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Invited State-Of-The-Art Review

Limited interventions to improve male fertility

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ABSTRACT

Identifying treatments for male infertility has received limited focus, partly because of the success of assisted reproductive techniques (ART), where only few spermatozoa are needed to fertilise the oocyte in vitro. The successful development of ART has created a paradox because we now initiate treatment of the woman even when male-factor infertility is the cause of the couple's inability to conceive. Increased awareness of lower fertility rates, focus on reproductive problems, and the MeToo movement have stimulated interest in male infertility, although neither researchers, governments, nor the pharmaceutical industry are investing sufficient resources to revolutionise infertility treatment by developing innovative therapies for male infertility. This review summarises the challenges we face in developing novel treatment options for male infertility, highlights prior efforts and presents several considerations for future studies. Hopefully, in the near future, we will be able to offer treatment options for subsets of infertile men rather than solely relying on their healthy partners undergoing hormone treatment and subsequent ART, but this requires that authorities, funding bodies, researchers, the pharmaceutical industry and the infertile men themselves prioritise efforts to achieve this.

KEY POINTS

- Semen quality is prone to substantial intraindividual variation, especially for men with severely impaired semen quality, which requires large placebo-controlled studies to claim effects.
- No treatment can be used in all infertile men, so we need to identify subgroups of men that can be selected for a given treatment.
- The most promising treatment options for male infertility focus on hyperstimulation with FSH and LH, which can be achieved by using these compounds or aromatase inhibitors/antioestrogens.
- Vitamins, antioxidants and minerals may have a role in male reproduction, but large studies demonstrating benefits are still lacking.

Most of us assume we can have the children we want whenever we wish. However, infertility affects millions worldwide, with an estimated 800 million couples experiencing infertility in their lifetime [1-4]. In about half of these couples, male factor contributes to the issue, and it is the sole cause in roughly 30% of all infertility cases [5-6]. Facing a diagnosis of infertility can be devastating for couples, especially in countries with limited access to assisted reproductive technologies (ART). Even in countries like Denmark, where ART is publicly funded, infertility often causes considerable stress, which can lead to anxiety, depression and possibly other health issues manifesting later in life. The emotional burden associated with infertility can also increase the risk of relationship breakdown; even in Denmark, some couples separate during ART treatment.

ART is the mainstay, but different treatment approaches are used depending on the couple's specific infertility problem. Intrauterine insemination (IUI) is used for mild semen quality impairment, while in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) are applied for more severe cases [7]. These approaches carry potential adverse effects and complications for the women, including hormonal hyperstimulation, oocyte retrieval and embryo transfer - placing a substantial physical and emotional burden on women, while the infertile men's contribution is limited to providing semen samples [7-8]. This treatment imbalance in ART raises ethical concerns, as reproductively healthy women are frequently treated when the male partner has reproductive problems. Addressing this discrepancy requires increased research focused on male infertility [9]. In the future, infertile men should ideally be offered cost-effective treatments targeting the underlying causes rather than relying solely on ART, which currently yields pregnancies in only about 30–50% of cycles and 70% of couples bringing home a baby after three IVF cycles [10].

Several studies worldwide have documented a semen quality decline [11]. However, in Denmark, prospective annual monitoring over 20 years has shown stable sperm concentrations, despite many men having low semen quality [12]. The exact reasons for having impaired semen quality remain unclear, but factors occurring during adulthood, such as sedentary lifestyles and exposure to drugs, and also environmental toxins and pollutants occurring during foetal development, have been proposed as possible causes [13]. During the past 20 years, many countries, including most

EU nations, have observed a considerable increase in the average age of women at first childbirth. Combined with the low semen quality, this aggravates infertility, which may decline in the future if the increasing age trend continues.

Currently, no effective medical treatments to improve sperm quantity and quality in larger fractions of men exist. This represents a considerable unmet clinical need, as recently reviewed [14]. Due to the lack of targeted therapies for male infertility, the only option available is often the costly, invasive and time-consuming ART, predominantly focusing on and affecting the female partner. Furthermore, ART accounts for a larger share of all live births in Europe, raising concerns about societal sustainability and the need to improve success rates. The financial burden often limits access to ART, especially in countries where the cost is not fully subsidised. This highlights an urgent need for aetiology-focused, affordable treatments that address the root causes of male-factor infertility.

Spermatogenesis and reproductive hormones

The primary functions of the testes are the production of sex steroids and spermatozoa [13, 15]. Testicular size reflects the number of sperm produced. Within the seminiferous tubules, Sertoli cells support the germ cells at all maturation stages – from diploid spermatogonia to haploid spermatids – that elongate and mature into spermatozoa. This process, termed spermatogenesis, takes approximately 68–74 days in humans, and comprises the differentiation process from spermatogonial stem cells to fully developed spermatozoa. Sertoli cells are essential for spermatogenesis, providing nourishment and facilitating germ cell maturation. Their function is tightly regulated by endocrine factors, primarily hormones that act on them indirectly, both during development and in adulthood. In adult men, Sertoli cell activity is primarily regulated by follicle-stimulating hormone (FSH), secreted by gonadotropic cells of the anterior pituitary. During spermatogenesis, Sertoli and germ cells produce inhibin B [13, 16], which provides negative feedback on FSH secretion and serves as a clinical marker of the Sertoli-germ cell interaction and function of the hypothalamic-pituitary-gonadal (HPG) axis. Additionally, Sertoli cells secrete anti-Müllerian hormone (AMH), which plays a crucial role in foetal male sexual differentiation and may also serve as a marker of Sertoli cell function in adulthood [13, 17]. Testosterone, produced by Leydig cells in the interstitial space of the testes, is the principal sex steroid in males. Its secretion is stimulated by luteinising hormone (LH), also released by the anterior pituitary. Testosterone is several-fold higher inside the testicles than in the serum and is important for Sertoli cell function and a high production of spermatozoa. Testosterone is involved in various functions beyond reproduction, including secondary sexual characteristics, libido, muscle mass, bone metabolism, erythropoiesis and lipid homeostasis [13]. Additionally, oestradiol, synthesised from testosterone via aromatase activity in the testes, is present at lower levels but contributes to spermatogenesis by modulating effects on germ cells via oestrogen receptors. Approximately 80% of circulating oestradiol in men is produced peripherally from androgens. Both testosterone and oestradiol exert negative feedback on LH release at the hypothalamic-pituitary level, and serum LH levels are used clinically to evaluate Leydig cell function and to distinguish between primary (testicular) and secondary (hypothalamic-pituitary) hypogonadism.

Male Infertility

Male infertility is defined as the inability to conceive after 12 months or more of unprotected intercourse. The aetiology of this condition is highly heterogeneous, resulting from genetic, anatomical or hormonal factors. However, many cases remain idiopathic [5, 6, 13]. The diverse underlying causes complicate treatment, and a single intervention is unlikely to benefit all infertile men. Assessment of male infertility involves detailed medical history, physical examination (including ultrasonography of the testes), semen analysis and hormonal evaluation. Medical history should include duration of infertility, previous pregnancies, use of anabolic steroids, urogenital infections or surgeries and childhood conditions such as cryptorchidism or pubertal anomalies. A physical exam assesses secondary sexual characteristics, testicular size and consistency, presence of varicocele and vas deferens, penile abnormalities and scrotal pathology. Ultrasonography helps identify structural anomalies, echogenicity and testicular tumours. Hormonal testing typically includes analyses of serum FSH and testosterone levels; whereas additional testing of LH, inhibin B and possibly AMH may help diagnose conditions like hypogonadism or obstructive azoospermia. Genetic testing is also recommended, including karyotyping to detect conditions such as Klinefelter syndrome, Y chromosome microdeletions and other abnormalities. Despite extensive evaluation, many cases remain idiopathic. Semen analysis is key in the panel of tests applied because it is predictive of male fertility potential. Following WHO guidelines (2021, sixth edition), assessing semen volume, sperm concentration, motility and morphology is recommended. Due to intra-individual variability, more than one analysis is recommended. Abstinence for some days before testing ensures more accurate results, as sperm parameters are influenced by time since the last ejaculation, but also other factors, for instance, high fever. Traditionally, the number of motile sperm and sperm concentration are used as key indicators of male fertility potential, given their correlation with time to pregnancy and success rates in intrauterine inseminations (IUI), but also other variables, such as sperm morphology, are predictive of male fertility.

Treatment of male infertility

Treatment of male infertility is contingent upon the underlying aetiology. This emphasises the crucial need for a comprehensive andrological evaluation of men presenting with infertility and impaired semen parameters. Currently, only a limited number of conditions – such as varicocele (surgical correction), obstructive azoospermia (testicular sperm aspiration) and hypogonadotropic hypogonadism (gonadotropin replacement therapy) – have well-established treatment options, although their success rates vary [18]. In many cases, the female partner still needs to undergo

ART to conceive [9]. Consequently, in many instances of male infertility, including those classified as idiopathic, no definitive targeted therapies are available [18]. Various interventions have been attempted, but it is important to note that, due to considerable intra-individual variability when using semen quality as the primary endpoint, all clinical studies should compare active treatments with matched placebo-treated controls [18-26].

Most studies have focused on hormonal treatments, particularly the use of luteinising hormone (LH)/human chorionic gonadotropin (hCG) and follicle-stimulating hormone (FSH), owing to their well-characterised role and effect in hypogonadotropic hypogonadism. The therapeutic approaches examined can be broadly divided into three categories: [1] hormonal therapy targeting the hypothalamic-pituitary-gonadal (HPG) axis, supplementation with minerals, antioxidants and vitamins [18-26], and repurposing of existing medications, along with lifestyle interventions [27–30]. An overview of these strategies and results follows, summarising current knowledge and highlighting areas requiring further research.

Gonadotropins, aromatase inhibitors and selective oestrogen receptor modulators

Men with hypogonadotropic hypogonadism typically exhibit azoospermia due to complete absence of sperm production. Treatment with human chorionic gonadotropin (hCG), an LH receptor agonist administered twice weekly, followed by FSH given either daily or three times weekly, has been shown to induce spermatogenesis in most affected men [19–21]. This efficient treatment modality is also important because it has improved the physiological understanding and facilitated the exploration of FSH monotherapy or combined FSH and hCG treatment in infertile men without hypogonadotropic hypogonadism. While some studies report positive outcomes, others find no significant improvement in semen parameters, with a recent review summarising these findings in detail [31]. A Chinese study examining FSH hyperstimulation in infertile men demonstrated a substantial increase in sperm production [32], prompting Ferring Pharmaceuticals to initiate a large-scale investigation into this approach. Unfortunately, the trial was not completed. The strategy of FSH hyperstimulation continues to attract interest, with efforts to refine candidate selection using specific criteria [33] or biomarkers such as serum anti-Müllerian hormone (AMH), a marker of Sertoli cell function [17]. While FSH hyperstimulation, with or without hCG, may benefit a selected subgroup of infertile men, its clinical applicability remains uncertain due to the need for prolonged daily injections over several months and the associated high cost. Nevertheless, this approach may attract interest from pharmaceutical companies developing FSH-based therapies. Alternative pharmacological strategies involve agents that stimulate endogenous FSH and LH production, such as selective oestrogen receptor modulators (SERMs] for instance clomiphene and tamoxifen, or aromatase inhibitors like letrozole, anastrozole and recently, leflutrozole [34-35]. These drugs can be administered orally, are cost-effective, and have shown comparable efficacy to FSH stimulation in some studies, though their benefits are also limited to a subset of infertile men and may possibly cause lower libido and other sexual issues that lessen optimism. Optimising predictive biomarkers and diagnostic criteria is essential to identify likely responders and avoid unnecessary treatment of infertile men unlikely to benefit.

Minerals, vitamins and antioxidants

Accumulating evidence suggests that deficiencies or low-normal serum levels of minerals such as calcium, magnesium, phosphate, zinc and possibly other minerals may influence gonadal function and semen quality in both fertile and infertile men [22-26, 36]. However, it remains unclear whether supplementation can directly alter mineral concentrations in the testis and male reproductive tract and improve semen quality. Many intervention studies lack proper placebo controls, limiting the strength of their conclusions. Even a large multicentre trial using high doses of folic acid and zinc showed no benefit in infertile men [24]. This could be due to drug inefficacy, or be confounded by a lack of baseline mineral level measurements, as it would be expected that men with deficiency would benefit, while men with normal levels probably would have a lower effect, and some of these men may be more prone to experiencing toxic levels of folic acid and zinc. Similarly, high-dose vitamin D and calcium supplementation in vitamin D–deficient infertile men did not improve semen quality, which may be due to the high dosage used, as smaller studies using lower dosages suggest potential benefits [22-23]. In addition, indirectly acting antioxidants /plant extracts (e.g. extract of pomegranate fruit + galangal rhizome and chokeberries (Aronia spp.)) have been shown to increase semen quality, which implies that they may have a longer-lasting effect than shorter-acting antioxidants such as vitamin C [37-38]. The heterogeneity and methodological limitations of other vitamin and antioxidant studies complicate interpretation, underscoring the need for better-designed research trials.

Repurposed drugs and lifestyle intervention

Several pharmaceuticals approved for other indications have been studied with the aim of repurposing them to treat male infertility. Angiotensin-converting enzyme (ACE) inhibitors, proposed to enhance testicular blood flow, have shown promising effects in some studies but lack reproducibility across populations [39-42]. Preclinical evidence indicates that testicular function may be affected by bone-derived signalling molecules such as osteocalcin and FGF23 [43-46], suggesting that medications targeting bone metabolism could be repurposed. For instance, denosumab, a monoclonal antibody against RANKL used in the treatment of osteoporosis, was shown to improve sperm production and reduce germ cell apoptosis in preclinical models. Subsequent RCTs with denosumab treatment have yielded mixed results – some suggesting a beneficial effect in selected infertile men, but overall, large controlled studies have failed to demonstrate definitive efficacy [47-48]. Other repurposed pharmaceuticals, such as the diabetes drug metformin, have also been explored, with some studies indicating improved semen parameters in infertile men, but concerns about potential adverse effects on offspring have been raised [49-51]. Although results from metformin studies are inconsistent regarding the improvement of male infertility, the most recent data indicate no harmful effects. In general, infertile men have a higher risk of developing metabolic syndrome; thus, weight loss strategies, including the use of GLP-1 receptor agonists, show promise with relatively large increases in sperm production in non-placebo-controlled studies. However, additional rigorous, placebo-controlled research is required for validation [28]. The negative impact of lifestyle factors – including smoking, alcohol intake, caffeine consumption and sedentary behaviour – on semen quality remains unconfirmed by intervention studies and has largely been established by observational data [29-31]. Therefore, recommendations to adjust such lifestyle factors in infertile men are not based on solid evidence. Interestingly, reductions in maternal smoking have not demonstrated measurable improvements in testicular function in offspring, suggesting that such observational data should be interpreted cautiously [12].

Conclusion

For the vast majority of infertile men, there are currently no effective medical treatments, while infertile men with a few defined underlying causes do experience improved semen quality following specific interventions. Currently, the most promising approaches for the treatment of infertile men include hormonal hyperstimulation with SERMs or aromatase inhibitors or even FSH hyperstimulation, followed by lifestyle modifications, particularly weight management and correction of deficiencies in antioxidants, minerals or vitamins, although placebo-controlled evidence is needed. It is imperative that future research comprises adequately powered, randomised, placebo-controlled trials of sufficient size to account for the high variability in semen parameters and to establish evidence-based treatments for selected groups of patients, ideally pre-selected based on biomarkers or clinical characteristics.

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