Management of Male Infertility Secondary to Chemotherapeutic Agents During Childhood Cancer Treatment

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Case Presentation

A 33-year-old male with a history of Hodgkin lymphoma at age 14 presents with his wife to discuss fertility. He and his wife have been attempting pregnancy for the last 1 year, without success. His wife has recently undergone fertility testing and results thus far have been normal. She has regular menses, is not on birth control pills, and has achieved no prior pregnancies. The patient does not remember having a discussion about his fertility at the time of his lymphoma diagnosis. He had achieved puberty at the time of cancer treatment but did not cryopreserve sperm. The patient does have a history of chemotherapy, radiation therapy, and stem cell transplant. He does not report any recent fevers or history of urological trauma, including testicular torsion. He does not report a history of prostatitis, epididymitis, nor orchitis. He denies a history of post-pubertal mumps. There is no known family history of fertility problems. He is not taking any current medications. He is able to find his lymphoma treatment history and reports that he was treated with Cytoxan, Adriamycin, vincristine, IV methotrexate, intrathecal methotrexate and ARA-C, ifosfamide, VP-16, L-asparaginase, and cisplatin. He received 2500 cGy of mini-mantle radiation. He received his bone marrow transplant 2 years after the initial diagnosis and was treated with ARA-C, VP-16, cisplatin, thiotepa, and Cytoxan. On exam, his penile exam is normal, with no evidence of plaques or induration. His urethral meatus is normal. His testes are descended bilaterally with no evidence of abnormal masses or tenderness. Both testes are 10 cc in volume. Epididymis, vas deferens, and cord structures are normal bilaterally.

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52.1 Assessment and Diagnosis

The most likely etiology for the patient's infertility is related to his cancer treatment. Cytotoxic cancer therapies can negatively affect sperm production. Sperm cells divide quickly and are, therefore, susceptible to chemotherapy-induced damage. Permanent infertility can result if spermatogonial stem cells are damaged to the point that they can no longer produce maturing sperm cells. The risk of chemotherapy causing infertility varies depending upon the patient's age, the type of drug used, and the doses of the drug given. Sperm banking is a reliable strategy to preserve fertility in male patients who receive gonadotoxic chemotherapy [1]. Chemotherapy drugs and the risk of infertility in men are listed in Table 52.1. Higher doses of these drugs are more likely to cause permanent fertility changes. Combinations of drugs can lead to greater toxicity. The risks of permanent infertility are even higher when males are treated with both chemotherapy and radiation therapy to the abdomen or pelvis. In addition, radiation directed at the central nervous system can affect the hypothalamus and pituitary gland leading to a decrease in LH or FSH. Reduction

Table 52.1 Chemotherapeutic agents and risk of infertility

Highest risk of infertility	Lower risk of infertility
Actinomycin D	5-fluorouracil
Busulfan	6-Mercaptopurine
Carboplatin	Bleomycin
Carmustine	Dacarbazine
Chlorambucil	Daunorubicin
Cisplatin	Doxorubicin
Cyclophosphamide	Epirubicin
Cytarabine	Etoposide
Ifosfamide	Fludarabine
Lomustine	Methotrexate
Melphalan	Mitoxantrone
Nitrogen mustard	Thioguanine
Procarbazine	Thiotepa
	Vinblastine
	Vincristine

in these hormone levels can lead to a decrease in sperm production and infertility.

Hormonal therapy can also affect sperm production. These medications can also cause sexual side effects, such as a lower sex drive and erectile dysfunction. The decrease in sperm production and sexual side effects usually start to improve once patients have completed therapy.

Our patient underwent hormonal testing and semen analysis. His hormone testing included an analysis of prolactin, LH, FSH, estradiol, and testosterone. His hormonal levels are normal, except for low testosterone and elevated FSH. Results of his two semen analyses show azoospermia with normal volume.

Volume (ml)			
Value	**Low**	**High**	**Units**
3.2	1.0	5.0	ml
2.9	1.0	5.0	ml

Sperm concentration (M/ml)			
Value	**Low**	**High**	**Units**
0.0	20	200	M/m
0.0	20	200	M/m

% Motility (%)			
Value	**Low**	**High**	**Units**
0.0	50	100	%
0.0	50	100	%

% Normal morphology (%)			
Value	**Low**	**High**	**Units**
0.0	14	100	%
0.0	14	100	%

Based on this analysis, the patient was diagnosed with nonobstructive azoospermia secondary to the chemotherapy he received as part of his Hodgkin's lymphoma therapy.

52.2 Management

To address his infertility, he was offered clomiphene citrate therapy in preparation for testicular sperm extraction (TESE).

TESE and intracytoplasmic sperm injection (ICSI) were first introduced in 1993 for the treatment of obstructive azoospermia [2]. This technique was subsequently used for azoospermia secondary to nonobstructive etiologies [3]. Quantitative histological studies in patients undergoing TESE confirmed that there was a threshold amount of spermatogenesis that must be exceeded in order for spermatozoa to be released into the ejaculate [4]. Micro-TESE provides the advantage of allowing a surgeon to selectively identify the seminiferous tubules most likely to contain spermatozoa based on the larger and more opaque appearance of these tubules. With micro-TESE, successful sperm retrieval has been reported in up to 63% of men [5], whereas conventional and more limited sperm retrieval procedures have reported success rates from 20% (percutaneous testicular biopsies) [6] to 45% (open testis biopsies) [7].

Clomiphene citrate is a well-established agent that has been reported in numerous studies to improve semen quality and increase pregnancy rates among the partners of men to whom it is administered. Clomiphene citrate increases pituitary secretion by blocking the feedback inhibition of estradiol, thereby increasing serum FSH and LH levels. The administration of clomiphene citrate may result in sperm in the ejaculate of patients with nonobstructive azoospermia or the simplification of testis sperm retrieval [8]. Surgeons often consider a course of clomiphene citrate administration prior to surgical sperm retrieval in patients with nonobstructive azoospermia.

52.3 Outcome

Our patient received chemotherapeutic agents at the time of puberty that resulted in azoospermia. He was not offered sperm banking at the time of his treatment. He, however, was able to successfully father two children after two cycles of micro-TESE and ICSI. Given his low testosterone levels, the patient was offered testosterone replacement therapy to manage symptoms of hypogonadism.

Clinical Pearls and Pitfalls

- Chemotherapy and directed radiation therapy can affect spermatogenesis temporarily and permanently.
- Sperm banking prior to receiving cancer therapies is an effective method to preserve fertility options but many patients are not offered this at the time of treatment.
- Newer techniques, such as micro-TESE with ICSI, have allowed men with nonobstructive azoospermia to have biological children even after cancer therapy.

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Review Questions and Answers

Q1. Why do some chemotherapy agents lead to male infertility and what factors increase the likelihood of this outcome?

A1. Sperm cells divide quickly and are, therefore, susceptible to damage induced by chemotherapy. Permanent infertility can result if spermatogonial stem cells are damaged to the point that they can no longer produce maturing sperm cells. The risk of chemotherapy causing infertility varies depending upon the patient's age, the type of drug used, and the doses of the drug given.

Q2. At the time of cancer treatment, what treatment factors can affect male fertility?

A2. Chemotherapy agents have varying likelihoods of resulting in male infertility and are listed in Table 52.1. Hormonal therapy can also affect sperm production. These medications can also cause sexual side effects, such as a lower sex drive and problems with erections. The decrease in sperm production and sexual side effects usually start to improve once patients have completed therapy. Radiation aimed directly at the testicles or at the pelvic region can affect male fertility by destroying spermatogenic stem cells. Radiation directed at the central nervous system can affect the hypothalamus and pituitary gland, leading to a decrease in LH or FSH.

Q3. What is the advantage of micro-TESE over other sperm retrieval methods in patients with nonobstructive azoospermia?

A3. Micro-TESE provides the advantage of allowing a surgeon to selectively identify seminiferous tubules most likely to contain spermatozoa based on the larger and more opaque appearance of those tubules. With micro-TESE, successful sperm retrieval has been reported in up to 63% of men, whereas conventional and more limited sperm retrieval procedures have reported success rates from 20% (percutaneous testicular biopsies) to 45% (open testis biopsies).

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