Asian Research Journal of Gynaecology and Obstetrics

4(2): 1-9, 2020; Article no.ARJGO.59053

Alternative Approaches in the Management of Male Factor Infertility: A Contemporary Review

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Authors' contributions

This work was carried out in collaboration between both authors. Author PSH designed and wrote the first draft of the manuscript. Authors AG and PSH managed the literature searches. Both authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Abdelmonem Awad M. Hegazy, Zagazig University, Egypt.
Reviewers:
(1) S. Joseph Philipraj, Sri Balaji Vidyapeeth, India.
(2) Manoj Kumar Patro, Sambalpur University, India.
(3) Hassan Ibrahim, South Valley University, Egypt.
Complete Peer review History: http://www.sdiarticle4.com/review-history/59053

Mini-review Article

Received 22 May 2020
Accepted 28 July 2020
Published 11 August 2020

ABSTRACT

Infertility is a major life crisis for married couples and the male factor contributes to approximately half of the cases. Evaluation of male infertility includes various diagnostic tools and there are new up to date treatment modalities. Current literature has been searched to review the risk factors and complementary therapies for the male partner of infertile couples.

Keywords: Lifestyle factors; obesity; heat exposure; cigarette smoking.

1. INTRODUCTION

Infertility affects about 15% of couples globally, amounting to 48.5 million couples. Males are found to be solely responsible for 20-30% of infertility cases and contribute to 50% of cases overall [1]. A population-based study from U.K. reported 10% prevalence of malefactor infertility in the general population [2]. According to the American Society for Reproductive Medicine (ASRM) [3], the aim of evaluation in males is to identify conditions that can be corrected and to the cases who need artificial reproductive techniques (ART) because of insufficient sperm count and/or quality [3]. Medical treatment and lifestyle changes can apply for correctable

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problems while ART is utilized for genetic problems [4].

An initial evaluation of the male consists of three primary components: History, physical examination and semen analysis. There is a general agreement about the importance of obtaining a reproductive history (including a sexual history) and semen analysis. Males of the unexplained infertility couples and those that remain infertile after correction of female factors should undergo a detailed physical examination and workup. The European Association of Urology states that medical history and physical examination are standard assessments in all men [5]. The necessity and timing of physical examination of the male partner are controversial issue and differ in different guidelines and countries [2]. Endocrinologic testing is recommended in men with abnormal semen parameters (particularly when the sperm concentration <10 million/ml), impaired sexual function or clinical findings that suggest a specific endocrinopathy [3].

This review aims to review the contemporary literature regarding malefactor infertility and management of cases with alternative approaches.

2. MATERIALS AND METHODS

Contemporary medical literature via PubMed, google scholars and others was searched with key-words of ‘malefactor infertility’, and ‘substantial drugs’, ‘depression’, ‘alternative treatment’, ‘acupuncture’. Randomized controlled trials (RCTs) and reviews were included in the study in particular.

3. RESULTS AND DISCUSSION

Potential risk factors for malefactor infertility include lifesytle factors, oxidative stress, medical and psychological disorders and genetics. Proposed management of these factors are lifestyle changes, supplementary medicines, medical and psychological therapies.

3.1 Obesity

Obesity is a global health care problem and may adversely affect male reproduction by endocrinologic, thermal, genetic and sexual mechanisms [6]. Sermondade et al concluded that being overweight and obese was associated with an increased prevalence of azoospermia and oligozoospermia in their meta-analysis in 2013 [7]. In a recent cross-sectional study, BMI was negatively associated with sperm concentration, total sperm count, progressive sperm motility, normal sperm morphology, and percentage of vital spermatozoa. A negative relationship was observed between BMI and total testosterone, sex hormone binding globulin, inhibin B and anti-Müllerian hormone (AMH) levels [8].

Obesity is not only correlated with reductions in sperm concentration and motility, but also increases sperm DNA damage and changes reproductive hormones; the excessive conversion of androgens into estrogens in redundant adipose tissue causes sexual hormone imbalance, subsequently resulting in hypogonadism. Secondly, adipokines produced by adipose tissue induce severe inflammation and oxidative stress in the male reproductive tract, directly impairing testicular and epididymal tissues. Moreover, increased scrotal adiposity leads to increase in gonadal heat, continuously hurting spermatogenesis. Therefore, obesity alters the systematic and regional environment crucial for spermatogenesis in testis and sperm maturation in the epididymis, and finally results in poor sperm quality including decreased sperm motility, abnormal sperm morphology and acrosome reaction, changed membrane lipids and increased DNA damage. Furthermore, recent studies indicate that epigenetic changes may be a consequence of increased adiposity; sperm DNA methylation and non-coding RNA modification are associated with BMI changes and proposed to inherit metabolic comorbidities across generations [9]. Craig et al has demonstrated that paternal obesity can affect offspring metabolic and reproductive phenotypes by means of epigenetic reprogramming of spermatogonial stem cells. Therefore, lifestyle changes and weight loss are important for the offspring’s future life [10].

Although obesity is a risk factor for affected sperm parameters, secondary male infertility was reported following bariatric surgery [11]. Di Frega AS et al. reported 6 secondary malefactor infertility cases who initially underwent serial semen analysis and resulted in non-obstructive azoospermia. A testicular biopsy showed complete spermatogenic arrest, despite the healthy appearance and normal sex hormone profiles. They concluded that, either the absorption of nutrients required for spermatogenesis was insufficient in these patients, or that the effect on the reproductive system was non-reversible [11]. Thus, over-weight males presenting for fertility evaluation should be counseled about weight-loss strategies. Patients should be warned about the negative impact of bariatric surgery on fertility. Cryopreservation of semen samples could be offered prior to the operation or a nutritional therapy can be developed to counteract these effects.

3.2 Heat Exposure

The data on the relationship between heat exposure and male infertility is incomplete mainly because of difficulties and ethical issues about performing human studies. It is konwn that heat exposure like heating car seats, varicocele, occupational exposure to heat and tight-fitting are related with the increased testicular heat [12,13]. But there is inconclusive data on the effect of the heat to the semen parameters. Exposure to heat was examined in animal studies and found a significant increase in testicular tissue oxidative stress and induction of testicular Leydig cell hyperplasia with heat exposure. Because Leydig cells produce testosterone upon stimulation with Luteinizing hormone (LH), mice exposed to heat also exhibited a significant reduction in the serum testosterone levels followed by a significant reduction in the percentages of progressively motile sperm and higher percentages of immotile sperm, when compared control mice. Badr G et al reported that treatment of heat stressed mice with camel whey protein (CWP) significantly restored the levels of reactive oxygen species and the activities of antioxidant enzymes in the testicular tissues nearly to those observed in control mice. These findings have shed light on the molecular mechanisms underlying improved testicular damage following CWP treatment [14]. Although the exact relationship between heat and seminal sperm parameters has not been clearly established yet, scrotal cooling was found to have positive effects on oligoasthenoterato-zoospermia; patients who applied nocturnal scrotal cooling for 12 weeks showed a signifcant improvement in sperm concentration, motility and morphology [15].

3.3 Cigarette (Tobacco) Smoking

Cigarette smoking is a major health problem with approximately 37% of reproductive age-group men are smokers in Europe. Toxins from tobacco smoking can potentially affect sperm development and function, with a negative effect on semen parameters. According to a meta-analysis performed on 5865 participants, exposure to cigarette smoking was found to be associated with reduced sperm count, motility, and morphology. Subgroup analyses indicated that effect size was higher in infertile men than in the general population and in moderate/heavy smokers than in mild smokers [16]. Smoking was reported to decrease the volume of seminal vesicles in contrast with increased serum testosterone levels [17].

Recent studies focused on the effect of cigarette and alcohol on sperm DNA. A study performed on 108 male infertile cases demonstrated that oxidative stress, DNA fragmentation and chromatin decondensation was exceeded to cause DNA damage. Indeed, changing lifestyle behaviour to prevent smoking and alcohol intake is crucial before starting the infertility treatment.

A committee opinion reported by American Society for Reproductive Medicine indicated that cessation of smoking is recommended to both female and male partners with stronger emphasis for female partners [18]. Future studies are needed with the outcomes including measures of fecundity and fertility, live birth rate as well as semen parameters.

Other life-style factors (drug usage, high-intensity sports, occupational exposures, endocrine disrupting chemicals).

Recreational and medical drug use, high-intensity sports and occupational exposures, endocrine-disrupting chemicals (EDCs/toxins) might have an impact on spermatogenesis, thus male fertility and health of subsequent offspring.

It is difficult to identify any occupational exposure uniquely related to poor seminal results but, self-reported lifetime exposure to lead was associated with poor morphology. Low motile sperm count was also related to self-reported lead and to hygienist-assessed glycol ether exposure [19].

A study from Nepal where lots of migrants work reported that occupational hazards in reproductive life are seen more frequently among the mental stress workers. It may be due to improper use of occupational safety clothes, equipment etc. Proper counseling, workplace safety rules and regulation policy should be clearly documented for all migrant workers. Occupational physicians shoud screen workers' health every 3 months. Education, awareness and changing attitude of work style are essential in this globalization era [20].

3.4 Oxidative Stress and Supplementary and Herbal Therapies

Oxidative stress has a negative impact on sperm function; mechanisms responsible for this include oxidative destruction of sperm lipid membranes, damage to gamete DNA both by gene mutation and by the direct breakdown of the DNA backbone, mitochondrial dysfunction and apoptotic cell death [21]. Thus, anti-oxidant therapeutic options are being extensively studied. Gharagozloo P. Et al reported that, Fertilix (a combination of carnitines, folic acid, lycopene, selenium, vitamin C, full-spectrum vitamin E and zinc) improved the sperm quality in male mice and fertilization rates of female mice by repairing the oxidative damage in sperm DNA [22].

Because antioxidants are inexpensive and easily available, they are extensively used worldwide by subfertile males. A Cochrane review evaluated the effectiveness and safety of supplementary oral antioxidants in subfertile men in 2019. Only randomized controlled trials (RCTs) were included in the analysis and they included 61 studies with a total population of 6264 subfertile men, aged between 18 and 65 years. Investigators compared any type, dose or combination of 18 different oral antioxidant supplement with placebo, no treatment or treatment with another antioxidant, among subfertile men of a couple attending a reproductive clinic. Use of antioxidants may lead to increased live birth rates with low level of evidence. When studies at high risk of bias were removed from the analysis, there was no evidence of increased live birth. Antioxidants may lead to increased clinical pregnancy rates compared to placebo or no treatment with low level of evidence. The miscarriage rate was reported in only three studies and there was no difference in miscarriage rate between the antioxidant and placebo or no treatment group with very low level of evidence. Gastrointestinal side effects by antioxidants may lead to an increase in mild gastrointestinal upsets when compared to placebo or no treatment with very low level of evidence. The study concluded that antioxidant supplementation in subfertile males may improve live birth rates and clinical pregnancy rates with low-quality evidence. Further large well-designed randomized placebo-controlled trials reporting on pregnancy and live births are still required to clarify the exact role of antioxidants [23].

The expected trials were published recently; Steiner AZ et al. reported a RCT to determine whether antioxidants improve male fertility, not only measured by semen parameters, but also DNA fragmentation after 3-6 months treatment period. The antioxidant formulation contained 500 mg vitamin C, 400 mg vitamin E, 0.20 mg selenium, 1,000 mg l-carnitine, 20 mg zinc, 1,000 µg folic acid and 10 mg lycopene daily, versus placebo. The study concluded that antioxidants do not improve semen parameters or DNA integrity among men with malefactor infertility in terms of in vivo pregnancy or live-birth rates [24].

Another RCT reported to have evaluated the effect of daily folic acid and zinc supplementation on semen quality and live birth in 2370 infertile couples. Study population received either 5 mg folic acid and 30 mg elemental zinc (n = 1185) or placebo (n = 1185) daily for 6 months. The study concluded that, this supplement did not significantly improve the semen quality and live birth rate while gastrointestinal complaints were minimally increased [25].

Omu et al. in their study randomized 45 men with asthenozoospermia (>or=40% immotile sperm) into four therapy groups: zinc only; zinc + vitamin E and zinc + vitamin E + C for 3 months, and non-therapy control group. They concluded that zinc therapy reduces asthenozoospermia through several mechanisms such as prevention of oxidative stress, apoptosis and sperm DNA fragmentation [26]. Another RCT investigating the effects of folic acid and zinc sulphate supplementation on the improvement of sperm function in 83 subfertile oligoasthenoteratozoospermic (OAT) men reported that sperm quality tended to be improved by this supplements but it was not statistically significant [27].

A prospective study on patients with idiopathic oligoasthenoteratozoospermia reported that, treatment with CoQ10 (200 mg/day or 400 mg/day) resulted in a significant increase in sperm concentration, progressive motility and total motility. CoQ10 therapy also increased total antioxidant capacity in a dose-dependent manner; with the greater improvement shown in men who took 400 mg/day than in those who took 200 mg/day [28].

Nada EA et al. studied the effect of Tamoxifen and L-carnitine treatment on seminal parameters wia reducing the oxidative stress in 60 patients. It was reported that Tamoxifen and L-carnitine were effective to improve seminal quality in terms of malondialdehyde levels, sperm concentration, sperm morphology, ultrastructural head, acrosomal and mitochondrial anomalies and malondialdehyde, sperm motility, sperm morphology, ultrastructural mitochondrial and tail anomalies, respectively. The most beneficial effect was reported in combination therapy of this two agents [29].

Saffron (Crocus sativus) was reported to have a positive effect on erectile dysfunction but no improvement on seminal parameters [30,31].

Barratt CRL et al reported that there was low-quality evidence to recommend the use of supplemental antioxidant therapies and very low quality of evidence to recommend the use of herbal therapies for the treatment of men with abnormal semen parameters and/or male infertility [2].

Qilin pills (QLPs), a classic Traditional Chinese Medicine formula for treating male infertility, were evaluated in terms of the effects on spermatogenesis, reproductive hormones, oxidative stress, and the testis-specific serinekinase-2 (TSSK2) gene in a rat model of oligoasthenospermia. The authors concluded that QLPs have a therapeutic effect on a rat model of oligoasthenospermia, and this effect is manifested as improvement of semen quality and testis histology, gonadal axis stability, decreased oxidative stress, and the regulation of testis-specific spermatogenesis-related gene TSSK2 [32].

'Effect of phosphodiesterase-5 inhibitors (PDE5is) on the treatment of male infertility' and 'The effectiveness of Korean medicine treatment in male patients with infertility' are two ongoing prospective studies whose results will be enlighten on this subject [33,34].

3.5 Medical or Psychological Disorders

The female partner is always in the center of infertility evaluation but recent studies showed that men should be evaluated with a multi-disciplinary approach including the endocrine, metabolic, psychologic and life-style aspects. Major depression is known to be more common in the male partner of infertile couples than fertile males and degree of depression worsens the outcome of infertility treatment [35]. Depression and anxiety in subfertile males are associated with lower secretion of sex hormone-binding globulin and dehydroepiandrosterone sulfate, and higher secretion of cortisol and prolactin. This causes decreased semen volume and sperm density [36]. Abnormal sperm motility and morphology were related to lower testosterone and higher LH and FSH levels. Psychological stress primarily lowers serum total testosterone level with a secondary rise in serum LH and FSH levels which alters the seminal quality. Stress management is warranted for male infertility cases [37].

Associations between malefactor infertility and cardiovascular disease seem to be primarily driven by higher rates of obesity and smoking among infertile men. A direct relationship exists between increased body mass index (BMI), waist circumference and higher rates of malefactor infertility. Sperm quality is negatively affected by obesity, which alters the secretion of luteinizing hormone (LH) from the pituitary gland as well as testicular sensitivity to LH. Abnormal levels of SHBG, follicle-stimulating hormone (FSH), inhibin B, and estradiol (E2) are also present in obese men, leading to poor sperm quality. Sleep apnea and diabetes, which are commonly observed in obese men, can further exacerbate these hormonal abnormalities.

Metabolic syndrome and cancer rates are higher in infertile men. About 0.5% of men who undergo infertility assessment are diagnosed with testicular cancer, which is 1.6–2.8 times higher than the rate for age-matched controls [38]. Rates of melanoma, thyroid cancer, leukemia and lymphoma is recently reported to be higher in infertile men and their first-degree relatives. The risk of childhood mortality due to congenital malformations were also increased in relatives of men with poor semen parameters, particularly among azoospermic men. These suggested associations may point to some underlying genetic, epigenetic or environmental factors that are shared between male infertility and comorbid conditions [39].

3.6 Acupuncture

Acupuncture, a nonpharmacologic therapy with minimal side-effects, according to various studies is beneficial for increasing the success of IVF. The mechanisms of acupuncture for improving the results of IVF are; modulating neuroendocrine factors, increasing blood flow to the uterus and ovaries, modulating immune factors; and reducing stress, anxiety, and depression. Acupuncture does not have reported side-effects, so that can be performed at each stage of the IVF procedure to increase the chances of successful IVF [40].

The data about the efficiency of acupuncture in male infertility cases are limited. Jerng UM et al reviewed the literature and reported that acupuncture increased the percentage of sperm with rapid progression and sperm concentration, but these two outcomes were substantially heterogeneous among the studies. No differences in pregnancy rate and any adverse events were found between acupuncture and control groups. Further large, well-designed RCTs are required to understand if acupuncture has beneficial effects on semen analysis results and malefactor infertility [41].

3.7 Genetic Screening

Lastly, sperm function is now known to be more important than sperm morphology. The evidence-based criteria for genetic screening of infertile men and the timing of evaluation is as discussed below:

In all infertile men with a known cause of spermatogenic failure, such as chemotherapy, bilateral mumps, orchitis with resultant atrophy or current use of anabolic steroids, and is presently severely oligozoospermic or azoospermic, it can be assumed that these are the proximate reasons for the reduced/absent spermatogenesis and no genetic evaluation needs to be undertaken. Tests such as karyotype analysis, Y-choromosomal microdeletion assay and cystic fibrosis (CF) mutation analysis are mandatory to perform. Both a karyotype and Y-chromosomal microdeletion assay are recommended in men without a known cause and who have a history, physical examination and hormonal assays consistent with severe oligozoospermia or non-obstructive azoospermia. Men with a sperm count <5 million/ml show a much higher rate of autosomal abnormalities than fertile populations (around 4%) (mostly Klinefelter syndrome). CF-mutation analysis is recommended in men with Congenital Bilateral Absence of the Vas Deferens or clinical CF [2].

4. CONCLUSİON

The male partner is responsible for a significant portion of infertility. Focusing mainly on the female partner in the evaluation of infertile couples may lead to underestimation of the problem. A detailed assessment of male partner in the diagnostic work-up of infertility should include detection and correction of risk factors in life-style, psychological support, acupuncture, antioxidative and supplementary medicine if needed. These interventions may improve not only conventional sperm parameters but also genetic material of sperm cell and IVF success rate eventually.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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PMCID: PMC4236334

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/59053