# Determining the differential impact of cancer and cancer therapies on male reproductive health: aiming for enhanced prognostic specificity

In this issue of *Fertility and Sterility*, Martinez et al. from the Centre d'Etude et de Conservation des Oeufs et du Sperme humain (CECOS) network publish an important contribution in the field of male fertility preservation: "Impact of Hodgkin or non-Hodgkin lymphoma and their treatments on sperm aneuploidy: a prospective study by the French CECOS network" (1). Since the publication of the American Society of Clinical Oncology recommendations on fertility preservation in 2006, oncologists and reproductive specialists alike have gained increasing familiarity with the notion that cancer therapies often have a deleterious and sometimes permanent effect on spermatogenesis and male fertility (2). What many oncologists, and what some specialists in the field of reproductive medicine do not fully realize, however, is that impairment of male reproductive potential often *precedes* the initiation of chemotherapy and radiation therapy in patients with cancer. This point is very eloquently illustrated in this most recent CECOS publication.

In this study, Martinez et al. prospectively assessed a cohort of men with Hodgkin (HL) or non-Hodgkin (NHL) lymphoma at baseline before the initiation of any cancer treatment, and then again at numerous time points after the initiation of treatment (3, 6, 12, and 24 months) (1). Besides simply considering bulk semen parameters, the authors added a new parameter to the analysis: sperm aneuploidy detected by means of fluorescent in situ hybridization (FISH) analysis. Patients were stratified not only by cancer type (HL vs. NHL), but also by the treatment regimen that they received: adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) ± radiotherapy versus cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone (CHOP)/mechlorethamine, vincristine, procarbazine, prednisone (MOPP)–doxorubicin, bleomycin, vinblastine (AVP).

The manuscript is a natural extension of a 2014 publication by the same CECOS group, in which the authors reported that at the time of diagnosis, men with lymphoma had lower semen parameters and higher sperm DNA fragmentation rates than control subjects (3). In the current manuscript, the authors provide two new and important insights. First, they report that sperm aneuploidy is elevated at baseline for men with HL and NHL before the commencement of cancer treatment. In addition, the authors found differing rates of improvement in both spermatogenesis and sperm aneuploidy depending on the lymphoma treatment regimen used. More specifically, semen parameters were significantly decreased at 3 and 6 months after treatment with the ABVD ± radiotherapy or CHOP/MOPP-ABV regimens. Furthermore, for men receiving the ABVD ± radiotherapy regimen, the sperm aneuploidy rate was elevated only at 3 months after initiation of treatment, with levels found to be lower than pretreatment values at the 1- and 2-year time points. In contrast, patients in the CHOP/MOPP-ABV treatment group had semen parameters and sperm aneuploidy rates that were abnormal at baseline and did not return to normal until 2 years after initiation of treatment.

The findings of this study are important for several reasons. First, this data allow physicians and patients to more specifically consider the effects that individual lymphoma treatment regimens might have on both semen analysis parameters and sperm aneuploidy rates. Second, the longitudinal nature of the study provides specific data on anticipated recovery in semen parameters, depending on the treatment protocol that the patient received. This information is especially important, given the lack of data on the enduring effects of individual chemotherapeutic regimens. We are seeing a movement toward defining the effects of specific oncologic treatment protocols, as exemplified by Green et al. in their 2014 study correlating cumulative alkylating agent exposure with changes in semen analysis parameters (4). Patients and clinicians alike crave this important information in the setting of formalized oncofertility care, and the time is right to begin the painstaking process of aggregating and reporting outcomes for commonly used oncologic treatment regimens (5).

A final point about the Martinez et al. work (1) bears mention. The notion that sperm aneuploidy was abnormal in both the HL and NHL patient groups at baseline is both provocative and concerning. Although the authors speculate as to possible mechanisms, they ultimately state that there is no clear root cause linking "cancers and sperm genome alterations before any treatment is given." Given the elevated sperm aneuploidy values in the CHOP/MOPP-AVP cohort, the authors urge that "couples must be advised to use contraception for 2 years after lymphoma treatment if chemotherapy such as CHOP/MOPP regimens was used." This recommendation might be regarded by some investigators as being premature, given that the CHOP/MOPP treatment arm in this study consisted of only eight patients. Additional studies are clearly needed to both confirm and expand upon these findings.

In conclusion, Martinez et al. (1) are to be congratulated for providing increasingly granular data regarding bulk semen parameters and the genetic condition of sperm at the time of lymphoma diagnosis as well as at different time points after the initiation of treatment. The authors' prospective multicenter methodology is a strength of their work, and their contribution provides a model for other centers to emulate. Clearly, there is a clinical need for this data, given the high survival rates for lymphoma patients and the desire of the vast majority of these survivors of reproductive age to procreate with the use of their own sperm.

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