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CHAPTER

Infertility Following Cancer Chemotherapy

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Cytotoxic chemotherapy has produced sustained clinical remissions and cures for many patients with Hodgkin's disease,[1] acute lymphoblastic leukemia,[2] choriocarcinoma,[3] testicular carcinoma,[4] and other malignant and nonmalignant disorders. As detailed in subsequent chapters, most of the commonly used antineoplastic drugs produce immediate toxicities in organs composed of self-renewing cell populations such as bone marrow, skin, and gastrointestinal tract epithelium. Pancytopenia, stomatitis, alopecia, and nausea and vomiting occur frequently but generally are not prolonged or irreversible once chemotherapy is completed. Some antitumor agents are associated with more delayed toxic effects, such as the cardiomyopathy of doxorubicin (Adriamycin) or the pulmonary fibrosis associated with bleomycin, which may become clinically apparent even after chemotherapy is completed. However, as patients continue to survive longer after chemotherapy, previously unrecognized toxic effects are becoming manifest. Important among these late effects is infertility, which is of particular concern for successfully treated patients hoping to return to a normal lifestyle. In this chapter we will consider this late effect of cancer chemotherapy.

GONADAL DYSFUNCTION AFTER CANCER CHEMOTHERAPY

Neoplastic disease and its treatment can potentially interfere with any of the cellular, anatomic, physiologic, or behavioral processes that make up normal sexual and reproductive function. Indeed, many drugs used in the treatment of cancer have profound and often lasting effects on the testis and the ovary. Both germ cell production and endocrine function may be altered. These effects are generally related to the age, pubertal status, and menstrual status of the patient as well as to the particular drug class, dosage, or combination administered.

Chemotherapy Effects in Men

The adult testis functions as both an exocrine and endocrine gland, producing spermatozoa and testosterone. Spermatogenesis proceeds in the seminiferous tubules, which constitute over 75% of the mass of the testis, while the interstitial cells of Leydig carry on the endocrine functions of the gland. The remainder of the testis consists of supporting and vascular tissues necessary for the protection and nourishment of the developing spermatozoa.

The seminiferous tubules are lined by stratified epithelium composed of two cell types: spermatogenic cells and Sertoli cells. The spermatogenic cells are arranged in an orderly fashion; spermatogonia lie directly on the basement membrane, and primary and secondary spermatocytes, spermatids, and maturing spermatozoa progress centrally toward the tubular lumen. Sertoli cells also lie on the basement membrane. These specialized cells help to maintain the blood-testis barrier and to regulate the release of mature spermatozoa from the germinal epithelium.[5]

In any area of the seminiferous tubule, five to six generations of germ cells can be identified. These generations are not randomly distributed but occur in fixed cell associations. Thus spermatids at a particular stage in their development are always associated with the same types of spermatocytes and spermatogonia. Six typical cell associations in the human testis synchronously evolve in the process of sperm maturation. A complete series of cell associations constitutes a cycle of the germinal epithelium, and each cell association may be considered a stage of the cycle. The entire process of spermatogenesis proceeds continuously throughout the tubule, and it has been estimated that 64 to 90 days elapse from spermatogonial stem cell mitosis to release of mature spermatozoa from the seminiferous epithelium.[6]

Spermatogenesis is a dynamic and complex process divided into three phases: (1) proliferation of spermatogonia to produce spermatocytes and to renew the stem cell pool, (2) meiotic division of spermatocytes to reduce the chromosome number in the germ cells by half, and (3) maturation of the spermatids to become spermatozoa.[7] Cytotoxic agents could affect this process in a number of ways: (1) a specific cell type within the germinal epithelium might be selectively damaged or destroyed, (2) the proliferative and meiotic phases of spermatogenesis might proceed normally, but sperm maturation might be abnormal, leading to functionally incompetent mature spermatozoa, or (3) chemotherapy might damage Sertoli cells, Leydig