Iatrogenic Infertility

15

Giovanni Beretta

15.1 Introduction

There are surgical treatments and a number of chemotherapeutic agents and drugs commonly used in therapies that may cause male infertility [1]. When the dispermia is due to medical or surgical causes, it is called iatrogenic infertility [2]. While reviews of iatrogenic causes of infertility in Western Europe reveal that these contribute to approximately 5 % of infertility both in men and women, in Africa this rate is higher [3].

15.2 Chemotherapeutic Drugs

The use of chemotherapeutic drugs in the treatment of cancer and in the management of autoimmune disease can interfere with fertility.

The *alkylating chemotherapy* agent group does the most damage to fertility. These drugs include cyclophosphamide (Cytoxan), chlorambucil (Leukeran), busulfan (Myleran), procarbazine (Natulan, Matulane), nitrosoureas (Carmustine, Lomustine), nitrogen mustard (Mustargen), and L-phenylalanine mustard (Alkeran). In high doses, platinum-based chemotherapy agents (cisplatin, oxaliplatin) or drugs like bleomycin (Blenoxane), often used to treat testicular cancer, can also damage fertility.

G. Beretta
Andrological and Reproductive Medicine Unit, Centro Demetra,
via Della Fortezza 6, Firenze 50129, Italy
e-mail: giovanniberetta@libero.it

G. Cavallini, G. Beretta (eds.), *Clinical Management of Male Infertility*,
DOI 10.1007/978-3-319-08503-6_15

15.2.1 Cyclophosphamide

Cyclophosphamide is one of the most frequently prescribed chemotherapeutic drugs. It is an anticancer and immunosuppressive agent commonly used in men of reproductive age and, when used in high dose or in combination regimens, can cause severe germ cell damage [4]. The damage done to spermatogenesis by cyclophosphamide appears to be dose dependent. A daily dose of 3.7 mg/kg body weight will produce oligospermia or even azoospermia, and this change is frequently permanent. Cyclophosphamide can also interfere with Leydig cell function, resulting in a reduced secretion of testosterone, thus increasing problems relating to infertility [5].

15.2.2 Chlorambucil

This is an aromatic nitrogen mustard that also acts as an alkylating agent. It is used in the treatments of lymphomas as well as in the management of leukemia. It can interfere with spermatogenesis, and its use frequently leads to azoospermia. Recovery in terms of fertility is very variable.

In the management of various types of cancer, it is common to use several different anticancer drugs in combination so that the effect upon the cancer is maximal. All these combinations will always give unpredictable and very uncertain recovery rate in terms of infertility [5] (Table 15.1).

It is very important to suggest patients to cryopreserve their semen before any chemotherapeutic treatment to save potential future fertility, as spermatogenesis will only return to normal in no more than 50 % of patients treated [6]. Certain cancers can cause men to have poor sperm quality, even prior to treatment [7, 8]. It is estimated that about 40 % of men with Hodgkin's disease and 50 % of those with testicular cancer will have low sperm counts at the time of diagnosis [9, 10]. This does not mean that these men should not consider sperm banking, as advances in reproductive techniques have made even poor-quality specimens useful for reproduction [11, 12].

15.3 Common Drugs That Can Cause Male Infertility

There are numerous drugs and medications that have been shown to have adverse effects on male fertility, acting through diverse mechanisms [2].

The mechanisms of impaired fertility include direct effects on germ cells or their supporting cells, on the delicately balanced HPG axis, on erectile or ejaculatory function, and on libido.

In a thorough fertility evaluation of the male partner, the physician should determine what medication the patient is taking and his social habits involving alcohol consumption, tobacco, and recreational drug use. Simply discontinuing the offending agents can reverse most adverse effects from drugs and medications.

Table 15.1 List of the drugs that can cause male infertility

Chemotherapy (dose to cause effect)	Known effect on sperm count
Chlorambucil (1.4 g/m^2)	Prolonged or permanent azoospermia
Cyclophosphamide (19 g/m^2)	
Procarbazine (4 g/m^2)	
Melphalan (140 mg/m^2)	
Cisplatin (500 mg/m^2)	
BCNU (1 g/m^2)	Azoospermia in adulthood if treated before puberty
CCNU (500 mg/m^2)	
Busulfan (600 mg/m^2)	Azoospermia likely, and they are often given with other highly sterilizing agents, adding to the effect
Ifosfamide (42 g/m^2)	
BCNU (300 mg/m^2)	
Nitrogen mustard	
Actinomycin D	
Doxorubicin (770 mg/m^2)	When used alone, cause only temporary reductions in sperm count. In conjunction with above agents, may be additive in causing azoospermia
Thiotepa (400 mg/m^2)	
Cytarabine (1 g/m^2)	
Vinblastine (50 g/m^2)	
Vincristine (8 g/m^2)	
Amsacrine	When used in conventional regimens, cause only temporary reductions in sperm count. In conjunction with above agents, may be additive in causing azoospermia
Bleomycin	
Dacarbazine	
Daunorubicin	
Epirubicin	
Etoposide	
Fludarabine	
Fluorouracil	
6-mercaptopurine	
Methotrexate	
Mitoxantrone	
Thioguanine	

Adapted from Devita et al. [5]

15.3.1 Nitrofurantoin

Nitrofurantoin has been shown to reduce the sperm count in animals and humans. This suppression is short and never permanent after the cessation of treatment.

15.3.2 Cimetidine

Cimetidine is an H2 inhibitor commonly used in the treatment of dyspepsia. It binds to the androgen receptors interfering with sperm production. Its action is short lived and reversible [2].

15.3.3 Sulfasalazine (Salazopyrin)

This drug is still widely used for the therapy of various different inflammatory bowel disorders, especially for ulcerative colitis. It causes a reduction of concentration and motility of the sperms and also alters the shape of sperm head. Upon cessation of therapy, the sperm count and motility will returns to normal [2].

15.3.4 Sex Steroids

Estrogens and testosterone will reduce gonadotropin secretion, and thus, therapy with testosterone will rapidly lead to azoospermia.

15.3.5 Gonadotropin-Releasing Hormone Analogs and Antiandrogens

These drugs, especially in the depot form, are frequently used in the treatment of hormone-dependent prostate cancer. These drugs quickly lead to azoospermia. Antiandrogens block the action of testosterone and can cause erectile failure. As prostate cancer is becoming more common and occurring in younger men, these aspects must be seriously considered [13–15].

15.4 Radiation Therapy

After World War II, with the use of atomic energy and the following incidental irradiation of men, it became clear that sperm production could be reduced to zero due to the effects of irradiation. In 1964, McLeod reported that the accidental exposure of men to radiation after an accident at the Oakridge Nuclear Plant caused azoospermia in more than half of them [16]. Radiation has its most potent effect upon spermatogonia, the type B spermatogonia being the most sensitive.

Radiation therapy can slow down or stop sperm cell production if the testicle is in or near the target area for the radiation. A lead shield can help protect the testicles, but radiation "scatters" within the body, so it is impossible to shield the testicles completely.

The likelihood of infertility after radiation depends on the dose to the testes, shielding, and fractionation (single dose vs. multiple doses). Doses as small as 0.1 Gy can result in decreased sperm counts, and doses of 1.5–4 Gy can result in permanent sterility. As previously noted, the Leydig cells (responsible for testosterone production) are less sensitive to the effects of radiation, with damage occurring at 30 Gy in mature males (20 Gy in prepubescent males).

If the testicles are not the primary radiation targets, shielding can be used. This technique protects the testicle(s) from receiving radiation. Fractionation is the technique of dividing the total dose of radiation into multiple smaller doses. For most side effects, fractionation is used to lessen their severity, but in this case

fractionation (multiple smaller doses) causes more damage to sperm than a larger, single radiation dose.

Total body irradiation (TBI) is a technique used for preparation for stem cell and bone marrow transplants. As the name implies, it is irradiation of the entire body. It is estimated that 80 % of men who undergo TBI will have permanent azoospermia.

For those without permanent azoospermia, sperm counts are at their lowest 4–6 months after treatment. Counts typically return to their pretreatment levels 10–24 months after treatment but can take longer in those who received higher doses.

Radiation damage to the part of the brain that controls hormone production can sometimes interfere with the hormone messages that control sperm production [6].

15.5 Surgery

If the cancer surgery requires the removal of both testes, fertility is affected because of the inability to produce sperm [17, 18].

Surgery on the prostate, bladder, urethra, or colon can result in a condition called retrograde ejaculation.

In normal ejaculation, the semen is propelled through the urethra and the opening to the bladder closes off, allowing the semen to exit the penis. In retrograde ejaculation, the opening to the bladder does not close, allowing the semen to enter the bladder instead of exiting the penis. While this condition is not medically harmful, it does impair fertility [19].

Men with testicular cancer or colon cancer sometimes have surgery that can damage nerves involved in orgasm. The result may be a "dry orgasm," or the sensation of pleasure but without ejaculating any semen. Following a successful nerve-sparing radical prostatectomy, most men will have return of erections but will not be able to have children by natural means [20].

There should be no seminal fluid after the prostatectomy, so they will be "infertile" by natural means, but with in vitro fertilization techniques, it is still possible for a man to father a child after a radical prostatectomy. In this case intracytoplasmic sperm injection (ICSI) of single spermatozoon surgically recovered from the testis could lead to a pregnancy [21–23].

*Video: Sperm recovery after testicular sperm extraction (TESE)*https://www.youtube.com/watch?v=45W5XkzHy7w

Testicular cancer is associated with impaired spermatogenic function, even before orchiectomy, with a degree of dysfunction higher than that caused by local tumor effect [7].

Oligospermia is observed in more than 60 % of patients at the time of diagnosis of testicular cancer [8].

Storing sperm in a sperm bank before the operation is a recommended procedure for those men hoping to father children after the operation [24].

Last but not least, the vas deferens or the testicular blood supply may be injured or ligated at the time of inguinal surgery, hernia repair, hydrocelectomy, or varicocelectomy [25–27].

References

1. Meirow DA, Schenker JG (1995) Infertility: cancer and male infertility. Hum Reprod 10(8):2017–2022
2. Nudell DM, Monoski MM, Lipshultz LI (2002) Common medications and drugs: how they affect male fertility. Urol Clin North Am 29(4):965–973
3. Kuku SF, Oseghe DN (1989) Oligo/azoospermia in Nigeria. Arch Androl 22:233–238
4. Trasler JM, Hales BF, Robaire B (1986) Chronic low dose cyclophosphamide treatment of adult male rats: effect on fertility, pregnancy outcome and progeny. Biol Reprod 34(2): 275–283
5. DeVita VT, Hellman S, Rosenberg SA (2005) Cancer: principles & practice of oncology, 7th edn. Lippincott Williams & Wilkins, Philadelphia
6. Giwercman A, Petersen PM (2000) Cancer and male infertility. Baillieres Best Pract Res Clin Endocrinol Metab 14(3):453–471
7. Eisenberg ML, Betts P, Herder D, Lamb DJ, Lipshultz LI (2013) Increased risk of cancer among azoospermic men. Fertil Steril 100:681–685 [Medline]
8. Mulcahy N (2013) Male infertility increases overall cancer risk. Medscape Medical News. 21 June 2013. Available at http://www.medscape.com/viewarticle/806619. Accessed 30 July 2013
9. Carrol PR, Whitmore WF, Herr HW et al (1987) Endocrine and exocrine profiles of men with testicular tumors before orchiectomy. J Urol 137:420
10. Richie JP (1990) Clinical stage I testicular cancer: the role of modified retroperitoneal lymphadenectomy. J Urol 144:160
11. Lee SJ, Schover LR, Partridge AH et al (2006) American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 24:2917–2931
12. Raman JD, Nobert CF, Goldstein M (2005) Increased incidence of testicular cancer in men presenting with infertility and abnormal semen analysis. J Urol 174(5):1819–1822; discussion 1822
13. Beretta G, Zanollo A (1989) Intranasal gonadorelin in the treatment of cryptorchidism. Arch Ital Urol Nefrol Androl 61(3):333–335
14. Bouloux P, Warne DW, Loumaye E, FSH Study Group in Men's Infertility (2002) Efficacy and safety of recombinant human follicle-stimulating hormone in men with isolated hypogonadotropic hypogonadism. Fertil Steril 77(2):270–273
15. Beretta G, Fino E, Sibilio L, Dilena M (2005) Menotropin (hMG) and idiopathic oligoasteno teratozoospermia (OAT): effects on seminal fluid parameters and on results in ICSI cycles. Arch Ital Urol Androl 77(1):18–21
16. MacLeod J, Hotchkiss RS, Sitterson BW (1964) Recovery of male fertility after sterilization by nuclear radiation. JAMA 187(9):637–641
17. Houlgatte A, De La Taille A, Fournier R, Goluboff ET, Camporo P, Houdelette P (1999) Paternity in a patient with seminoma and carcinoma in situ in a solitary testis treated by partial orchidectomy. BJU Int 84(3):374–375
18. Jacobsen KD, Theodorsen L, Fossa SD (2001) Spermatogenesis after unilateral orchiectomy for testicular cancer in patients following surveillance policy. J Urol 165(1):93–96
19. Reynolds JC, McCall A, Kim ED, Lipshultz LI (1998) Bladder neck collagen injection restores antegrade ejaculation after bladder neck surgery. J Urol 159(4):1303
20. Jacobsen KD, Ous S, Waehre H, Trasti H, Stenwig AE, Lien HH et al (1999) Ejaculation in testicular cancer patients after post-chemotherapy retroperitoneal lymph node dissection. Br J Cancer 80(1–2):249–255
21. Palermo G, Joris H, Devroey P, Van Steirteghem AC (1992) Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet 340(8810):17–18
22. Omurtag K, Cooper A, Bullock A et al (2013) Sperm recovery and IVF after testicular sperm extraction (TESE): effect of male diagnosis and use of off-site surgical centers on sperm recovery and IVF. PLoS One 8(7):e69838

23. Hauser R, Yogev L, Paz G, Yavetz H, Azem F, Lessing JB et al (2006) Comparison of efficacy of two techniques for testicular sperm retrieval in nonobstructive azoospermia: multifocal testicular sperm extraction versus multifocal testicular sperm aspiration. J Androl 27(1):28–33
24. Lewis R (2013) Freezing sperm a viable option in azoospermic men. Medscape Medical News [serial online]. 12 Aug 2013. Available at: http://www.medscape.com/viewarticle/809355. Accessed 28 Aug 2013
25. Zahalsky MP, Berman AJ, Nagler HM (2004) Evaluating the risk of epididymal injury during hydrocelectomy and spermatocelectomy. J Urol 171(6 Pt 1):2291–2292
26. Wantz GE (1984) Complications of inguinal hernia repair. Surg Clin North Am 64:287–1984
27. Beretta G (2005) Surgical treatment methods for obstructive azoospermia and surgical retrieve of spermatozoa for ICSI. Ital J Sex Reprod Med 3:159–165