MICRONUTRIENTS AS AN ALTERNATIVE TO FERTILITY TREATMENT IN MEN WITH SUBCLINICAL VARICOCELE

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A varicocele is an enlargement and twisting of the vessels that drain the testicle, the veins of the pampiniformis plexus. By examining an unselected sample, a varicocele can be determined in approximately 15-20% of men. In the case of an evaluation of men who suffer from primary infertility, i.e. not able to father a child, the percentage increases to 40%; while with secondary infertility, i.e. with earlier fertility and current infertility, it increases to 70%. (ASRM: Practice Committee, 2006). Despite decades-long research, the exact causes, the way the varicocele affects the testicles, sperm quality and ultimately reproductive ability have not been completely clarified, and the optimum treatment and its indication are the topic of ongoing debate.

Varicoceles are usually formed with the onset of puberty likely due to genetic susceptibility. This occurs due to venous valves either missing or impaired in their function in the vessels of the pampiniformis plexus, which work in interaction with unfavourable anatomical factors on the left side where varicoceles are usually first formed. The congestion of blood that results from the longer course of the vein and from the unfavourable angle at which it leads into the subsequent vein also leads to an increase in temperature of the area concerned, which negatively affects the sperm. Another factor that impairs sperm quality, and one of the most important pathophysiological and therapeutic approaches, is increased oxidative stress in the testicles of men with varicoceles. The proven imbalance between reactive oxygen species and antioxidant capacity in patients with varicoceles (Agarwal et al., 2006), and the suspected impaired use of the antioxidant coenzyme Q10 (Mancini et al., 2005), lead to a predominance of the radicals and thus to oxidative damage. These manifest themselves particularly in cell membranes, which contain a high portion of unsaturated fatty acids, as for example the membranes of sperm (Kodentsova et al., 1994).

Despite the points mentioned, the effects of the varicocele on fertility continue to be disputed. Because although the varicocele is the most frequently diagnosed cause of so-
called male factor infertility, nearly two thirds of those affected are nevertheless fertile. (ASRM: Practice Committee, 2006) A study by the WHO showed however that sperm quality decreases over the course of time with a longstanding varicocele (WHO, 1992), which points to progradient impairment of testicle function.

Sperm formation per se and its impairment due to the clinical characteristics of the varicocele is however based on a complicated and not yet completely investigated system. During spermiogenesis, which lasts on average 72 days, mature haploid sperm result from immature spermatocytes through mitosis and meiosis. This process can be affected by micronutrients, which offer a new approach for the treatment of varicoceles, and is also in part controlled by these. The substances of particular note in this regard are zinc, selenium, folic acid and carnitine.

Selenium is built into many enzymes and proteins that use it to perform their function, for example GPx (glutathione peroxidise), an antioxidant enzyme found only in the epididymis and in the nucleus of sperm. Of the approximately 24 selenium enzymes that have already been identified, the activity and expression of GPx4 is the highest in the testicle; it guarantees the structural protection of the energy source of the sperm, the mitochondria. In mice it could be shown that a lack of mitochondrial GPx4 leads to infertility (Schneider et al., 2009). This form of infertility is above all characterised by morphological defects in the sense of instability of the mid-pieces of the sperm. The selenium concentration in the testicles, which increases with the quantity of exogenous uptake (Shalini et al., are 2005), is higher than that of the blood plasma, which points to the indispensable nature of selenium for the development and maturing of spermatozoa. The highest concentration of the trace element zinc is found in the prostate gland and in the testicle, which affords this substance a central role in spermiogenesis and in the maintenance of a sperm quality sufficient for
A zinc deficiency results in reduced spermiogenesis and a decreased production of testosterone, the receptor of which contains zinc in its binding domain, as do all steroid hormone receptors. Moreover, in animal studies it could be shown that a zinc deficiency impaired sperm motility, i.e. mobility, both regarding the motility period as well as the number of motile sperm (Yamaguchi et al., 2009). Additionally, there is a positive correlation between sperm density and the concentration of zinc in the blood (Bakalczuk et al.). A zinc deficiency also leads to dysfunction of the gonads, to a shrinking of the seminiferous tubules and to a drop in testicle weight (WHO Manual, 2001).

Folic acid can be regarded as a component in the synthesis of DNA, RNA transfer and the amino acids cysteine and methionine and thus as essential for the reproduction cycle in the development of germ cells (Ebisch et al., 2007). Additionally, the antioxidant potential of this substance can protect against damage done by free radicals (Joshi et al., 2001).

L-carnitine, the concentration of which is up to 10 times higher in the spermatozoa and the fluid of the epididymis than in the circulating blood, has a positive influence on sperm motility. Further, antioxidant characteristics are attributed to the substance and it plays a key role in the metabolisation of long-chain fatty acids (Agarwal et al., 2004).

While the use of individual substances which are indispensable in spermiogenesis could offer a therapeutic approach, there is still general disagreement in how to proceed after diagnosis of a varicocele and the indication for treatment. According to the French Association of Urology, a surgical or interventional therapy should be sought when applying the following points: the varicocele must be palpable, i.e. clinically detectable, the infertility of the couple, which is defined by one year of unprotected sexual intercourse without achieving pregnancy, must be documented, whereby a female factor has been excluded, and at least one abnormal sperm parameter is present, in addition to a volume reduction of
the affected testicle. (Wagner et al., 2007) The surgical or interventional treatment of subclinical varicoceles, i.e. those only detectable by ultrasound, provides contradictory findings with respect to improving the sperm parameters and fertility. (Jarow et al., 1996)

Treatment with micronutrients represents another, substantially newer form of the sub- or infertility treatment of varicocele patients. While micronutrients and antioxidants are already used regularly in men with idiopathic fertility disorder and with predominantly positive results, this therapy option for men with varicoceles is still relatively unexplored, particularly compared with surgical or interventional radiological forms of treatment. Building on the theory that varicoceles lead to an increasingly inflammatory altered environment burdened by oxidative stress, studies that used anti-inflammatory drugs (NSARs such as e.g. Cinnoxicam) and antioxidant substances (vitamin E, glutathione, coenzyme Q10 etc.) observed predominantly positive results. (Cavallini et al., 2003; Mancini et al., 2005) Even the use of L-carnitine or L-acetylcarnitine to transport substances essential to fatty acids seems to hold therapeutic potential on its own or in combination with an anti-inflammatory drug. (Cavallini et al., 2004) The therapeutic use of micronutrients, such as zinc, selenium, folic acid etc., has to date been investigated very little in connection with varicoceles, but it has brought significant improvements as a combination preparation with antioxidants. (Imhof 2009)

In the context of this pilot study, after the exclusion of infections, aspermia and hormonal disorders, 55 men (age: 18-43; Ø 32a) with subclinical varicocele (WHO classification 0.1), two pathological spermiograms (at least one month apart) and an unfulfilled desire for children for more than 2 years (Ø 2.7 years) took a combination of micronutrients, which contains L-carnitine, L-arginine, vitamin E, folic acid, zinc, selenium, glutathione and coenzyme Q10 over three months. The post-treatment evaluation resulted in an
improvement of all sperm parameters and the occurrence of a pregnancy in 41.18%.

Influence on sperm quality of patients with subclinical varicocele:

<table>
<thead>
<tr>
<th>Subjects n</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=55</td>
<td>n=51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volumes (ml)</td>
<td>3.21</td>
<td>3.71</td>
<td>15.57%</td>
</tr>
<tr>
<td>Density (millions)</td>
<td>56.53</td>
<td>63.25</td>
<td>11.88%</td>
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<tr>
<td>Motility total (%)</td>
<td>50.35</td>
<td>58.37</td>
<td>15.99%</td>
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<tr>
<td>Motility rapidly progressive (%)</td>
<td>14.59</td>
<td>20.97</td>
<td>43.72%</td>
</tr>
<tr>
<td>Morphology (% normal)</td>
<td>22.39</td>
<td>26.47</td>
<td>18.22%</td>
</tr>
<tr>
<td>Pregnancies</td>
<td>21</td>
<td>21</td>
<td>41.18%</td>
</tr>
</tbody>
</table>

A treatment with micronutrients seems to offer a possibility of improving sperm quality and thus fertility particularly for men with subclinical and low-grade varicoceles, for whom a surgical or interventional cure is not indicated or holds more risk than benefit.

References


