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Infertility and Testis Cancer

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Testicular cancer is one of the few malignancies that affect men in their reproductive years. Testicular cancer represents the most common solid organ tumor in young men between 20 and 35 years of age. The National Cancer Society predicted that 8250 new cases of testicular cancer would be diagnosed in the United States in 2006 [1]. Fortunately, testicular cancer is also one of the most curable malignancies with 370 testicular cancer-specific deaths predicted for 2006. The incidence of testicular cancer therefore correlates with a 1 in 300 lifetime risk for developing testicular cancer and a 1 in 5000 lifetime risk for dying from testicular cancer. The objective of superior testicular cancer treatment includes not only cure but also the preservation of quality of life. The preservation of fertility and sexual function represent important quality-of-life parameters in these young men. To determine how testicular cancer impacts fertility it is important to understand how infertility is assessed and how infertility and testicular cancer are interrelated.

Development of infertility and testicular cancer may arise from congenital abnormalities in testicular maturation, such as gonadal dysgenesis, cryptorchidism, or carcinoma in situ. Additionally, exposure to certain gonadal toxins or trauma impacts testicular integrity, including spermatogenesis and the blood–testis barrier. As a result of these factors, many men presenting with testicular cancer are found to have abnormal semen analysis parameters before initiation of treatment. With the increase in delayed childbearing and the use of assisted reproductive technologies, men presenting with a primary complaint of infertility can be found to have incidental testicular neoplasms [2].

The presence of a testicular neoplasm affects the local testis environment, the pituitary–gonadal hormonal milieu, and the body systemically. Aberrations in any of these factors can adversely affect spermatogenesis. The psychologic impact inherent in the diagnosis of testicular cancer can also affect sexual function and fertility as a result. These tumor-related effects on fertility are compounded by the potentially deleterious effects of treatment modalities, such as pelvic radiation, chemotherapy, and retroperitoneal lymph node dissection (RPLND).

Despite these risk factors for infertility, it is important to stress to patients the preventive methods and treatments for infertility associated with testicular cancer and treatment. In patients who have successfully treated testicular cancer and preserved fertility, the potential effects on genetic integrity must be evaluated. This article reviews the causative factors for infertility in men who have testicular cancer and the treatments available for preserving or restoring fertility.

Diagnosis of infertility

Infertility is defined as the inability to conceive after 1 year of unprotected intercourse, with 75% of patients able to conceive after 6 months and 90% of patients able to conceive after 1 year [3]. This inability to conceive can be caused by male or female factors. Twenty percent of cases result from solely male factors, whereas 40% of cases are caused by male and female factors combined; therefore, male-factor infertility affects 60% of infertile couples [4]. The evaluation of male

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infertility begins with a thorough history that includes a sexual history, past medical history, and family history. Pertinent information garnered from the sexual history includes frequency and timing of coitus and potency. A patient's past medical history is equally important and provides information regarding congenital abnormalities, cryptorchidism, inguinal or retroperitoneal surgery, radiation, infections, medications, toxic exposures, and past pregnancies. A family history may reveal cystic fibrosis, congenital anomalies, or hormonal abnormalities. Once a satisfactory history has been obtained, the physician can proceed to a physical examination. The physical examination should be directed to evidence of hormonal imbalances, testicular volume, paratesticular pathology, and prostate abnormalities. The physical examination is supplemented with the semen analysis evaluating volume, sperm concentration, motility, and morphology. Hormonal analysis includes serum follicle stimulating hormone, luteinizing hormone, testosterone, and prolactin. Finally, a scrotal ultrasound and transrectal ultrasound are included if indicated. It is only after the completion of this evaluation that a decision can be made regarding treatment options. Patients who have testicular cancer presenting with infertility should be evaluated using these parameters to ensure an accurate diagnosis and appropriate treatment regimen.

Relationship between infertility and testicular cancer

Theoretically, any cause that adversely affects testicular function can result in infertility and testicular tumorigenesis. Many studies evaluating testicular cancer have documented an increased risk for abnormal semen analysis parameters in patients who have testicular tumors. Of 15 patients presenting with germ cell tumors, 10 (66%) had evidence of abnormal spermatogenesis, including poor motility, low sperm concentration, or low semen volume [5]. Conversely, studies have been published documenting an increased risk for testicular cancer in patients presenting with infertility. This connection is clearly documented in a large population-based study in Denmark including 32,442 men who underwent semen analysis from 1963 to 1995. Men who had abnormal semen analyses had a 1.6-fold increased risk for developing testicular cancer compared with the general Danish population. In evaluation of specific semen analysis parameters, a low sperm concentration, decreased motility, and increased abnormal motility were specifically associated with increased development of testicular cancer [6]. An evaluation of 3800 men presenting with infertility and abnormal semen analyses in the United States revealed a 20-fold increased risk for testicular tumors when compared with the population based on the SEER database [7].

These observational studies are confirmed with evaluation of testicular histopathology. Carroll and colleagues [8] examined testicular tissue from eight patients who had mediastinal or retroperitoneal germ cell tumors and found abnormal testicular tissue in all patients, including fibrosis, decreased spermatogenesis, interstitial edema, Sertoli cell only, and Leydig hyperplasia. On retrospective review, these patients had a well-documented history of infertility. These studies provide evidence for a common cause responsible for low semen quality and tumorigenesis. Evaluation of these potential causes is essential to understanding the association between infertility and testis cancer.

Abnormal testicular development

During fetal development, male and female embryos begin to differentiate at the end of the sixth gestational week [9]. Early in the seventh week testicular development begins and depends on many factors, including chromosomal integrity and normal endocrine function. Abnormalities in testicular maturation, such as cryptorchidism, are often associated with infertility and tumorigenesis. Cryptorchid testes have abnormal germ cell morphology, varying degrees of gonadal dysgenesis, and are exposed to elevated intra-abdominal temperatures. As early as 3 years of age abnormal spermatogonia and Sertoli cells can be found in cryptorchid testes. This abnormal development progresses to fibrosis, basement membrane degeneration, and deposition of myelin and lipids [10].

The association between cryptorchidism and tumorigenesis was first described in 1851 by Le Comete [11]. Subsequently many population-based studies have confirmed this relationship. The reported relative risk for testicular cancer in patients who have cryptorchidism is 3 to 14 times higher than the expected incidence [12–14]. Additionally, the detrimental effect of cryptorchidism on fertility is also well documented. A multicenter

retrospective review of 162 patients who had cryptorchidism revealed significantly lower sperm concentrations and morphology compared with normal controls. Patients who had retractile testes also had decreased sperm concentration and morphology. Despite these abnormal semen analysis parameters in patients who had retractile testes, the risk for azoospermia was significantly higher in patients who had cryptorchidism [15].

Impaired spermatogenesis, cryptorchidism, and germ cell tumors represent a spectrum of abnormal testicular development and are often interrelated. Andersson and Skakkebaek and colleagues propose that this spectrum of testicular maldevelopment should be classified as testicular dysgenesis syndrome [16]. Their hypothesis advocates a common cause, either genetic or environmental, for cryptorchidism, hypospadias, impaired spermatogenesis, and testis cancer. An evaluation of contralateral testis biopsies in patients who had germ cell tumors including 218 specimens revealed carcinoma in situ in 8.7%, immature seminiferous tubules in 4.6%, and Sertoli cell only pattern in 13.8% of patients. Ultimately 25.2% of patients who had germ cell tumors had evidence of testicular dysgenesis in the contralateral testis [17].

Estrogen exposure in utero represents one such factor proposed as a cause for male genital abnormalities. This hypothesis is supported by animal studies demonstrating the teratogenic effect of estrogen exposure during early embryonic development. Murine embryos exposed to ethinyl oestradiol at embryonic day 13 had a higher risk for cryptorchidism and a trend toward increased testicular teratomas [18]. A case-control study of 108 men who had testicular cancer demonstrated that maternal exposure to exogenous estrogens during the early first trimester was associated with an eightfold increased risk for testicular cancer [19]. The development of testicular cancer or infertility is multifactorial and depends on a series of alterations in the developmental process. At times these alterations may result from a single causal factor during development. Despite this common origin, the association between germ cell tumors and infertility may result from the factors relating to systemic imbalances produced by the tumor itself.

Systemic cancer effects

Malignancy has a wide range of effects on the body, including metabolic derangements, hormonal imbalances, and thermoregulatory changes. These alterations may result from the tumor itself or the body's cytokine response, including increased interleukins and tumor necrosis factors. Investigations of young men who have testicular cancer and Hodgkin's disease suggest that the systemic effects of malignancy alter testicular function and impair spermatogenesis. This evidence results from studies documenting decreased fertility before the initiation of treatment. An evaluation of 158 men at the time of diagnosis of Hodgkin's disease revealed abnormal semen analyses in 70% of men with 8% of patients having azoospermia. The risk for impaired spermatogenesis increased with elevated acute phase reactants and advanced clinical stage [20].

Local tumor effects

Tumors of advanced stage not only produce a heightened systemic reaction but also disrupt the local architecture and functioning of the testis itself. Presumably, more advanced tumors cause a greater disturbance in testicular structure. Invasive germ cell tumors of higher stage are associated with worse semen quality than germ cell tumors of lower stage [21]. This finding may be caused in part by perturbation of the blood–testis barrier. The integrity of this barrier prevents formation of antisperm antibodies that may adversely impact fertility. Although normal fertile men have a 5%–8% incidence of antisperm antibodies, studies have reported men who have testicular cancer to have an 18%, 21%, and 73% incidence suggesting that germ cell tumors disturb the blood–testis barrier [22–24].

This disruption in testicular architecture corresponds to a disruption in testicular function. A review of radical orchiectomy specimens in 28 patients revealed impaired spermatogenesis most apparent within 3 mm of the tumor margin [25]. This local effect of germ cell tumors is supported by a histologic comparison of orchiectomy specimens removed for malignant tumors versus benign tumors; testes with benign tumors revealed significantly fewer abnormalities in spermatogenesis versus testes with malignant tumors. In the presence of malignant tumors, abnormalities in spermatogenesis increased with decreasing distance from the tumor margin [26]. Confirmatory evidence for a direct effect of the cancer process itself exists in the many reports documenting an improvement in fertility after orchiectomy. One such study, evaluating semen analyses in nonrelapsing men on a surveillance protocol for stage I

nonseminomatous germ cell tumors (NSGCT) revealed a significant increase in mean sperm concentrations from 26 to 39 $\times$ 10^6/mL in the year postorchiectomy [27].

Endocrine factors

Normal spermatogenesis depends on normal hormonal equilibrium. Hormonally active tumors can disrupt the hormonal balance and adversely affect spermatogenesis. Germ cell tumors are often hormonally active and can produce β–human chorionic gonadotropin (β-HCG) and α-fetoprotein (AFP). A quantitative analysis of biopsy specimens in 53 men who had seminoma demonstrated a correlation between increased β-HCG and decreased spermatogenesis in the contralateral testis [28]. A paracrine–endocrine mechanism is described in which β-HCG stimulation of intratesticular estradiol production impairs spermatogenesis [29]. Hansen and colleagues [30], using multiregression analysis, determined that an elevated AFP was associated with a decreased total sperm count in patients who had nonseminomatous germ cell tumors. In addition, the authors noted that 33% of patients presenting with germ cell tumors had an elevated serum follicle stimulating hormone (FSH).

The subfertility documented in patients who have malignancy can also be attributed to disruption of the hypothalamic-pituitary-gonadal axis. FSH and luteinizing hormone (LH) are often abnormal in men who have malignancy. Men who have untreated Hodgkin's disease were found to have significant hypogonadism with low FSH and serum testosterone when compared with normal controls. Despite abnormally low serum testosterone, these patients had normal levels of LH suggestive of pituitary or hypothalamic dysfunction [31]. Men who had testicular cancer and an elevated FSH before initiation of therapy are noted to have lower posttreatment fertility than men who had normal FSH before initiation of treatment irrespective of treatment modality [32]. Klingmuller and colleagues [33] confirmed this correlation in patients who had seminoma and suggest using pretreatment FSH as a prognostic indicator for predicting posttreatment spermatogenesis.

Cancer treatment and fertility

The association between the development of testicular germ cell cancer and infertility is well known although the causative factors are still being investigated. Also documented is the potential for improved fertility after the primary tumor is removed at radical orchiectomy. Cancer treatment therefore has the potential to reverse impaired spermatogenesis associated with testicular neoplasia. The treatment of testicular neoplasm is a complex paradigm involving histology, stage, and patient selection. After radical orchiectomy, four treatment options are currently available; surveillance, RPLND, radiation, and chemotherapy. These treatments impact reproductive function and have distinct implications for posttreatment fertility.

Surveillance

Postorchiectomy surveillance is a viable treatment option for men who have stage I testis tumors for patients who are willing to adhere to a strict follow-up regimen. Surveillance protocols allow patients to avoid post-RPLND ejaculatory disturbances and gonadotoxic therapies but approximately 20% of men relapse and ultimately require additional treatment. Men who relapse on surveillance protocols and require gonadotoxic treatments may be at greater risk for infertility than men initially treated with nerve-sparing RPLND [34].

In men who are monitored on a surveillance policy without relapse, semen analysis parameters, including sperm concentrations, may remain stable or actually improve after orchiectomy. Carroll and colleagues [35] noted that 50% of patients who have stage I NSGCT and initial oligospermia or azoospermia recovered normal sperm concentrations within 4 to 19 months postorchiectomy. This finding is supported by Jacobsen and colleagues [27] who evaluated repeat semen analyses of 80 men on surveillance for stage I NSGCT and found a significant increase in mean sperm concentrations at 1 year postorchiectomy. At baseline, 40% of these men had sperm counts less than 10 $\times$ 10^6/mL and 5 of the 28 men who attempted to conceive before malignant diagnosis had been evaluated for infertility. Men successfully followed on surveillance can expect a stable or improved semen quality postorchiectomy.

Retroperitoneal lymph node dissection

The removal of retroperitoneal lymph nodes entails a delicate dissection of tissues and structures surrounding the aorta and inferior vena cava, including the retroperitoneal postganglionic sympathetic nerves. These nerves overlie the aorta and join to form the hypogastric plexus

in the pelvis. The ampullary vas deferens seminal vesicles, periurethral glands, internal sphincter, bulbourethral, and periurethral musculature receive innervation from these nerves. The surgical disruption of these nerves during RPLND or pelvic node dissection can result in retrograde ejaculation or anejaculation depending on the severity of the nerve injury. The presence or extent of retroperitoneal disease often dictates the type of lymph node dissection performed and affects the preservation of ejaculatory function. Unilateral and nerve-sparing RPLND techniques [36] provide the greatest potential for normal ejaculatory function. In comparing patients who underwent postchemotherapy modified bilateral template RPLND [37] versus postchemotherapy nerve-sparing technique in Norway from 1980 to 1994, antegrade ejaculation was preserved in 11% versus 89% of patients, respectively. Anejaculation was documented in 75% of patients after modified bilateral template RPLND versus 5% of patients after nerve-sparing RPLND. Median ejaculatory volume decreased from 4.4 mL before RPLND to 2.5 mL post-RPLND with the largest decrease observed in patients undergoing modified bilateral template RPLND [38]. Donohue and colleagues [39] documented 76% of men status post nerve-sparing RPLND for stage 1 NSGCT who attempted to conceive were successful. In summary, advances in surgical techniques have allowed for the preservation of ejaculatory function and significantly reduced the risk for infertility associated with RPLND.

Radiotherapy

In rats, testicular irradiation results in transient intratesticular edema and spermatogonial arrest but recovery of spermatogenesis is observed 4 weeks postradiation [40]. Human studies that include testicular biopsies reveal that spermatogonia are the most sensitive germ cells to radiation and can be affected by doses as low as 10 cGy [41]. In men receiving radiotherapy for Hodgkin's lymphoma, the testicular dose ranged from 6 to 70 cGy. Patients who received greater than or equal to 20 cGy were documented to have a transient dose-dependent increase in FSH in the first 2 years following radiotherapy. This finding correlated with transient oligospermia that recovered within 18 months posttreatment [42].

Men diagnosed with stage 1 and 2a seminoma often receive adjuvant infradiaphragmatic radiation therapy. Although gonadal shielding minimizes irradiation of the testis, unintended gonadal exposure doses occur [43]. Centola and colleagues [44] documented a mean testicular radiation dose of 44 cGy with a range from 28 cGy to 90 cGy in men receiving infradiaphragmatic radiation treatment of seminoma with gonadal shielding. In patients receiving pelvic and periaortic radiotherapy, declines in sperm counts are often seen in the first year after radiotherapy but can gradually improve within 2 to 3 years following treatment [45]. Buchholz and colleagues [46] performed a retrospective analysis of 212 patients who had stage 1 or 2a seminoma treated with orchiectomy and adjuvant radiotherapy with gonadal shielding from 1975 to 1997 with a mean follow-up time of 8 years. All patients received ipsilateral pelvic and periaortic radiation with a median total dose of 2611 cGy and 2702 cGy in patients who had stage 1 and stage 2a, respectively. An evaluation of semen analyses revealed no correlation between increased radiation dose and abnormal sperm concentration, with 56% of men having a normal sperm concentration. Seventy-three patients responded to a retrospective questionnaire; of these patients, 15% attempted to conceive children postradiotherapy. Seven of 11 couples (64%) were successful in achieving pregnancy without assisted reproduction and 6 of 7 couples delivered healthy infants with one spontaneous abortion. Men receiving infradiaphragmatic radiotherapy for seminoma may experience a transient decrease in sperm counts but can anticipate a recovery of spermatogenesis.

Chemotherapy

The current chemotherapy regimens for testicular cancer have significantly increased survival. The side effects of chemotherapy therefore have become increasingly important. Because systemic chemotherapy targets rapidly dividing cells, disruption of spermatogenesis represents a common side effect of chemotherapeutics. Chemotherapy-related oligospermia and azoospermia are not unique to patients who have germ cell malignancies and have been documented in patients treated for leukemia, lymphoma, and other solid organ malignancies. An evaluation of 314 patients status post gonadotoxic treatment of these malignancies revealed a significant decrease in sperm concentration and semen volume. Patients who had germ cell tumors had the lowest pretreatment sperm concentration (40.6×10^6/mL) and the highest percentage of posttreatment oligospermia but the

lowest incidence of posttreatment azoospermia. The predisposition toward gonadal dysfunction in men who have germ cell tumors continues to impact posttreatment fertility, but less intensive chemotherapy regimens may minimize the risk for posttreatment azoospermia [47].

Bleomycin, etoposide, and cisplatin (BEP) regimens are used as adjuvant therapy for nonseminomatous germ cell tumors and for treatment of metastatic seminomas. Rats treated with BEP had decreased testicular and epididymal weight, decreased sperm count, and decreased motility, but treatment did not affect fertility, pregnancy loss, litter size, or sex ratio [48]. Additionally, rats demonstrated decreased serum testosterone, intratesticular testosterone, and numbers of LH receptors and after exposure to cisplatin [49]. Mice exposed to cisplatin demonstrated a dose-dependent loss of differentiating germ cells resulting from apoptosis [50].

Human studies reveal perturbations in serum LH, FSH, and testosterone. In a study of German men treated with cisplatin-based chemotherapy regimens, 89% of men had elevated FSH levels at 12 months postchemotherapy and this elevation persisted for more than 8 years posttreatment in 64.3% of men [51]. This sustained elevation of serum FSH represents long-term damage to Sertoli cell function. An evaluation of men treated for NSGCT demonstrated elevated serum LH levels in 59% of men who received chemotherapy and decreased sperm counts and semen volume in comparison with men treated with orchiectomy alone [52]. Semen analyses obtained from 30 men 24 to 78 months after BEP chemotherapy revealed 23% oligospermia, 20% azoospermia, abnormal morphology, and decreased motility; unfortunately no pretreatment semen analyses were available to establish baseline spermatogenic function [53]. Petersen and colleagues [54] compared semen analyses and hormonal profiles from 33 men treated with conventional-dose BEP to data obtained from 21 men treated with high-dose BEP and found azoospermia in 19% and 47% of men treated with conventional-dose BEP and high-dose BEP, respectively. In addition, FSH levels were significantly higher in men who received high-dose BEP. No difference in testosterone or LH was noted between the groups.

These abnormalities in semen analyses and hormone levels are not necessarily permanent and the potential for normalization of endocrine and spermatogenic function exists. A review of semen analyses from patients who had germ cell neoplasms treated with cisplatin-based chemotherapy at the Royal Marsden Hospital demonstrated that improved sperm counts were present in 48% and 80% of patients at 2 and 5 years postchemotherapy, respectively. Even more encouraging, the probability of achieving normal sperm counts was 22% and 58% at 2 and 5 years, respectively. High pretreatment sperm counts and the use of carboplatin versus cisplatin were associated with an increased probability of improved fertility postchemotherapy [55]. In summary, systemic chemotherapy for germ cell malignancies affects both Sertoli cell and Leydig cell function and has the potential to permanently impair spermatogenesis. Recovery of spermatogenesis is possible but men who have elevated FSH, high-dose cisplatin therapy, and low pretreatment sperm counts are at increased risk for long-term infertility.

Preservation and restoration of fertility

Currently, men who have testicular cancer have many options available to preserve fertility and potential paternity. The availability of sperm cryopreservation, advances in assisted reproductive techniques (ART), and testicular sperm extraction (TESE) provide the potential for fatherhood for men unable to conceive as a result of testicular cancer treatments. It should be noted that men who have testicular cancer status post chemotherapy have decreased fertilization rates per in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycle and a decreased pregnancy rate compared with men who have testicular cancer treated without chemotherapy [56]. Sperm cryopreservation should therefore be recommended to men who have germ cell neoplasms before the initiation of treatment when possible.

Records of 67 couples referred for ART for male factor infertility following treatment of malignancies, including testicular cancer and lymphoma, were reviewed to determine the options used and success of various treatment modalities. Eighty-two percent of men cryopreserved sperm before treatment and 58% of men used cryopreserved sperm for ART. A total of 151 cycles of ART were completed, including 55 intrauterine inseminations (IUI), 82 ICSI, and 14 ICSI-frozen embryo replacements, with a corresponding delivery rate of 11.1%, 30.5%, and 21%, respectively [57]. A separate study evaluating the

viability of cryopreserved sperm obtained from men before antineoplastic treatment revealed an overall 18.3% pregnancy rate and 7% IUI, 23% IVF, and 37% ICSI pregnancy rates [58]. In men who have true anejaculation or azoospermia, TESE can provide viable sperm for ICSI. An evaluation of 12 men who had azoospermia status post chemotherapy documented motile spermatozoa in 41.6% of men after TESE [59]. In 17 azoospermic men postchemotherapy, testicular biopsies performed at the time of TESE revealed Sertoli cell only in 76% of patients and hypospermatogenesis in 24% if patients. Of these patients, 45% had successful sperm extraction that resulted in live births in 22% of couples [60]. The ability to preserve fertility through ART is an option for men who have persistent azoospermia or anejaculation after treatment of testicular cancer and cryopreservation should always be recommended to enhance the potential for paternity.

Teratogenic potential

Current cancer treatment regimens and reproductive technologies allow many men to be cancer survivors and new fathers. In the setting of malignant testicular dysgenesis and potentially gonadotoxic therapies, many of these men are concerned regarding the potential risk for increased congenital anomalies. Exposure to etoposide in mice resulted in disomy, centromeric abnormalities, and increased diploid sperm in comparison with controls [61]. Mice treated with BEP did not demonstrate an increased risk for pregnancy loss, but offspring of mice treated with BEP for 9 weeks had a significantly higher rate of neonatal mortality than offspring of mice treated for only 6 weeks [48].

In humans, assessment of sperm integrity before and after treatment of germ cell neoplasms did not reveal a higher DNA fragmentation index after diagnosis of germ cell tumors in comparison with controls but did reveal a higher DNA fragmentation index up to 2 years after radiotherapy. This increased DNA fragmentation index was not noted after chemotherapy [62]. Fluorescence in situ hybridization (FISH) of semen specimens from five men after BEP treatment revealed a significantly increased frequency of diploidy and disomy 16, 18, and XY in comparison with healthy controls at 6 to 17 months after treatment [63]. Conversely, another study using FISH to assess the risk for disomy for chromosomes 1, 12, X, Y, and XY in men treated with BEP found no increased risk for numerical chromosomal abnormalities [64].

Many retrospective studies involving patient-reported pregnancy outcomes have investigated the risk for early pregnancy loss and perinatal morbidity and mortality in children fathered by men who had testicular cancer and found no increased risk for pregnancy loss or congenital anomalies [65]. Spermon and colleagues [66] sent questionnaires to 305 men who had germ cell tumors from 1982 to 1999, 226 of whom responded to evaluate fertility before and after treatment. Using patient questionnaires, Spermon and colleagues [66] documented a 66% and 43% conception rate in patients attempting to conceive within 1 year before the diagnosis of testicular cancer and after treatment, respectively. The rate of congenital anomalies was approximately 4% before and after treatment of germ cell neoplasms. Given this data regarding the potential for chromosomal abnormalities in the posttreatment period, sperm cryopreservation should be performed before the initiation of gonadotoxic treatment. Additionally, men should be counseled to postpone conception for approximately 12 to 18 months after treatment to minimize the risk for potential fetal anomalies [67].

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