptors retuned to some of the things that may be appropriate for your patients," Dr. Gerrity said.

The list of drugs used to manage and treat rheumatic diseases that are known to affect reproductive health include, but may not be limited to, cyclophosphamide, chlorambucil, nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, methotrexate, and leflunomide, she said.

With respect to cyclophosphamide treatment for lupus nephritis, for example, while the cytotoxic-induced damage is reversible in some tissues of rapidly dividing cells, the damage to the ovary, with its limited number of germ cells, tends to be progressive and irreversible, she said, noting that, "in studies, up to 70% of adult female patients taking daily oral cyclophosphamide and nearly half of those receiving a monthly intravenous pulse developed amenorrhea and experienced permanent ovarian failure within a year of first dose."

The alkylating agent chlorambucil has been shown to affect both male and female fertility. "Studies have shown that adult and adolescent women taking chlorambucil exhibit an increased rate of ovarian failure," Dr. Gerrity said. "[The drug] may cause an arrest in follicular maturation, stromal fibrosis, and a decreased number of ova in the ovary, leading to delayed onset of menstruation and amenorrhea."

In adolescent and adult male patients, chlorambucil, either alone or in combination with prednisone or azathioprine, has been linked to temporary azoospermia. "This may be due to inhibition of DNA synthesis in developing sperm and damage to the cells of the seminiferous epithelium," noted Dr. Gerrity.

Male patients taking sulfasalazine, methotrexate, cyclophosphamide, and leflunomide may also face the risk of oligospermia and impaired sperm motility, while women taking NSAIDs may have trouble conceiving because the drugs can inhibit blastocyst implantation, Dr. Gerrity said.

In the technique of ovarian tissue cryopreservation, portions of the ovary or the entire ovary are removed and the cortical tissue is frozen and later reimplanted.

Among the "routine" fertility preservation options available to patients, Dr. Gerrity explained, are sperm banking, testicular tissue banking, GnRH analogs or antagonists, and donor sperm for men and embryo or egg banking and emergency in vitro fertilization, ovarian tissue cryopreservation, donor eggs, and gestational carriers for women.

"Embryo banking and in vitro fertilization are routine in the infertility clinic and involve stimulating women with high doses of fertility drugs to cause them to produce a lot of eggs that can be fertilized in the laboratory to produce embryos that can then be stored for later implantation."

However, there are drawbacks to this option: "It's expensive, and it requires at least 3 weeks of preparation and treatment before egg retrieval, which may not be medically reasonable for some patients," she said.

Another roadblock, until recently, was the fact that banking of eggs had been technologically impossible, and banking of embryos required a sperm source. "For some people without a partner, facing a life-threatening disease or long-term therapy that would impair their fertility, the prospect of undergoing a $12,000 procedure to retrieve eggs and then having to pick the man of their dreams out of a catalog is an overwhelming prospect," Dr. Gerrity said.

Fortunately, thanks to a "political fluke" in Europe, there have been tremendous advances within the last year, leading to the ability to successfully freeze eggs for later fertilization.

"About 2 years ago, the Italian government made the freezing of human embryos illegal in that country, meaning that all of the patients in Italy undergoing [in vitro fertilization] could only add sperm to eggs that could safely be returned to their uterus—usually two to three eggs," Dr. Gerrity explained.

Faced with the prospect of having to waste the majority of eggs retrieved from patients, "the Italian scientists kicked into gear and solved the problem we've been working on for more than 20 years: They broke the code on how to freeze eggs, so now frozen eggs yield the same pregnancy and fertilization rates as fresh eggs," she said. "For the patients needing to bank eggs before starting fertility-impairing drug treatment, at least they don't also have to select a sperm donor on the spot."

Although the success rates associated with frozen egg fertilization are high, the technology is still considered investigational in the United States, "which of course is an issue when dealing with third-party payers."

A new frontier for fertility preservation in women is ovarian tissue cryopreservation, whereby portions of the ovary or the entire ovary are removed and the cortical tissue is frozen and later reimplanted into the patient. "This is a technique that we are using extensively in young girls and prepubertal girls with cancer and in patients who have to begin so quickly that taking 3 weeks out to stimulate ovaries is just not possible," said Dr. Gerrity. "Although the freezing of the tissue is simple, the challenge has been in 'waking it up' once it's reimplanted. This has been the focus of research over the last 2-3 years, and it has paid off. In the past 6 months, there have been reports of about 14 pregnancies with transplanted ovarian tissue following chronic treatment or chemotherapy."

Upon implantation, all of the women began menstrual cycling again and became pregnant spontaneously, she said. This technique is only an option for those patients who can be withdrawn from their fertility-compromising drugs or drugs that are contraindicated in pregnancy for the period of conception and gestation, she added.

For patients who cannot carry a pregnancy because it would be unsafe or unwise to withdraw from therapy, "gestational carriers may be the best option," said Dr. Gerrity. "Unlike true surrogates, who lend their eggs and their uterus, gestational surrogates just lend their uterus to the effort, carrying to term the fertilized embryos from the patient and her partner."

In order to determine the best fertility preservation option for an individual patient, "it's important to have the patient sit down with a reproductive endocrinologist," Dr. Gerrity stressed. "As the part of this process, it's critical that [the referring physician] keeps an open line of communication with the reproductive endocrinologist. Be clear about what you can do in terms of treatment," she said. ■