Identifying at-risk populations: are we simply not doing enough fertility preservation procedures?

In the case series presented by Pecker et al. (1), the potential pitfalls and harrowing complications of ovarian stimulation in a morbidly ill population of patients with sickle cell anemia (SCA) are presented to broaden our understanding and highlight the risks of fertility preservation procedures in this precarious population. Given the relatively infrequent occurrence of fertility preservation in this population, we appreciate the opportunity to observe secondhand the fascinating and terrifying case histories presented therein. The undertaking of these treatments, however justifiably motivated, should make us pause in wonder at the audacity of the patients so driven to seek fertility preservation. Unlike the potentially life-saving power of experimental end-stage disease treatments that may prolong life for recipients who have no other resort, fertility preservation procedures offer a chance only for future family building. Fertility preservation procedures and their uncertain and as-yet unfulfilled promise, however, may provide motivation and value for the patient, a secondary benefit other than the endpoint of family building.

Increased survivorship of childhood cancers, improvements in the management of chronic diseases that result in reduced morbidity, and advances in fertility preservation techniques allow us to offer reproductive treatment options to patients who would have previously been too unhealthy or unable to build families. During hematopoietic stem cell transplant (HSCT) candidate patients face gonadotoxic therapy akin to those used to fight neoplasia. These treatments, such as the use of alkylating agents and irradiation, are well known to impair future fertility by damaging ovarian reserve.

Severely ill SCA patients may be cured of their disease by HCST, but gonadotoxic pretreatment for this disease altering therapy is likely to render the patient sterile. Since HCST is complicated and difficult, it is only offered to patients suffering the most from the ravages of SCA, which is defined by clinically significant end-organ damage. SCA and its associated co-morbidities complicate the ovarian stimulation and oocyte retrieval process.

In the report by Pecker and colleagues (1), the authors provide particularly insightful detail whose significance might otherwise go unnoticed by physicians unaccustomed to working with this population, such as the unusual baseline profiles of SCA patients and the compensations associated with their management. Reproductive endocrinologists familiar with the treatment of severe ovarian hyperstimulation syndrome are aware that inexperience in its management can lead to disastrous consequences. Superficially logical treatment options may lead to exacerbation of secondary pathology, such as the management of third-space fluid shifts. Likewise, specialized knowledge of SCA characteristics and how these patients may respond differently than healthy peers can make a critical and life-saving difference in their care. For example, patients with SCA are at high risk of thromboembolism and, due to chronic disease impact on renal function, face elevated risks that may further worsen complications of ovarian hyperstimulation syndrome.

The report highlights how ill these patients are, which is typical of the subpopulation of SCA patients considering HSCT. However, this population represents an extreme, since only severely ill patients are candidates for HSCT. Perhaps if HSCT treatments become less toxic, they can be offered to healthier patients, thereby expanding the candidate pool for fertility preservation and provides us with candidates who are less likely to be injured by complications of fertility preservation treatments.

Given these realities, one wonders if there is an earlier stage, at least for some patients who are not yet at the tipping point of seeking HSCT and whose end-organ damage is not as clinically significant or for whom the impact is less severe, that would make fertility preservation procedures safer to perform. Clearly, this ideal cannot always be achieved for SCA patients: one subject in this case series was very young, which raises other thorny ethical issues, given the decision to offer to a minor of 15 years-age a non-disease modifying treatment with unpredictable success that carries the potential for life-ending complications.

Should we offer untested treatments to these patients since there is little outcome data in this population? The authors report that few patients who have completed both fertility preservation and HSCT have yet attempted pregnancy with cryopreserved tissue. And, to the authors' admission, the final endpoint of family building is still in much doubt, not only from the uncertainty of the outcome of fertility preservation, whatever modality employed, but because of the health of the potential future recipient or her ability to engage a suitable gestational substitute to carry the intended pregnancy. Yet given the potential for potentially curative HSCT and its unfortunately gonadotoxic pretreatment, fertility preservation adds promise to the lives of those afflicted with SCA.

Performing fertility preservation procedures in the population described in this case series amounts to tertiary prevention: limiting the impact or toxicity of the treatment of disease effects. To offer it to less-ill SCA patients would undoubtedly mean performing fertility preservation procedures for some patients who would never reach the need for HSCT and its accompanying gonadotoxic pretreatment.

Pecker et al. (1) point out that to qualify for HCST, severe disease complications must be manifest, which makes their elective fertility preservation treatments all that more precarious to perform. Are we failing this population by waiting too long to act? If we wait for these patients to qualify for pretreatment for HCST with gonadotoxic protocols, we almost certainly are past achieving peak results. Given that chronic disease can cumulatively result in severe end-organ damage, should we be seeking opportunities for fertility preservation in patients for whom gonadotoxic therapy and gonadectomy are not part of tertiary prevention of disease? For patients in whom chronic disease may render fertility preservation treatment risky, should we aim to offer treatment prior to the onset of these complications, however unpredictable this timeline may be? Planning non-acute treatment cycles can lead to optimization of patient-specific stimulation and lead to

additional gamete banking. Indeed, identifying patients for whom the slow progression of chronic disease may lead to future infertility can provide an opportunity to intervene before end-stage disease increases treatment-related risks or renders such treatments futile.

Ideally, when achievable, should oocyte cryopreservation for these special populations be performed before they become seriously ill? The ethics of providing these treatment options is a serious concern for our profession (2). Yet, should we be expanding our use of fertility preservation?

The pinnacle of medical therapy, so rarely attained, is the primary prevention of disease: by intervention, altering a patient's path so that the impact of disease is not experienced. Although reproductive aging is not a pathological entity, infertility is a disease worthy of treatment regardless of its origin, including that caused by advanced reproductive age. Can we identify patients who are at risk of suffering the consequences of reproductive aging, and are interventions on their behalf beneficial to them? Given the improvements in technique, isn't it time to recommend routinely to some category of healthy patients that they act for primary prevention of infertility rather than manage secondary prevention?

Since fertility preservation to circumvent reproductive aging is not recommended by our professional societies and since reproductive aging itself is an obstacle that will lower the success of fertility preservation treatments, should we be defining special healthy populations for whom fertility preservation is appropriate and recommended? Should women beyond a certain age who have not started family building be encouraged to seek fertility preservation if family building is a goal? At what point do the scales tip in favor of performing these procedures, balancing the loss of fertility against the loss of efficacy of treatment? Certainly, if it can be justifiable to offer fertility preservation procedures to gravely ill patients for whom the outcome is at least equally uncertain as for healthy peers but for whom the risks of complications from these procedures is higher than the general, healthy population, isn't it incumbent on us to recommend fertility preservation procedures before the natural potential for fertility has declined? Although the professional society opinion regarding the elective use of fertility preservation procedures for combating the age-related decline in fertility is clear (3), one wonders if there is an appropriate population for whom childbearing has already been deferred and for whom the significant loss of fertility potential looms that the routine offer of fertility preservation procedures would be suitably appropriate.

Practitioners at the vanguard of medical therapy who seek to push the boundary of care for the benefit of their severely ill patients deserve our admiration but should also make us introspectively wonder that we are not doing enough for our healthy populations.

Eric Flisser, M.D.
Reproductive Medicine Associates of New York, New York, New York

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