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Causes of fertile disturbances in oncological male patients

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It has been known for a long time that oncological therapy may influence male fertility while sometimes neglected but important cause of infertility in cancer patients is the fact that certain malignancies exert an adverse effect on the testis before treatment.
Therapeutic cancer regimens may have significant, undesirable consequences on the fertility. Surgical treatment can damage the neurovascular mechanisms controlling erection, emission and ejaculation what can prevent the delivery of spermatozoa and result in subfertility. Radiation therapy is used in a number of malignancies including Hodgkin's disease and germ cell tumours and disturbances in gonadal function through various mechanisms. A majority of men treated with chemotherapy are affected with indeterminate periods of azoospermia, decreased libido and erectile dysfunction.
Additionally, we have to consider in oncological patients also factors, which can influence on fertility, such as impact of another drugs, endocrine diseases, diseases of external genitals, congenital and heredital diseases, infections and immunological diseases, impact of nutrition, bad habit, environment and psychological factors.

Key words: infertility male; neoplasms - therapy; radiotherapy - adverse effects; antineoplastic agents - adverse effects; surgery - adverse effects

Introduction

Prevalence of infertility varies from country to country. It is estimated that 5 to 8 % of couples have problems with infertility in developed countries but in developing countries up to 30 % of couples have these problems.[1] Referring to the information of the World Health Organization about one in every ten couples wishing to have a child experiences some form of infertility problem. Extrapolated to the global population this means that up to 80 million people may be suffering from infertility.[2] Due to the increase of inflammations of the genital tract, particular caused by sexually transmitted diseases, due to endometriosis, birth postponement of the first child and more stress the number of infertile couples is increasing.[2,3]

Although we do not have exact data about the prevalence of infertility in Slovenia, we can, as to the above mentioned information and as to the fact that 10 000 couples marry every year[4] that it exists 25 % out of married relations, conclude that more than 1000 couples confront with the problem of fertility every year.[3] So, we must be greatly aware of the problem of

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infertility in Slovenia and give a lot of thought to it.

The causes of infertility are multiple. By the average population its cause is in 30 to 50 % in man[5] or it is estimated that in developed countries in 25 to 30 % the cause of infertility is in man whereas in 20 to 24 % in both partners.[2, 6] Semen factor is the cause of infertility in 18 % to 31 %, in 15 to 28 % of cases there are many factors which cause the infertility;[7] one of these is also the oncological treatment.

At the Institute of Oncology 6551 patients were treated in 1991, 3324 of them were male patients. At the age when fertility is the most present (20 to 60 years old), there were 1145 patients i.e. 34,4 % of all oncological male patients; among those there are also such whom the trouble in fertility presents a great problem.[8] In other countries the situation is comparable to ours. In the United Stated there are more than 26 000 men between 17 and 50 years old, who are afficted with cancer each year.[9]

The surgical, radiation and chemotherapeutic regimens that are used to attain the present high survival rate of oncological patients often induce irreversible damage to the testis.[10–12] However, the modern therapeutic approaches to oncological patients are not only aimed at cure but also ensuring the least possible side effects and the optimal quality of life which naturally includes preserved fertility.[12, 13] This issue has become particularly important in younger patients with good response to therapy, such as are the patients with testicular tumours, Hodgkin's disease and with tumours of childhood.[14–17] As to the information of the Register of Cancer Patients in Slovenia there is a relatively small number of these patients.[8] Although it is not clear whether the incidence of infertility in men is increasing due to environment factors or whether it is better discovered,[18] it is found out that the number of patients with testicular tumours, Hodgkin's disease and with tumours of childhood is too small to influence essentially on the incidence of infertility in a certain nation. The infertility represents a great individual problem in these patients, so doctors should not neglect it.

Nonspecific effects of neoplasia on testis function

Sometimes neglected but important cause of infertility in cancer patients is the fact that certain malignancies exert an adverse effect on the testis before treatment.[19–21] Hodgkin's disease and testicular germ cell malignancies have associated testicular injury manifested by damage to the spermatogenic stem cell line early in the course of the disease not related to local tumour effect or metastasis.[22, 23]

It is supposed that the reason may be a primary dysgenesis in the remaining testis,[24, 25] elevation of serum's HCG hormone in hormonally active tumours,[21] local effect of the tumours on contralateral testis – with temperature in scrotum and with vascularisation change,[26] or possibly the influence of stress in young men who suffer from a newly diagnosed malignant disease.[25]

Some simply talk about the histological peculiarity of patients with testis cancer as many are discovered at the assessment of infertility or about the fact that testis tumours should have occurred more often in patients with common disturbance of spermatogenesis,[21, 27] whereas the non-specific effect of malignant tumour on contralateral testis should have been the most important additional factor influenced on spermatogenesis.

It is interesting that other malignant diseases do not badly effect on spermatogenesis at the initial stadia of the diseases.[15] On the contrary, all malignant tumours in progressed stadia of the disease connected with the patient's cachexia and bad condition have weak effect on gonadal function.[22]

Surgical treatment

Surgical treatment of cancer has no direct deleterious effect on testicular function. Retroperitoneal lymph node dissection, abdominal aneurysm repair, abdominoperineal resection, and operations that damage the neurovascular mechanisms controlling erection, emission and eja-

culation can prevent the delivery of spermatozoa and result in subfertility.[19]

Retroperitoneal lymph node dissection
After a radical retroperitoneal lymph node dissection, such as performed in nonseminomatous cancer and Hodgkin's disease, patients are infertile initially as a result of sympathetic nerve damage that interferes with emission and antegrade ejaculation.[28] The quantity of semen emission can be essentially reduced,[29] the damage of lumbar sympathetic ganglia also produces retrograde ejaculation,[30] or the absence of ejaculation can be estimated.[6, 31]

Another pelvic operation
With the interruption of parasympathetic innervation by a pelvic operation – such as cystectomy, total prostatectomy or rectal operation – the loss of erection can be expected.[19, 32]

It is not so uncommon that abdominal surgery damages the neck of the bladder and causes retrograde ejaculation.[6] This occurs following the disruption of internal sphincter.

Various extensive operations
Extensive operations, frequent in the oncological surgery, may cause with non-specific effect temporary disturbances both in the function of Leydig's cells and in spermatogenesis.[33]

Vascular injury following hernioplasty
Vascular injury and testicular atrophy following hernioplasty mostly occur in surgery of infants and cause fertility disturbances.[30] Patients with testicular tumours usually suffer more from ingvinal hernia than others;[6] therefore it is clear that with such patients hernioplastic operations are more frequent and consequently the danger of vascular injuries is much greater.

Radiotherapy

This effect of ionizing radiation to the male reproductive system both by animals and human beings was quite often documented.[11–13, 15, 16, 19, 34]

Radiotherapy of the hypothalamic and pituitary region
In oncology the mentioned region is irradiated in case of various pituitary gland tumours, brain tumours, craniopharingeomas, nasopharyngeal carcinomas as well as leukemias and medulloblastomas. In such situation the hypothalamus or the pituitary gland may be situated in or at the margin of the radiation field.

The estimated tumour dose 40 Gy to the hypothalamus causes in 30% deficiencies in gonadotropin secretion due to the defect of the release of gonadotropin releasing hormone.[35] At dose 40 to 70 Gy already 60% of patients are with disturbances; at dose up to 24 Gy thes disturbances were not noticed. However, an exact correlation between dose and type or extent of hypothalamic or pituitary hormone deficiencies – consequently the fertility as well – has not yet been described.[12, 35]

Direct exposure to ionizing rays at total body irradiation
Total body irradiation prior to bone marrow transplantation can cause severe oligo- or azoospermia but the testosterone levels in the serum were normal. There was no evidence of direct damage to the hypothalamic-pituitary axis. By the total body irradiation usually 10 to 13,2 Gy in 5 or 6 fractions are applied. By the majority of children the gonadal dysfunction is observed at the just mentioned dose. Therefore the long-term endocrine management is needed.[36, 37]

Radiation of the infradiaphragmal region
By the irradiation of the infradiaphragmal region gonads are irradiated most frequently – either by means of direct irradiation (which is not often) or by scatter radiation.

Due to scatter radiation i.e. by the irradiation of patients with testis tumours azoospermia or oligoastenospermia turns up but such state can later improve.[38, 39]

Irradiation effects on spermatogenesis with single dose irradiation
Single gonadal dose of 0,5 to 0.78 Gy causes marked oligospermia and decreased sperm con-

centration in the semen to about two million per ml 11 weeks post irradiation. Spermatids seemed to be damage after 4.0 to 6.0 Gy, since the number of agile spermatozoa was signifi cantly decreased afterwards.[12, 40] However, single dose irradiations rarely occur in clinical practice.

Irradiation effects on spermatogenesis with fractionated irradiation

In spermatogenesis the most sensitive cells to irradiation are spermatogonia, particularly stem cells in the mitotic phase. As new spermatogonia enter the mitotic phase, the fractionated irradiation destroy them again and again and that is far more harmful as a single irradiation itself.[41, 42] Such permanent azoospermia has to be presumed after the irradiation in patients with seminal tumours at the fractionated gonadal dose 1,5 Gy or at a single dose 8,6 Gy.[43] Later cell stages, i.e., spermocytes, spermatids and spermatozoa, are less sensitive to irradiation and a higher dose is needed.[44]

Patients with Hodgkin's diseases and seminomatous testicular tumours are treated with external beam radiation. Despite gonadal areas are usually shielded by scatter radiation, the testes receive 1 ore more per cent of the total dose.[38] A cumulative dose of 0,5 Gy to the testis is not exceeded and it can be accepted.[45]

Chemotherapy, hormonal therapy and another drugs

Cytotoxic drugs

It is well known that azzospermia and severe oligospermia are usually seen after intensive chemotherapy.[14, 33, 46–48] Cytotoxic drugs interfere with the function of Leydig's cells and disturbance spermatogenesis. The exact events of spermatogenesis sensitive to specific agents are being investigated in animal systems. In the human the most significant are alkylating agents, i.e. cyclophosphamide[14, 33, 46] Low dosage affects the germinal cells during division with resultant oligospermia. Higher dosage produces aspermia. Testicular biopsies of aspermic patients after therapy have shown a complete loss of germinal epithelium with intact Sertoly and interstitial cells.[47]

Cytotoxic drugs do not influence directly on dividing cells, but can increase the sensitivity of cells on ionizing radiation as well. They can influence on cell cycle to distribute more cells into more sensitive phases of cell cycles. Such functioning is observed for example by 5-fluorouracil and vincristine. Other cytotoxic drugs can increase the sensitivity of cell on radiation with direct damage of DNA and with the prevention of its cure, i.e. cisplatin in etoposide.[48, 49]

The influence of cytotoxic drugs on spermatogenesis was clinically mainly studied, among others, also on patients with Hodgkin's disease and those with germinal testicular tumours. Six cycles of chemotherapy, following the scheme COPP (Cyclophosphamide, Vincristine, Procarbazine, Prednisolone), involving patients with advanced Hodgkin's disease cause permanent azzoospermia or sterility. The MOPP combination (mechlorethamin, vincristin, procarbazin in prednison) turned out to be therapeutically efficient but very harmful as fertility concerned; so it was tempted to replace it by ABVD (adriamycin, bleomycin, vinblastin and dacarbazine).[50]

Also with germinal tumours alkylatin agents turned out to be extremely toxic.[14, 46] This chemotherapy should cause disturbance in fertility even in 60 % regardless whether combined with radiotherapy or not.[15] The combination of cyclophosphamid and adriamycin with actinomycin D, vincristin and medroxi-progesteron acetate caused for example aspermia by the whole group of patients suffering from testis tumour. Aspermia was diagnosed 3 years after the therapy.[24]

Cisplatin is the most efficient chemotherapeutic by the testis cancer therapy and fortunately it only roughly influences on spermatogenesis.[50] It is stated that spermatogenesis can in 50 % recover 1 to 2 years after the application of cisplatin. Toxication remains more or less invariable when cisplatin is combined with etoposid, bleomycin and vinblastin.[13] Four cycles of the

combination cisplatin with bleomycin and vinblastin cause in 96 % azoospermia which recovers in 50–60 % in the period from 1 to 3 years. In a half of all cases couples were able to conceive if they wanted to.[25]

There is no evidence that significant genetic abnormality is heritable if recovery occurs.[51]

Hormonal agents

Ciproteron acetate (*Androcur*) and flutamide (*Flucinom*) are mainly peripheral antiandrogens and are used in the therapy of prostatic cancer. They inhibit the functioning of androgens on the cell level. They competitively take the positions of cell receptors for androgens.[52] Diuretic *spironolacton* (Aldactone) has similar functioning.[52, 53]

Medroxiprogesteron inhibit the formation of testosterone in Leydig's cells.[33]

LHRH agonists influence on the hypothalamic-pituitary axis. After the prior rise of production of gonadotropins, this production decreases.[54]

Anabolic steroids taken by some sportsmen may impair spermatogenesis.[6]

Another drugs

We shouldn't forget that there are not only anticancer drugs which influence on the fertility in oncological patients but other drugs as well.

Digitalis raises the serum level of estrogens and decreases the serum level of testosterone[33] or it competitively binds to androgen's receptors in cytoplasm.[53]

Cimetidine and in lesser degree ranitidine inhibit the functioning of androgens on the cell level, similarly as peripheral antiandrogens do.[6, 33]

The impairments of spermatogenesis are caused also by sulfasalazine and nitrofurantoin.[33]

Antihypertensive medications can interfere with ability of ejaculation.[6, 30]

Antiholinergic drugs as well as tranqvilizers may cause disturbances in potency.[30]

Other causes of fertile disturbances

Fertile disturbances in male oncological patients occur mostly because of the above mentioned causes. The exact analysis of each case shows that there are many other causes which should also be considered.

Illnesses of endocrine organs

The illnesses of endocrine organs may cause the lack of androgens formation which is clinically known as hypogonadism. As to the location of the damage we distinguish: hypothalamic (tertiary), pituitary's (secondary) and gonadal (primary) hypogonadism. Hypogonadism can begin because of the oncological disease, its treatment or because of any other disease such as Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, Cushing's syndrome, hemachromatosis or various congenital diseases, virus and bacterial infections which we shall talk about later.[52]

We shouldn't forget the physiological hipogonadism which appears because of involute processes in the old age and could be a combination of all three hipogonadisms that gradually turn out as atrophy of testes. Vascular and endocrine changes, changes of blood testis barrier and Sertoli's cells begin when growing old. This leads to the reduction of sperm count in the seminal fluid and to an alteration in spermatozoa's form and their motility.[55]

The infertility is quite common in diabetic patients but its frequency is more and more reduced for the insulin treatment.[5] In spite of the proper treatment retrograde ejaculation can arise and could be the first sign of diabetic neuropathy.[56]

Also in patients with thyroid's diseases (hyper- and hipothyroidism)[57] disturbances with fertility are often observed; this can be seen in patients with suprarenal diseases as well.[5]

Diseases of male external genitalia

We talk about *criptorchidism* when testis is not seen. It is usually about non-descent testis which lies in retroperitoneal or intraperitoneal space.[58] If testes are exposed to intraabdomi-

nal temperature after the age of puberty, sterility will be inevitable in spite of later treatment.[30] Similar situation appears with ectopic testis when testis lies out side of normal descensus and can't be drawn to scrotum.[59]

Atrophy of testis has various causes, it could be the result of torsion of testis or iatrogenic injury by orchidopexy at non-descent testis.[60]

Acute Mumps orchitis, may lead to testicular atrophy. If mumps atrophy is bilateral, sterility will result.[30, 60] Virus orchitis can be caused also by echo virus, lymphocytic choriomeningitis virus, arboviruses of group B,[61] and by herpes virus as well. Other infections as gonorrhea and tuberculosis may cause similar injuries of testes[30, 60] or cause obstructions of ductus deferens.[30] Autoimmune illnesses, which affect more gland at the same time, can exceptionally be the cause of autoimmune orchitis and hipogonadism.[33]

Varicocele can be the cause of decreased sperm motility, oligospermia and an increase of immature sperm forms in the ejaculate.[62] Clinical varicocele is detectable on routine physical examination and is present in 15 percent of men. There is convincing evidence that varicoceles cause a progressive decline in semen quality and that a minority of men with varicoceles are subfertile because of them.[6, 63] In spite of that varicocele is the most frequent reason of male infertility which is to be found in 40 % of infertile men.[30]

Especially dangerous is Acute testis trauma with rupture of the tunica albuginea.[30]

Congenital and heredital diseases

There are many described congenital and heredital diseases where disturbances in the stage of somatic development (also diseases of male external genitalia) and consequently about disturbances with fertility are stated. Such diseases are i.e. congenital anorchism, aplasia of Leydig's cells, monorchism, polyorchism, sinorchism, congenital anomalies of uretrhra and penis, pseudo-Turner's syndrome, Klinefelter's syndrome, Infantile testis.[57, 58, 60, 64, 65]

Infections

Besides Mumps orhitis infections of urinary tract which should be the cause of male infertility are often documented. However, this does not really occur so often as the exact analysis shows.[66] Gonorrhoea and tuberculosis are just two of them but, nevertheless, they can cause epididymal obstruction.[30] Recently the infections of epididymis with Chlamydia have become important. Mainly in developing countries other infections i.e. fungous ones with higher serum level of aflatoxin are noticed.[67]

Each acute febrile illness may cause the impairment of spermatogenesis usually lasting for 3 months.[68, 69]

Immunologic infertility

Men with high levels of antispermal antibodies in their semen have reduced fertility. This concerns mainly IgG and IgA antibodies which bind to spermatozoon while IgM are too big and they can't pass into tubules of the testis. Antisperm antibodies should be suspected in patients with clumping of sperm, in sperm with poor motility, in decreasing ability of sperm penetration through cervix, at weak perfusion of semen into the ovum or at unexplained infertility. The diagnosis is made by documentation of antisperm antibodies in the serum and the semen.[6, 70]

Other diseases

Granulomatous diseases, especially lepra, mechanically destroy testicular tissue. Patients suffering from chronical kidney failure have decreasing testosterone synthesis and impaired spermatogenesis.[33] In patients suffering from liver cirrhosis the atrophy of testes may occur.[57] Patients suffering from muscular dystrophies are often affected by primary hypogonadism,[61] whereas by paraplegia spermatogenesis is impaired.[6, 33]

Extended burns, myocardial infarction, lead poisonings, long lasting fever cause temporary or permanent impairment of spermatogenesis as well.[6, 30, 33]

Lifestyle factors

There are different opinions as the influence of nutrition on fertility concerns. It is known that fertility is impaired by avitaminoses[5] and that cachexia causes a temporary impairment both in the functioning of Leydig's cells and in spermatogenesis.[52]

Cigarette smoking has mild but negative effect on spermatogenesis and may contribute to infertility – for example, in men with varicocele.[6, 63]

Alcohol decreases the level of serum testosterone but it may cause direct impairments of spermatogenesis.[33] Alcohol causes peripheral neuropathy and consequently disorder of potency.

Marijuana and heroin decrease the concentration of serum testosterone and inhibit the function of hypothalamic-pituitary axis.[52] Cocaine has similar harmful effects.[6]

Environment

Excessive exposure to heat as for example saunas can decrease sperm production.[6] Certain workers are greatly exposed to heat as for example plumbers, cooks, etc.[71] It is documented that working with arsenic or lead,[6] cadmium and pesticide is harmful for spermatogenesis, whereas this couldn't be proved in case of chrome.[71]

Psychological factors

For psychological stress temporary impotence is possible,[50] but its influence is much greater on spermatogenesis.[5] It is obvious that any kind of disease, including oncological one, has stress effects on patients[72] and in such a way also on spermatogenesis.

Ejaculatory disturbances

Men who have a spinal cord injury, diabetes neuropathy, or multiple sclerosis or who have undergone retroperitoneal lymph node dissection or have a psychogenic disorder may present with failure of emission.[6, 56]

Retrograde ejaculation is more often.[30] It should be suspected in men with an absent ejaculate or an ejaculate of less than 1.3 ml.[6]

Disorder of potency

Sexual problems, including disorder of potency, where the male has normal semen quality occurred in about 5 % of patients with fertility impairments.[30] The etiology of potency disorders can be various. Besides psychological causes the somatic ones are important too. They can be neurogenic, hormonal or vascular.

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