Preserving Fertility in Rheumatologic Disease

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

Several 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 conditions can be devastating in terms of reproductive health,” accord- ing to Marybeth Gerrity, PhD, 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 be- coming 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 Ameri- can College of Rheumatology.

In order to effect this change, it’s im- portant not only to consider the pharma- cology and reproductive impact of the list of drugs used to treat rheumatologic diseases, but also to have a heightened awareness of the types of standard fertili- ty preservation options, “so you can at least have your receptors return 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-inflam- matory drugs (NSAIDs), sulfasalazine, methotrexate, and leflunomide.

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 lim- ited number of germ cells, tends to be progres- sive and irreversible, she said, noting that, “in studies, up to 70% of adult female patients taking daily oral cyclophos- phamide and nearly half of those receiv- ing a monthly intravenous pulse developed amenorrhea and experienced permanent ovarian failure within a year of therapy.”

The alkylating agent chlorambucil has been shown to affect both male and female fertility. “Studies have shown that adult men who undergo whole body irradiation to treat leukemia 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 on- set of menstruation and amenorrhea.”

In adolescent and adult male patients, chlorambucil, either alone or in combina- tion with prednisone or azathioprine, has been linked to temporary azoospermia. “This may be due to inhi- bition of DNA synthesis in the seminiferous tubules and possibly also to re- sistance of the cells to the seminiferous epithelium,” not- ed Dr. Gerrity.

Some drugs, such as sulfasalazine, methotrexate, and leflunomide may also face the risk of oligospermia and impaired sperm motil- ity, while women taking NSAIDs may have trouble conceiving because the drugs may weaken or damage the lining of the uterus, Dr. Gerrity explained, are sperm banking, testicu- lar tissue banking, GnRH analogs or controlled ovarian hyperstimulation, donor eggs, and gesta- tional carriers for women.

“Embryo banking and in vitro fertiliza- tion are routine in the infertility clinic and involve stimulating women with high dos- es of fertility drugs to cause them to pro- duce 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 three weeks out to stimulate ovaries is- sued for oral or injectable gonadotropins so fertility can be increased enough to produce a viable egg.”

“Another roadblock, until recently, was the fact that banking of eggs had been technologically impossible, and banking of embryos requires 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 cat- alog 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 em-

bros 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 surgeons, the in- novators and inventors who 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 success rate 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 not without investiga- tional use in the United States, “which of course is an issue when dealing with third-par- ty payers.”

A new frontier for fertility preservation in women is ovarian tissue cryopreserva- tion, whereby portions of the ovary or the entire ovary are removed and the cortical tissue is frozen and later reimplanted into the patient. “Unfortunately, we are using extensively in young girls and prepubertal girls with cancer and in pa- tients who have to begin so quickly that taking 3 weeks out to stimulate ovaries is just not possible,” said Dr. Gerrity. “Al- though the freezing of the tissue is simple, the challenge has been in ‘waking it up’ once it’s reimplanted. This has been the fo-cus 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 fertility impairment.”

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 preg- nancy because it would be unsafe or un- wise to withdraw from therapy, “gesta- tional carriers may be the best option,” said Dr. Gerrity. “Unlike true surrogates, who lend their eggs and their uterus, gesta- tional surrogates just lend their uterus for chronic treatment or chemotherapy.”

In order to determine the best fertility preservation option for an individual pa- tient, “it is important for the patient sit down with a reproductive endocri- nologist,” Dr. Gerrity stressed. “As the part of this process, it’s critical that [the referring physician] keeps an open line of communi- cation with the reproductive endocri- nologist. Be clear about what you can do in terms of treatment,” she said.