I.3.8 Iatrogenic Causes of Abnormal Spermatozoa

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Key Messages

- Many drugs, in particular cytostatic and hormonally active agents, can exert deleterious effects on male fertility.
- Vasectomy and vasectomy reversal can result in formation of antisperm antibodies; therefore patients should be counselled accordingly.
- Inguinal hernia repair may be complicated by obstruction of the vas deferens.
- Lumbar sympathectomy can result in ejaculatory disorders.
- Cryobanking of spermatozoa for patients undergoing unavoidable drug treatment affecting male fertility or irradiation is strongly recommended.

I.3.8.1 Definition

Iatrogenic causes of male fertility disturbances are coded when the abnormal spermatozoa are considered to stem from medical or surgical causes. This diagnosis requires the following to be true:

- History of medical treatment with possible adverse effect on fertility
- And/or history of surgery with possible adverse effect on fertility

I.3.8.2 Aetiology and Pathogenesis

I.3.8.2.1 Medical Treatments

Therapeutic drugs may cause a temporary or permanent disturbance of male fertility by impairment of the following functions: spermatogenesis, epididymal sperm maturation, sperm transport, sperm metabolism, motility, capacitation and egg penetration.

I.3.8.2.2 Gonadotoxic Interventions

Testicular cancer, Hodgkin’s disease, non-Hodgkin lymphomas and leukaemia may affect young people, and the disease or its treatment may have deleterious effects on fertility. Impairment of spermatogenesis substances with direct antiproliferating effects on the germinal epithelium is caused by alkylating substances such as cyclophosphamide and chlorambucil and after cytostatic treatment with cisplatin and adriamycin as well as methotrexate and vincristine or bleomycin.

I.3.8.2.3 Further Drugs with Possible Negative Influence on Fertility

Apart from cytostatic agents, direct inhibition of proliferation of the spermatogenesis can be caused by neuroleptics and tricyclic antidepressives (Neumann 1984), by antiemetics and antiepileptics, as well as by antibiotics and chemotherapeutics at higher dosages and long-term treatment (nitrofurantoin, co-trimoxazole, gentamicin and niridazole). Salazosulphapyridine leads to a direct inhibition of spermatogenesis by absorption of toxic metabolites (sulphapyridine). More agents with potentially blocking effects on spermatogenesis belong to the groups of analgesics and immunosuppressants. However, reliable studies are not available for most of these frequently used drugs.

I.3.8.2.4 Hormones and Hormone Antagonists

Hormonal active drugs influence spermatogenesis indirectly by inhibition of the gonadotrophic functions of the pituitary. Impairment of spermatogenesis is possible by oestrogens, gestagens, androgens, anabolics, antiandrogens, luteinizing hormone releasing hormone (LHRH), gonadotrophin releasing hormone (GnRH) (super)agonists or antagonists and glucocorticoids. Drugs may interfere with androgen production by different mechanisms, for example, a decrease in LH production by opiates, blockage of enzymes for steroid production by aminoglutethimide and ketoconazole, an increase in testosterone metabolism by barbiturates, anticonvulsives and further liver enzyme-inducing agents, blockage of the effects of testosterone by androgen receptor antagonists such as cimetidine, spironolactone, cyproteronacetate, an influence such as the physiologic antagonist of androgen effects by digoxin with oestrogenic mode of action and drugs causing hyperprolactinaemia.

Reduction in sperm count, motility and percentage of normally formed sperm is reversible after discontinuation of administration of androgenic hormones. In bodybuilders who have taken anabolic steroids at doses exceeding those generally applied for clinical purposes by up to 40-fold, recovery of sperm numbers into the normal range may vary considerably after stopping the steroids. Time intervals between 4 and 12 months are reported (Knuth et al. 1989; Gazvani et
I.3 Male Factor Fertility Problems

al. 1997). In another case, the patient remained azoospermic even after 12 months of abstinence from the steroid and subsequent treatment with gonadotrophins was initiated (Menon 2003).

1.3.8.2.5 Drugs Affecting Sperm Function

Despite the major clinical significance of therapeutic drugs which may have an influence on gamete functions, there is only scarce knowledge on this subject because of the lack of epidemiological studies. There are reports on certain drugs demonstrating influences on sperm functions or sperm–egg interaction by in vitro tests or by application to small groups of patients. For example, treatment with the calcium-channel blocker nifedipine was shown to block sperm–egg interaction, obviously by alteration of the lipid composition of the cell membranes (Benoff et al. 1994). More relevant substances may be verapamil (alteration of sperm membranes, decline of sperm motility), antiepileptics (damage of sperm membranes, decline of motility), sulphasalazine (decrease in sperm count and motility), tetracyclines (in vitro direct toxic effect), macrolides at high concentrations (in vitro decrease in sperm motility), and amantadine and colchicine (impairment of sperm–egg interaction).

Finally, sperm motility can be impaired by damage of sperm membrane-bound functions. Drugs with motility-disturbing effects in vitro are nitrofurantoin, 2,6-diamino-3-phenazopyridine, tetracyclines, gentamicin, metoclopramide, imipramine, chlorpromazine, nortriptyline, lithium, trifluoperazine, levamisole, propranolol, phenotiamine, dibenamine, stropine and bentropinmesylate (Table I.3.6).

Table I.3.6. Drugs with possible influence on male fertility

<table>
<thead>
<tr>
<th>Suppression of spermatogenesis</th>
<th>Cytostatic agents</th>
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<tbody>
<tr>
<td>Hormones and hormonally active drugs: androgens, antian-</td>
<td>Haptenes and autoantibodies (such as niridazole, salazosulphapyridine)</td>
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<td>drogens, oestrogens, progestagens, glucocorticoids, ana-</td>
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<td>bolics, cimetidine, spironolactone, digoxin, ketoconazole</td>
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<td>Psychotropic drugs, antiepileptics, antiepileptics, analgesics,</td>
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<td>certain antibiotics and chemotherapeutics, anthelmintics</td>
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<td>such as niridazole, salazosulphapyridine</td>
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<tr>
<td>Impairment of sperm function</td>
<td>Calcium channel blockers (sperm motility and sperm-egg binding)</td>
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<td>Antiepileptics (sperm motility)</td>
<td>Sulphasalazine (sperm count and motility)</td>
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<td>Antibiotics (sperm motility)</td>
<td>Amantadine and colchicine (Sperm–egg interaction)</td>
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<td>Psychotropic drugs, alpha- and beta-blockers (sperm motility)</td>
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<tr>
<td>Inhibition of sperm transport</td>
<td>Antihypertensive drugs</td>
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<td>Psychotropic drugs</td>
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1.3.8.2.6 Inhibition of Sperm Transport

α-Adrenolytic acting substances influence sperm transport by inhibition of the emission phase (chemical sympathectomy) of the ejaculatory reflex: antihypertensive drugs (guanethidine, reserpine, methylodopa), psychotropic drugs (thioridazine, chlorprothixene, tricyclic antidepressives, chlordiazepoxide), ganglion blockers (hexamethonium, mecamylamine) as well as alpha receptor blockers (phenotiamine, phenoxybenzamine) (Forman et al. 1996; Rowe et al. 2000) (Table I.3.6).

1.3.8.2.7 Surgery

There may be temporary depression of fertility, which may last for 3–6 months after any surgical procedure, particularly after general anaesthesia has been administered.

Testicular biopsy may result in a temporary suppression of spermatogenesis. Unsuccessful operations such as herniotomies or corrections of testicular maldescent may result in damage to the vas deferens and testis, respectively, with subsequent loss of testicular function. Iatrogenic obstructions may have been provoked by herniotomies (particularly during infancy) or surgical procedures at the ejaculatory ducts or vasographs of the ductus deferentes using irritating contrast media. Incidentally performed epididymal incisions or biopsies during testicular biopsies usually result in obstructions as well. Hernia repair may additionally result in an immunological reaction with production of antisperm antibodies. This may also occur after hydrocelectomy or any other genital or inguinal surgery. Vasectomy is the most common cause of surgical obstruction and also results in production of antisperm antibodies.

Aspermia may be caused by disturbances of the function of the bladder neck after transurethral prostatectomy, treatment of urethral valves in infancy, bladder neck incision for outlet obstruction, lumbar sympathectomy, retroperitoneal lymphadenectomy as well as abdominoperineal surgery.

Urinary catheterization may be complicated by urinary tract infection or by urethral stricture. Urethral stricture repair may result in pooling of ejaculate material in a flaccid segment of the urethra and its contamination with urine. There may be ejaculatory disturbance after reconstructive surgery for hypospadias, epispadias and vesicouretal exstrophy.

Operations for varicocele, testicular torsion or testicular maldescent are recorded separately. Other operations should be noted if the investigator suspects relevance to infertility (Rowe et al. 2000).