

Inflencing factors on male reproductive health: obesity, varicocele, and the up-to-date questions of non-hormonal therapy

PhD theses

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1. INTRODUCTION

The infertile relationship is defined by the WHO as the inability of achieving a spontaneous pregnancy despite regular, unprotected sexual intercourse within one year. Although the world's population shows continuous growth, infertility became a serious health problem affecting even more couples in western developed countries. In Hungary ~20% of the couples seek medical treatment because of infertile relationship. A male factor can be identified in half of the infertility cases. As a result of the revolutionary development in the diagnostics of male infertility in the last decade, the rate of idiopathic infertility has been significantly reduced, although still accounts for 25-30% of the cases. Infertility can be a consequence of several factors: genetic and epigenetic disorders, developmental failures, infections, immunological problems, endocrine disruptors, environmental pollution, oxidative stress, lifestyle etc.

The selection of the thesis topics aims a deeper insight into the effect of several parameters, showing a most recently growing impact on male fertility. The impact of the male body composition on fertility is not well known and studied, this is one of our selected topics. Our research was supplemented with the impact of varicocele on male fertility focusing on the new indication criteria

and analysing the results of several modern surgical treatment modalities. An up-to-date clarification of the non-hormonal treatment option for male infertility is also given in the thesis.

1. The effect of proper lifestyle on fertility has long been known for women, unfortunately, it is a less studied issue in men. Genetic factors, associated diseases, endocrine issues affect body parameters, but the most significant factor is clearly the lifestyle.

2. Varicocele is considered to be a „hot topic” at all andrology and urology congresses. Guidelines have been drastically changed in recent years, the correct indication criteria and the optimal technique of interventions have become more evident. In Hungary, our study is the first one to control the effect of varicocele on male fertility with an outstanding number of patients and compare the effectiveness of the most optimal surgical techniques performed using the new indication criteria. Findings can help to design a proper patient selection for surgery and to perform the most effective technique in the andrology practice.

3. Non-hormonal drug treatment of male infertility is currently lacking any evidence. The only choice is the sometimes over-the-counter used antioxidant therapy. The effect of several antioxidant agents, the administration of the drugs and the duration of the therapy are still lacking evidence. As being easily overdosed,

adverse effects might occur. The third main point of the thesis is the up-to-date analysis of this issue.

2. OBJECTIVES

2.1 Lifestyle factors: the role of obesity in fertility

Our first aim was to assess the relationship between obesity and fertility parameters. Current body parameter categories are defined by the WHO on the basis of the BMI (Body Mass Index - defined as the body mass divided by the square of the body height, and is universally expressed in units of kg/m^2 , resulting from mass in kilograms and height in metres). The other most important factor is central obesity, which is characterized by the abdominal circumference on the one hand and the waist-to-hip ratio (Waist-to-Hip Ratio - WHR) on the other. In contrast to BMI, WHR takes more detailed differences in body composition into account, and has been shown to be a more sensitive indicator of the pathogenic role of body parameters. One of the aims of our research was to demonstrate the relationship between markers of obesity and classical sperm parameters and to demonstrate the fertility-damaging effects of high body fat. We also aimed to show the difference in correlation: we performed a comparative statistical analysis of the sensitivity of BMI and WHR.

2.2 Varicocele

Our study was the first in Hungary to examine the relationship between the severity of varicocele and classical sperm parameters on a large patient number. As further aims of the study the usefulness the new indication criteria was analysed and the effectiveness of different update surgical techniques (microsurgery and laparoscopy) was compared.

2.3 The role of antioxidants in the treatment of male infertility

A comprehensive literature review is given in the thesis to provide a more detailed insight into the current situation of non-hormonal medical treatment of male infertility. The current state of the evidence was controlled regarding the indication, duration, dosage, and efficacy of antioxidant therapy.

3. METHODS

3.1 Sperm analysis

Sperm analyses for both the lifestyle factors and varicocele study were performed according to the WHO Laboratory Manual for the Examination and Processing of Human Semen 5th edition (2010).

3.2 Lifestyle factors: the role of obesity in male infertility

Between January 2011 and January 2018 total of 1,188 patients with male infertility of unknown origin were admitted at the Semmelweis University, Department of Urology, Andrology Centre. Body parameters were assessed according to current standards based on the 2010 WHO recommendation. After standardization of the values, SAS V9.4 software (SAS Institute Inc. Cary (NC)) was used for statistical analysis.

3.3 Varicocele

Two hundred and six patients with palpable varicocele were screened at the Andrology Center of the Department of Urology,

Semmelweis University. Body mass index, central obesity and endocrine testing (TSH, FSH, LH, Prolactin, total testosterone, estradiol) were also performed. Epidemiological data are detailed presented. In the varicocele prospective multicentre clinical trial, the recommended new indication criteria were used: infertile relationship for at least 1 year, palpable varicocele (Grade II and Grade III by the Dubin-Aleamar classification), reflux shown by the colour Duplex ultrasound examination and sperm parameters below the WHO lower limit reference levels. The recommended new indication criteria were used for the surgical treatment: infertile relationship for at least 1 year, palpable varicocele (Grade II and Grade III by the Dubin-Aleamar classification), reflux shown by the colour Duplex ultrasound examination and sperm parameters below the WHO lower limit reference levels. Forty-five patients met these inclusion criteria and were randomized. Inferential statistical comparison of the efficacy of subinguinal microsurgical and laparoscopic interventions was completed.

3.4 The role of antioxidants in the treatment of male infertility

A systematic literature search was performed including meta-analyses, systematic review reports, randomized controlled studies, cross-sectional studies, and summary reports from

professional publications of the last 15 years. One hundred and twenty-five publications could be selected with an overall number of 12,805 patients from infertile relationships who underwent various antioxidant treatments. Pregnancy- and live birth rates, improvement of sperm parameters-, and DNA fragmentation index were used as primary outcomes. Results are summarized.

4. RESULTS

4.1 Lifestyle factors: the role of obesity in male infertility

Quality controlled and compromised data were used to the final study sample of 1,169 patients. The mean age was 38.1 years, mean height and weight were 180.6 cm and 87.3 kg, respectively – the mean BMI was 26.8. The mean waist and hip circumference were 100.9 cm and 94.8 cm, respectively – the mean waist to hip ratio was 0.94. The mean sperm concentration and total sperm count were 48.7 M/ml and 164.9 M (significantly over the WHO lower reference limits), respectively. The mean per cent of progressive motility and normal sperm morphology was 21.2% (clearly asthenozoospermia) and 4.8, respectively. A significant negative correlation was confirmed between sperm parameters and body composition (BMI and WHR) categories. This correlation was also controlled on the age-adjusted linear regression models, where both BMI and WHR showed a significant negative correlation with the classical sperm parameters. When comparing the standardized parameter estimates for BMI with those for WHR for each semen parameter, the parameter estimate for WHR was significantly lower (indicating a stronger negative association) than

that for BMI for progressive motility and total sperm count, but not for sperm concentration or normal morphology.

4.2 Varicocele

After a detailed exploration of the preoperative epidemiological data and randomization, 45 surgical interventions (23 microsurgical and 22 laparoscopic varicocelectomies) were performed until the admission of the manuscript for publication and the closure of the thesis.

In the preoperative endocrine analysis FSH (accepted marker of spermatogenesis) was found to be higher in more severe varicocele cases (Gr.III.): showing the fact of greater testicular damage (7.03 IU/l in Gr.II., versus 7.53 IU/l Gr.III. ($p = 0.76$)). There were no significant difference in total testosterone (tT) levels between these two groups. A substantial difference was measured in the mean sperm concentrations, resulting - surprisingly – higher level in Gr. III. patients (33.42 versus 30.94 M/ml). Significant asthenozoospermia (progressive motility: 14.4% in Gr.II. and 15,2% in Gr.III.) and teratozoospermia (3.7% in Gr.II. and 3.8% in Gr.III.) was found in both of these patient groups.

When evaluating postoperative data, improvement in sperm parameters can usually be expected after 6-7 months, but the three-

month postoperative values are also a proven indicator of the possibly beneficial effect of the surgery. Results were also controlled by the severity of varicocele. A clear, tendentious improvement was seen in the mean sperm concentrations (27.19 M/ml versus 34.35 M/ml - $p = 0.48$). Analysing these data regarding the severity of varicocele, in Grade II. and Grade III. sperm concentration improved from 25.79 M/ml to 33.56 M/ml ($p = 0.62$), and from 27.76 M/ml to 37.51 M/ml ($p = 0.51$), respectively. The preoperative 11.19% mean progressive motility improved to 14.69% ($p = 0.25$). In terms of the severity of the disease improvement was observed in Grade II. and Grade III. from 9.5% to 14.75% ($p = 0.24$) and from 12% to 12.54% ($p = 0.89$), respectively. Regarding normal sperm morphology no significant improvement was observed (mean values before and after surgery was 2.8% and 2,39% ($p = 0.52$), respectively. The worsening trend observed in the three-month postoperative control was more severe in Grade III. patient group compared to the Grade II. (2.84% to 2.8% ($p = 0.97$) versus 2.39% to 2 % ($p = 0.58$). Negative changes in sperm morphology after varicocelectomy are not unique, often can be seen in the clinical practice.

Comparing the effects of the two surgical techniques (microsurgical and laparoscopic varicocelectomies) the three classical sperm parameters were considered as the primary

outcome measures: the changes of sperm concentration, progressive motility, and normal morphology were analysed. The improvement in sperm concentration after laparoscopic surgery was 7.5% (40 M/ml versus 43 M/ml ($p = 0.85$)). In contrast, we obtained a much better result with the microsurgical technique: 98.1% improvement after the procedure, as the initial average value of sperm concentration of 14.19 M/ml increased to 28.11 M/ml. ($p = 0.14$). Similar results were found in progressive motility for the favour of microsurgical technique (50.7% improvement versus 24.3%): the initial value of 13.5% improved to 16.8% ($p = 0.55$) by laparoscopic technique, while the improvement in microsurgery was found from 9% to 13.6% ($p = 0.22$). The microsurgical technique produced better results also regarding mean normal sperm morphology. After laparoscopy a worsening of the normal morphology was observed (3.62% to 2.89% - 20% deterioration, $p = 0.56$), whereas in patients underwent microsurgery a slight improvement was found (2.07% to 2.12%, $p = 0.94$).

4.3 The role of antioxidant supplements in the treatment of male infertility

The intact balance of the oxidant and antioxidant side is required for normal sperm function and male fertility. In case of a

change in the equilibrium oxidative or reductive stress status can occur.

In male infertility cases, oxidative stress is more frequently found, which results in a damaged sperm membrane and DNA fragmentation leading to sperm functional disturbances and infertility. Empiric antioxidant treatment is widely used to avoid the harmful effect of free radicals. The majority of the clinical studies analysing the effect of antioxidant treatment show a significant association between antioxidant supplementation and the improvement of standard semen parameters, DNA fragmentation index, pregnancy rate and live birth rate in infertile couples but due to the strong limitations of the published studies, these conclusions should be interpreted with more caution.

Adverse effect profile of antioxidants is favourable: a small number of studies report mild gastrointestinal symptoms.

No exact guidelines for the dose regimen or the treatment duration can be found. The use of antioxidants in male infertility cases seems to be excessive, using a wide range of antioxidant combinations at the same time with uncontrolled doses. Since antioxidants have not only beneficial effects but overdosing (in excess or due to the absence of synergistic compounds) can result in reductive stress status, which is as harmful to fertility. Therefore

an assessment of the actual individual redox status is recommended before treatment.

The prescription of antioxidant therapy should be initiated with more caution, patients should be informed about the empirical character of the therapy and the low evidence of a positive outcome with the unclear nature of duration and dosing.

Patients should be aware of the side effects of overdosing antioxidants which can be prevented by assessing the proper redox status before use. Future research should confirm the most effective combinations, the appropriate dosage, and the optimal duration of treatment to result in increasing pregnancy and live birth rates.

5. CONCLUSIONS

5.1. Lifestyle factors: the role of obesity in male fertility

Our results declared the importance and influencing role of body weight in male fertility. The most widely used parameters evaluating body composition (BMI and WHR) were inversely associated with the classical sperm parameters (sperm concentration, progressive motility, and normal morphology). As special importance of our study, the essential role of central obesity in the progressive sperm motility was pointed out, while no difference was found for sperm concentration and normal morphology. These findings indicate the potential role of central obesity for progressive sperm motility but not for the latter two classical sperm parameters.

5.2. Varicocele

A clear correlation between the severity of varicocele and spermatogenetic damage was revealed in our study: the main marker of sperm production, FSH indicated (slightly) greater damage on the spermatogonia in more severe cases. In parallel, additional classical sperm parameters such as motility and normal morphology showed the same trend. We should underline the importance of the new indication criteria: an improvement in the

sperm parameters were observed regardless of the surgical technique. Comparing the treatment methods, the advantage of the microsurgical procedure was proven over the laparoscopic technique.

5.3 The role of antioxidant supplements in the treatment of male infertility

We highlighted the importance of the intact balance of oxidant and antioxidant systems for normal sperm function and male fertility. The disturbance of this balance is harmful to male fertility: either oxidative or reductive stress can cause a significant defect of sperm function. With our recent review among the firsts in the international literature, we demonstrated the beneficial effect of the antioxidants used with right indications and strongly highlighted the danger of overdosing. An appropriately indicated antioxidant treatment can improve sperm parameters and pregnancy rates, but overdosing can cause reductive stress status, which also significantly impair sperm parameters, sperm function, embryonal development and male health. We recommend the correct examination of the appropriate redox status before the drug administration.

6. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

6.1 Publications related to the dissertation

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