

# Prevention of fertility disturbances in oncological male patients

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*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.*

*The most effective measure to prevent the occurrence of surgery-related damage of fertility in males is by replacing radical retroperitoneal lymphadenectomy with selective or unilateral lymphadenectomy; radiotherapy-related fertility damage can be prevented by shielding the remaining testicle from the scattered radiation; and chemotherapy-related fertility damage can be prevented by choosing the chemotherapeutic regimen which doesn't contain alkylating agents.*

*We have to consider other modalities of prevention, including eliminating lifestyle and environment factors which can influence fertility, adequate sexual behaviour, early treatments of cryptorchidism and treatments of infections.*

**Key words:** infertility, male - prevention; neoplasms; radiotherapy - adverse effects; antineoplastic agents - adverse effects; lymph node excision - adverse effects

## Introduction

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.<sup>1</sup>

The best approach to reduce the sterility problems is to decrease the chance of occurrence of infertility<sup>2</sup> since the efficiency of treatment is uncertain and unpredictable.<sup>3</sup>

In case of fertility impairment several methods of treatment exist. Following cancer treatment fertility status is also frequently unpredictable, it is therefore advisable for young male patients to store their deep-frozen sperm in a sperm bank prior to oncological therapy.<sup>4-8</sup>

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## Prevention of surgery-related damage

It is important that patient with testicular tumours are operated transinguinally but not transscrotally, otherwise the ipsilateral scrotal sac and inguinal lymph nodes must be postoperatively irradiated, which also means more scattered radiation to contralateral testis.<sup>1,9</sup>

Radical retroperitoneal lymphadenectomy was usually performed on patients with testicular nonseminomatous tumours and Hodgkin's diseases<sup>10-12</sup> and the most effective measure to preserve fertility in males is by replacing radical retroperitoneal lymphadenectomy with selective or unilateral lymphadenectomy.<sup>13,14</sup> In patients with such operations it is possible to preserve emission and ejaculation, most of semen analyses in majority of patients are considered to be in normal range and most of them are potentially fertile.<sup>13</sup> In this way the modified retroperitoneal lymph node dissection preserves the sympathetic outflow, retaining ejaculation in 75% of these men.<sup>15</sup>

In spite of the fact that fertility is usually not the central problem in patients with prostate cancer because of their advanced age, early detection of this disorder allows less extensive surgery, with fewer complications. For example, nerve-sparing radical retropubic prostatectomy, which preserves erectile function in many men by avoiding injury to the cavernosal neurovascular bundles, can be performed and prevent fertility disturbances.<sup>16,17</sup>

### Prevention of radiotherapy-related damage

The most effective measure to prevent the occurrence of radiotherapy-related fertility damage can be by shielding the remaining testicle from scattered radiation.<sup>1,9,18</sup>

Having already had unilateral semicastration prophylactically the retroperitoneal nodes only are treated and the irradiation of the remaining testicle should be avoided. The testicle is in any case exposed to the scattered radiation causing a degree of spermatogenesis impairment.<sup>19,21</sup> By shielding the remaining testicle gonadal dose should be kept lower than 1 Gy in order to avoid prolonged and frequently permanent azoospermia or hypoazoospermia.<sup>10,22,23</sup>

In Hodgkin's disease, when we irradiate the infradiaphragmatic region, the shielding of both testicles from scattered radiation is necessary. Contemporary radiotherapy techniques recommend the protection from scattered radiation, in case of gonadal dose higher than 0,5% .<sup>18</sup>

Attempts were made to reduce postirradiation injury by reducing the size of target volume<sup>24,25</sup> and thus decreasing the scattered radiation and in the same time increasing the distance between the target volume and testes.<sup>19,26</sup> Additionally, reducing the tumour dose or even by the omission of the postoperative irradiation<sup>24,25</sup> radiation side-effect can be avoided altogether.<sup>27</sup> Disease free survival is reduced and further studies are necessary to find patients where management by surveillance alone should be sufficient.<sup>27,31</sup> Nevertheless, it is important to irradiate patients with high energy photons because scattered radiation is reduced in such treatment.<sup>19</sup>

### Prevention of chemotherapy-related damage

Chemotherapy-related fertility damage can be prevented by choosing the chemotherapeutic regimen which doesn't include alkylating agents.<sup>32,33</sup>

Chemotherapy with alkylating agents is associated with fertility problems in 60% of patients regardless whether it is given in combination with radiotherapy or not.<sup>34</sup> Cisplatin, one of the most efficient agent, has fortunately only moderate damaging effect on spermatogenesis.<sup>5,35</sup>

Limiting the number of cycles administered to the minimum for achieving remission is also beneficial for preserving male reproductive ability.<sup>5,36</sup>

Cytoprotective techniques to limit testicular injury from the damaging effect of chemotherapy are currently ineffectual. The gonadal toxicity caused by chemotherapy and radiation was attempted to be reduced by luteinizing hormone releasing hormone (LHRH) analogues. It has been shown that non-pulsatile, chronic treatment with supraphysiological doses of LHRH analogues results in the suppression of the pituitary-gonadal axis and the suppression of spermatogenesis. Furthermore, there has been suggested that the inhibition of spermatogenesis during exposure to cytotoxic drugs and radiation might reduce or prevent gonadal toxicity. Experimental studies were encouraged,<sup>37</sup> but in none of clinical trials the influence on severity and duration of spermatogenesis impairment has significantly been shown.<sup>38-40</sup>

The administrations of some other drugs (i.e. antioxidants N-acetylcystein and ascorbate) before the administration of procarbazine have been effective by preserving spermatogenesis in an animal model. But the analogous studies in humans have not been published.<sup>5,41</sup>

During the oncological treatment there were also attempts to reduce spermatogenesis by administering of testosterone which can suppress gonadotropin secretion and in this way protect testicular function. There is no clinical relevance up to now as well.<sup>42</sup>

### Others principles of prevention of fertility disturbances

As the causes of fertility disturbance are manifold<sup>10</sup> we have to consider all other modalities of prevention, including the elimination of lifestyle and environment factors which can affect fertility, more appropriate sexual behaviour, early treatments of cryptorchidism and treatments of infections.

#### *Elimination of lifestyle factors*

One of the most important steps of the prevention of fertility disturbances is to eliminate all factors

that can affect fertility, such as bad nutrition,<sup>43,44</sup> cigarette smoking,<sup>45</sup> alcohol abuse,<sup>46</sup> use of illicit drugs such as marijuana and cocaine,<sup>43,44</sup> and some drugs as anabolic steroids, antihypertensive medications, cimetidine, anticholinergic drugs, etc.<sup>10,47</sup>

#### *Elimination of another environment factors*

Oncological patients should not work with arsenic and lead. They should avoid exposure to heat, such as in saunas or working as plumbers and cooks.<sup>10,48</sup>

#### *Sexual behaviour*

According to Howards, sexual intercourse is recommended every 48 hours in the middle of woman's cycle or at the time of ovulation.<sup>43</sup> Lower frequency of intercourse can result in missing the ovulation time, and also diminish the quality of the sperm (over 5 days of abstinence). In view of contradicting reports, namely, that frequent intercourse diminishes sperm concentration<sup>47</sup> or even improve it,<sup>49</sup> it should be cautiously recommended more frequent intercourse during the time of woman's ovulation if their libido is adequate.<sup>4,49</sup>

#### *Treatments of cryptorchidism*

Cryptorchidism is first treated with gonadotropines (HCG, LH-RH) and later with orchiopexy.<sup>47,50</sup> Orchiopexy must be performed between the age of 5 and 9 or else as soon as possible. Some argue that cryptorchidism should be cured by the age of 2, before histological changes occur,<sup>50,51</sup> but at any rate prior to puberty.<sup>47</sup> Adequate treatment reduces the chances of sterility, and also the incidence of malign alteration of testicles.<sup>52,53</sup> Only 75% and 50% fertility rate is reported for patients with successful unilateral and bilateral orchiopexy. The results, however, considerably improve if the procedure is performed before the age of 2. Hormonal treatment is recommended to start at the age of 10 months.<sup>50</sup>

#### *Treatments of infections*

It is imperative that uro-infections are treated effectively, preferably with regards to antibiogram of the agent.<sup>43</sup> Trichomonas or gonorrhoea require that the sexual partner is treated as well.

### Conclusion

Multimodality treatment has increased the survival of cancer patients in recent years. The quality of

life should also be taken into consideration during the cure. The maintenance of the reproductive capacity is of great concern to many young patients. The cause of sterility was attributed to the long-term side effects of oncological treatment in spite of the fact that the step of fertility disturbances can be decreased by the selected treatment. One of the most important steps of prevention of fertility disturbances is also, if possible, to eliminate all factors that can influence the fertility.

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