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Review

The Genetic Landscape of Male Factor Infertility and Implications for Men's Health and Future Generations

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Abstract: Infertility is a significant global health issue, affecting 8–12% of couples of reproductive age, with male factor infertility contributing to 30–50% of cases. Despite advances in assisted reproductive technologies, particularly intra-cytoplasmic sperm injection, male infertility remains understudied compared to female infertility. This review aims to explore the genetic underpinnings of male factor infertility, including identified genetic mutations, chromosomal abnormalities, and epigenetic factors, and to investigate the broader health implications for affected men. The emerging data suggest that male infertility is not only a reproductive issue but also a potential predictor of chronic diseases, including autoimmune disorders, cancer, and premature death. Additionally, the inheritance of male factor infertility and its potential effects on offspring health remains indeterminate. Studies have shown conflicting results regarding the impact of parental infertility and fertility treatments on the semen quality and reproductive health of offspring. This review summarizes the current understanding of the genetic causes of male infertility, highlights the impact of chromosomal disorders, reviews the spectrum of sperm quality and hormonal profiles, and discourses on the need for further research to clarify the relationships between parental subfertility, male infertility, and offspring health. By investigating these complex interrelationships, future research can help shape more effective diagnostic and treatment strategies for male infertility and its broader implications for men's health and future generations.

Keywords: genetic causes; male infertility; male subfertility; men's health; offspring health; semen quality

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1. Introduction

The World Health Organization (WHO) defines infertility as the failure to conceive after 12 months or more of regular unprotected sexual intercourse [1]. Treatment may involve intrauterine insemination (IUI), in vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI). While infertility refers to the inability to achieve a spontaneous pregnancy, subfertility is often described as any type of reduced fertility with a prolonged time to achieve a pregnancy. Historically, infertility has predominantly been viewed as a "female issue", leading to interest in research in female reproductive health. In contrast, male infertility remains less understood [2,3]. The introduction of assisted reproductive techniques (ART), specifically ICSI, further expanded this disparity, as the technology does not solve nor address the potential heritability or etiology associated with the underlying

cause of male factor infertility [4]. Furthermore, it can be argued that modern fertility treatments place an unfair burden on the female partner, who must undergo hormonal therapies, frequent scans, and invasive procedures. Even in cases of severe male infertility, the male partner experiences comparatively less involvement [3]. Along with the global decline in sperm counts [5] and advancements in genomic technology [6], this recognition has increased the urgency to investigate the causes and health-related risks associated with male factor infertility.

Male factor infertility is estimated to contribute to 30–50% of cases of infertility. Causes of male factor infertility may include varicocele, a history of cryptorchidism, or hypogonadism, although many cases are idiopathic, which may reflect unidentified genetic causes [7]. There are emerging data that male factor infertility is a predictor of poor health in men, as studies have reported a higher risk of certain chronic diseases, autoimmune diseases, and cancers [8–10]. Studies have found male factor infertility to be associated with an increased risk of premature death, which also supports the hypothesis of a genetic association, given that genomic instability previously has been identified among infertile men [11].

Globally, around 8–12% of couples of reproductive age are considered infertile. In certain regions, particularly Asia and Africa, the reported infertility rates are even higher [12,13]. However, such estimates should be interpreted with caution, as variations in infertility rates may be influenced by several factors, such as access to care and cultural norms. Nonetheless, a growing number of children are now being conceived through ART, with the introduction of ICSI marking a breakthrough in the management of severe male infertility [14]. Ultimately, this development means that more children are born by parents who are considered in- or subfertile, which has generated an interest in investigating the potential reproductive health of these children.

While most attention has been given to female infertility and the risk of adverse health outcomes in women and children [15,16], there has been a growing interest in understanding the impact of male factor infertility on men's health. Little is known about the reproductive health outcomes of males born to subfertile parents, and the adverse health risks associated with infertility may also be inheritable. This narrative review aims to summarize the current data on the genetic causes of male factor infertility, as well as the effects of parental infertility, subfertility, and semen quality on offspring.

2. Genetics and Male Factor Infertility

Spermatogenesis, the production of a mature male gamete, is a highly regulated multistep process in which numerous genes are expressed through successive mitosis, meiosis, and post-meiosis alteration. This dense intricacy increases the instances in which errors can occur, making male infertility a heterogeneous disorder among patients. Over the years, efforts to classify the etiologies of idiopathic infertility have resulted in multiple descriptions of autosomal chromosomes, sex chromosomes, and epigenetic chromosomal abnormalities. However, whole-genome sequencing (WGS) now prospects to unearth a new understanding of new genetic interactions responsible for iatrogenic male infertility. The following section briefly describes the mechanisms of genetic conditions that are well-known to affect male infertility (Table 1) while taking a closer look at new research findings based on whole-genome sequencing.

Table 1. Genetic mechanisms involved in male infertility.

Mechanism	Description	Key Features	Clinical Relevance
Sex Chromosome Anomalies			
Numerical (Aneuploidy)	Errors during cellular replication resulting in missing or extra chromosomes.	Common examples include Klinefelter syndrome (47,XXY), XYY syndrome, and XX male syndrome.	Associated with azoospermia and oligospermia; advancements in sperm retrieval and ICSI have improved fertility outcomes for affected individuals.
Y-Chromosome Deletions	Deletions in the male-specific Y chromosome (MSY), particularly in AZF regions (AZFa, AZFb, AZFc).	AZFa deletions associated with Sertoli-cell-only syndrome; AZFb deletions with spermatogenic arrest; AZFc deletions linked to oligozoospermia or azoospermia.	Successful sperm retrieval in ~50% of cases with AZFc deletions; genetic counseling recommended due to obligate inheritance of Y-chromosome anomalies.
X-Linked Disorders	Mutations or polymorphisms in X-linked genes affecting spermatogenesis and hormonal regulation.	Androgen receptor (AR) gene mutations linked to androgen insensitivity syndromes; TEX11 mutations causing meiotic arrest in idiopathic non-obstructive azoospermia (NOA).	Critical for identifying underlying causes of idiopathic infertility; highlights the importance of genetic counseling and targeted therapies.
Autosomal Anomalies			
Chromosomal Rearrangements	Structural changes, such as translocations or inversions, disrupting normal gene expression.	Robertsonian translocations commonly involve chromosomes 13, 14, 15, 21, and 22.	Found in ~1.6% of infertile men; associated with increased risk of miscarriage and congenital anomalies.
Mutations (e.g., CFTR)	Mutations in autosomal genes like CFTR (associated with congenital bilateral absence of the vas deferens).	Over 2000 mutations identified; spectrum of effects ranges from obstructive azoospermia to severe cystic fibrosis.	Recommended genetic screening and preimplantation genetic diagnosis (PGD) for affected couples undergoing ART.
Sperm Epigenome			
Epigenetic Dysregulation	Non-genetic changes affecting gene expression through DNA methylation, histone modification, or chromatin packing.	Altered DNA methylation and histone density linked to poor spermatogenesis and embryogenesis; paternal age may influence global methylation patterns.	Advances in whole-genome sequencing (WGS) and artificial intelligence offer potential for better understanding and therapeutic interventions in epigenetic-related infertility.

3. Sex Chromosome Anomalies

3.1. Numerical (Aneuploidy)

During an infertility workup, a karyotype is often an initial test performed for individuals with low sperm counts, especially for those with idiopathic non-obstructive azoospermia (NOA). This is due to the high incidence of aneuploidy, a numerical error occurring during cellular replication where there are either additional or missing chromosomes in a diploid pair in these patients. Studies have shown that the incidence of individuals with NOA and aneuploidy ranges from 11.4% to 24.9% [17,18].

Several sex chromosome aneuploidies commonly affecting fertility have been described, including XYY (1:1000 live-birth frequency) and XX male syndrome (1:20,000 live-birth frequency). However, Klinefelter's (KS) is the most common aneuploidy (1:500 live-birth frequency) found in 14% of men with NOA [19]. Given its prevalence, KS is the most studied of this group of genetic disorders. The phenotypic presentation of patients with KS is highly variable. However, atrophic testes (<10 cc and often <5 cc) and elevated FSH and LH (indicating primary testicular failure) are usually ubiquitous.

The mosaic heterogeneity found in KS partially explains the high phenotypic variability. Most patients (80–90%) with KS are non-mosaic (most common 47 XXY; least common 48, XXXY; 48, XXYY; 49, XXXXY), while the remaining individuals (10–20%) demonstrate varying degrees of somatic mosaicism (47 XXY/46XY) [20]. Mosaicism is highly heterogeneous in terms of affected cell lines (somatic vs. germline) and amount. Thus, patients with a normal peripheral leukocyte karyotype could harbor germline mutations, consequently falsely reducing the prevalence of the disease. Natural paternity for either form of the disease is rare, with studies demonstrating a low incidence of viable sperm in the ejaculate in those with the non-mosaic form (26%) [21] and an even lower incidence (8–25%) in those with the mosaic form [22,23]. However, several studies have confirmed that even 47 XXY germ cells can complete meiosis, leading to normal haploid gamete cells [24–26]. Later studies further demonstrated that most of the mature sperm (80–100%) found in 47 XXY individuals were haploid [27–29]. The meiotic mechanism by which aneuploid germ lines produce haploid gametes still remains unknown [30].

Non-mosaic KS is thought to be paternally derived in about 50% of cases and almost always occurs due to non-disjunction events during meiosis 1 [31,32]. The exact mechanism of non-disjunction in this population is unclear but likely due to a combination of recombination error and meiotic checkpoint laxity. Because of this, significant research has been conducted on genes regulating homologous pairing and crossover (CO) and chromosome synapsis during meiosis (SAC) [33,34]. A recent study by Lie et al. showed that knockout of USP26, a gene coding for ubiquitin-specific protease 26, which is necessary for successful homologous pairing and crossover, resulted in aneuploid mice offspring. Additionally, they performed whole-exome sequencing (WES) in human patients with KS and healthy controls, demonstrating several *USP26* mutations that are strongly associated with aneuploidy [35].

Clinically, advancements in sperm retrieval and ICSI have been detrimental to improving fertility rates among patients with KS. A study by Yarali et al. showed comparable pregnancy and implantation rates after ICSI among couples with men with KS (39 and 23%) and without KS (33 and 26%) [36]. The rate of euploidy among this group was 59%, emphasizing the importance of preimplantation genetic diagnosis (PGD) to ensure that the offspring are not aneuploid [37].

3.2. Deletions of the Y Chromosome

Not until recently has the entire sequence of the Y chromosome been mapped [38]. However, the male-specific region (MSY) has been detained for over 20 years [39]. Compris-

ing over 95% of the Y chromosome length, the MSY contains over 70 genes responsible for male sex differentiation and spermatogenesis (i.e., azoospermic factors a,b,c [AZFa,b,c]) [40]. The MSY contains several large palindromic sequences, termed "ampliconic regions", which do not cross over and instead undergo gene conversion (non-reciprocal transfer of inverted palindromic sequences within the same chromosome), which has allowed this chromosome to maintain its fidelity through evolution. However, large stretches of repeating DNA sequences are prone to structural reorganization due to DNA repair mechanisms such as nonallelic homologous recombination (NAHR), which is a process where highly similar DNA sequences may be duplicated or deleted [41]. As such, several MSY deletions and mutations have been described in infertile populations at a higher frequency than in fertile controls.

AZF microdeletions of the Y chromosome are the most common genetic anomalies found in infertile men, occurring in 10% of patients with NOA and 5% of those with severe oligozoospermia [42]. The disease prevalence may vary by nationality [43]. The genes in the AZF regions are crucial to spermatogenesis, with most being exclusively expressed in the testis [44]. The AZF region is conventionally described in three sections: AZFa, AZFb, and AZFc. AZFa is located on the proximal Yq11, whereas AZFb and AFZc partially overlap on the distal end Yq 11 [45]. Complete or partial deletions of any of these sections result in gene disruptions that are specific to each location, with varying effects on fertility. In cases of infertility due to AZF microdeletions, candidacy for testicular sperm extraction (TESE) is dependent upon the type of microdeletion that has occurred.

The AZFa region houses two genes of particular importance to spermatogenesis: *USP9Y* and *DBY*. Those with complete AZFa deletion often show Sertoli-cell-only syndrome or germ cell aplasia on a histological survey of testicular biopsies [40,46]. RBMY1 and PRY, the genes responsible for a testis-specific splicing factor and involved with apoptosis signaling, respectively, are found in the AZFb region. Complete AZFb deletion results in spermatogenic arrest upon histological review [47]. Rare incomplete deletions preserving both the RBMY1 and PRY genes have been associated with hypospermatogensis [48]. While there have been rare published occurrences of men with AZFb deletions with sperm retrieved [49–51], sperm is rarely retrieved in patients with complete deletions of AZFa and AFZb from either the ejaculate or testis [52]. The heterogeneity in lab practices and primer sequences used for PCR identification of the AZF region makes it hard to prove that outliers are not due to partial deletions or mosaicism [53,54].

The AZFc region is particularly susceptible to nonallelic homologous recombination events and, thus, makes up the most significant percentage (~80%) of AFZ deletions [55]. The phenotypic penetrance of AZFc deletions is more clinically heterogeneous, ranging from azoospermia (most common) to oligozoospermia. While several genes are coded for in this region, the gene most frequently connected with infertility is *DAZ*, as it is expressed in all stages of spermatogenesis [56]. While natural paternity in this population is rare [57], sperm retrieval is successful in about 50% of cases [53,58].

Given the increased susceptibility of the AZFc region to NAHR, many partial deletions are possible; the most clinically relevant is gr/gr deletion. Deletion of gr/gr results in a >50% loss of genes from the AZFc region (including *DAZ*), and spermatogenic phenotypes range heavily from azoospermia to normospermia [43]. Ethnicity may play a role in phenotype penetrance, given that within specific Y haplogroups (e.g., D2b, Q3, and Q1 found commonly in Japan and China), the deletion is constitutive, harboring no apparent adverse effect on spermatogenesis [40,59]. These findings remain controversial due to discrepancies in ethnicity and geographic control matching.

Regardless of mechanism or class, the inheritance of Y chromosome aberrations is obligatory in male offspring due to the unique lack of recombination with the X chromosome. This confers a known risk of subfertility in male offspring, so patients in this group should be encouraged to participate in genetic counseling before engaging in ART.

3.3. X-Linked Disorders

A high number of genes found on the X chromosome are only expressed in higher quantities in spermatogonia [60]. This signal has led to an investigation into many X-linked genes as potential disrupters of spermatogenesis in men with oligozoospermia and azoospermia. Due to the influence of intratesticular testosterone on sperm development [61], the X-linked androgen receptor (*AR*) gene has drawn much attention. Situated at Xq11-12, well over 1000 mutations [62] are known to affect this gene, with novel discoveries happening often [63]. Affected individuals show varying levels of phenotypic penetrance, ranging from female-appearing individuals with complete androgen insensitivity (AIS) to those with partial insensitivity demonstrating under-virilization (PAIS) and mild insensitivity appearing phenotypically male with impaired spermatogenesis (MAIS).

The leading genetic mechanism explaining the variable presentation is thought to be due to expanding CAG polymorphisms located within exon 1 of the *AR*, which are inversely proportional to receptor activity [64]. While some studies have demonstrated an inversely proportional relationship between CAG expansion and infertility [65,66], others have shown only a mild association [67] or no relationship [68]. Again, ethnic background and Y haplotype groups may play a part in this variable relationship [68,69], as reemphasized by a recent study demonstrating varying relationships between CAG length and sperm quality among three different Russian ethnic groups [70].

As mentioned previously, repetitive genetic sequences are prone to inborn errors. As such, longer polymorphisms could become unstable over successive generations, posing subfertility questions for daughters of infertile males with longer-than-normal CAG polymorphisms. However, several studies have shown stable inheritance of CAG lengths in daughters after ICSI [71–73]. More studies are needed to understand whether there is a threshold by which expansion may be seen in successive generations, as has been detailed with other diseases with CAG polymorphisms, such as Kennedy disease [74].

Kallman syndrome is a rare disease (1:30,000 frequency) that exhibits both X-linked, autosomal dominant, and recessive inheritance depending upon the affected gene [75]. Affected individuals' phenotypic expressions vary, but they classically present with delayed-onset puberty due to congenital hypogonadotropic hypogonadism (CHH) with hyposmia or anosmia. The disease is caused by the arrested migration of GnRH neurons to the hypothalamus during development [20]. The lack of testosterone in these patients inhibits spermatogenesis, leading to infertility.

The genetic mechanism of disease occurrence and transmission is highly heterogeneous, involving several potential gene regulators on both the autosomal and sex chromosomes. Hypothesis-driven WES strategies [76] have successfully identified new genetic targets in this disease, adding to the ~30 previously known genetic associations [77]. Two of the most studied forms of transmission involved X-linked transmission through the deletion of *KAL1* (Xp22.3) [76] and autosomal dominant inheritance through the deletion of *FGFR1* (8p11-12) [78]. In both these forms, spermatogenesis can be rescued in ~80% of patients through gonadotropin replacement over 1–2 years [79]. Due to many factors affecting inheritance and penetrance, PGD and genetic counseling should be considered when counseling patients experiencing infertility.

TEX11 mutation is the latest X-linked gene associated with NOA [80]. In a recent study, blood samples from 15 men with NOA were analyzed using a comparative genomic hybridization (CGH) array permitting the identification of a hemizygous deletion of TEX11 on chromosome Xq13.1. Screening in a larger cohort of 289 patients revealed a prevalence of 2.4% vs. none in controls ($p \leq 0.05$). The results were confirmed through immunohistological staining of testicular tissue, which demonstrated meiotic arrest and no expression of TEX11 expression in those with *TEXII* mutations and meiotic arrest. These results were validated in another large population study (n = 246), where the TEXII mutations were found in 1% of men with NOA [81].

4. Autosomal Anomalies

4.1. Rearrangement Anomalies (i.e., Deletions, Duplications, Inversions, and Translocations)

Chromosomal translocation and inversion describe two phenomena by which segments of DNA are transferred to a different location on the same or different chromosomes. These structural anomalies are most common in men with severe oligozoospermia ($<5 \times 10^6$/mL), with a prevalence 10 times higher than that observed in normozoospermia populations [82]. Given this statistic, the European Association of Urology (EAU) recommends routine genetic screening of those with sperm concentrations of $<10 \times 10^6$/mL[83].

The effect of translocations/inversions is highly dependent upon the location at which the break occurs, which may alter gene expression or disrupt chromosomal pairing during meiosis due to imbalances in chromosomal mass [84]. Robertsonian translocations (exchanges involving acrocentric chromosomes 13, 14, 15, 21, and 22) are the most common type of translocation found in infertile men (1.6%) [20] and confer an increased risk of miscarriage [85,86], among other congenital disabilities.

4.2. Mutations

Several diseases associated with male infertility are known to be caused by autosomal chromosome mutations. Of these, congenital bilateral agenesis of the vas deferens (CBAVD) is one of the most well-known causes of male infertility, although it affects a relatively small proportion (1%) of infertile men [87]. CBAVD is caused by a mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene (7q31.2) [88], coding for a transmembrane chloride protein found in the secretory epithelium, resulting in obstructive azoospermia through the absence of either one or both vas deferens. To date, over 2000 distinct mutations of *CFTR* have been discovered [89]. *CFTR* is inherited in an autosomal recessive pattern. However, it displays variable penetrance depending on the class of mutation [90]. The variable penetrance and recessive inheritance create a broad spectrum of clinical manifestations, spanning from severe cystic fibrosis (characterized by life-threatening pancreatic insufficiency and pulmonary disease) to individuals with CBAVD only [91].

The patient with CBAVD will typically have severe semen parameter derangements, including low volume (<1.0 mL), low pH (<7), and an absence of spermatozoa. Subfertility in offspring is possible depending on (1) paternal mutation severity and (2) maternal carrier status. Due to the potentially life-threatening consequences of inheriting two mutated CFTR alleles, CFTR screening is recommended for both male and female partners in the presence of CBAVD [90]. In scenarios where both partners are CFTR mutation carriers and pursuing ART, PGD is vital, given the 25% risk of inheriting two affected genes.

5. Sperm Epigenome

Epigenetics, or the study of how gene expression is regulated through several non-code-altering mechanisms (i.e., histone modification, DNA methylation, and protamine chromatin packing), is an ever-growing field in male factor infertility. Depending on these signals, gene expression patterns can be changed temporally and quantitatively. In contrast to somatic cells, germ cells are highly regulated by the epigenome at three distinct stages that have far-reaching implications for embryogenesis and spermatogenesis [92]. These stages, in chronological order, include (1) global erasure of DNA methylation signals (including imprinting signals that result in parental expression of specific alleles based on paternal or maternal inheritance) in primordial germ cells (PGCs); (2) de novo re-methylation during spermatogenesis determining gene imprinting, as well as chromatin repacking where ~90% histones are replaced with protamine; and (3) post-fertilization embryonic demethylation (imprinting preserved).

In 2009, a hallmark study was published demonstrating differences in methylation and histone density in genes crucial for embryo development [93]. This aligns with several ART studies demonstrating poor embryogenesis in men with altered histone modifications or DNA methylation [94,95]. Additionally, altered DNA methylation of imprinted genes (specific genes where allele expression is based on paternal or maternal inheritance) has been demonstrated in patients with oligozoospermia [95–98]. However, these studies focused primarily on a few imprinting genes and have yet to be corroborated in large cohorts. Furthermore, these studies identify epigenetic signals but have yet to elucidate the mechanism by which spermatogenesis is negatively affected.

Li et al. sequenced over 650 infertility-related genes in men with NOA (n = 757) [99]. Using a gene-based (analysis of groups consisting of tens to hundreds of associated genes) WES, they found that, of the 24 genes spanning nine groups of genes displaying excessive non-silent variants associated with NOA, 10 were clustered in the epigenetic gene group. While this may signal the importance of epigenetic pathways in deciphering NOA genetic phenotypes, effect studies are needed to confirm the functional consequences of these epigenetic variants and the exact mechanism of action.

Beyond cataloging epigenetic errors, significant effort is required to understand the conditions and extent to which environmental factors activate specific epigenetic pathways. For instance, paternal age has been linked to increased global methylation rates in sperm [100]—the mechanisms of action and if these changes are biologically relevant. Current epigenetic studies predominantly use one-dimensional analyses to associate common epigenetic markers with infertility, such as the relationship between histone density and embryo development. However, successful spermatogenesis involves highly complex, multidimensional processes, including gene expression integrity, DNA repair, and temporal expression profiles. Therefore, a more sophisticated modeling approach, incorporating advanced tools like proteomics, whole-genome sequencing, and artificial intelligence, is essential to comprehend the full impact of epigenetic regulation on male infertility.

6. Emerging Results from Whole-Genome Sequencing Studies

Despite extensive workup, the etiology of primary testicular failure remains unknown in ~40% of patients with impaired spermatogenesis [101]. Next-generation sequencing (NGS) methods, WES, and whole-genome sequencing (WGS) are tools that can close this gap by identifying rare or clustering signals in the genome. In previous years, the price of sequencing (>USD 1000) and the cost to analyze and store the data have been prohibitive factors for the comprehensive implantation of WGS [102]. However, the cost continues to decrease dramatically, with one company claiming it can sequence the human genome for USD 100 [103].

Still, WES, in which only the genome's protein-coding regions are sequenced, has been the most utilized NGS in male infertility. Compared to WGS, it generates significantly less data, making finding variants easier and more susceptible to type II errors. It has been most successful when used for hypothesis-driven analysis, where specific genes or gene families are scrutinized for mutations based on supporting biological evidence (i.e., DNAH1 in *multiple morphological anomalies of the flagella (MMAF))* [104], and less likely to identify gene candidates when studying sporadic diseases in non-related patients. In a 2014 report by the FORGE (Finding of Rare Disease Genes) Canada Consortium, WES was only successful in identifying genes in 45% of sporadic cases and 43% of recessive diseases in non-consanguineous families.

WGS, where both coding and non-coding regions are sequenced, has several advantages over WES, as it generates a higher level of resolution [105], information on copy number variants (CNVs) [106,107], and epigenomic information [108]. The limited number of recent male factor infertility studies utilizing WGS that have been published are primarily case reports or studies with small cohorts [109–116]. These studies primarily employ hypothesis-driven analysis, often in consanguineous families, to overcome the signal of non-significant signals across the genome. However, two recent studies demonstrate the utility of WGS in cases of sporadic NOA.

In 2022, Malcher et al. performed WGS on 39 patients with NOA, in six of whom WES failed to find any genes of interest [117]. Novel gene candidates for NOA were identified in 29 of 39 patients (74%), including 5 of 6 that had previously undergone WES. Based on a priori knowledge from the infertility literature and MutationTaster2 (a structural protein-modeling system with a pathogenic prediction accuracy of 88%) [118], the group identified 8 novel variants in 4 genes (*TKTL1, IGSF1, ZFPM2/FOZ2, and VCX3A*) predicted to be highly associated with NOA, 20 genetic variants previously associated with NOA in the literature, and 13 novel genes not previously associated with infertility. The group validated findings for *ESX1*, an X-linked gene only expressed in adult male testis [119,120], in a follow-up study mapping the function of *ESX1* as a promoter of cell differentiation [121]. While these results have yet to be validated in extensive cohort studies, they present a robust framework for identifying targets with a high likelihood of contributing to male factor infertility, particularly in NOA.

7. Parental Subfertility and Reproductive Health in Male Offspring

To date, there is limited research on how parental infertility and ART may affect the reproductive health outcomes of male offspring. Semen quality has been studied to determine associations with birth outcomes. In parallel, the semen quality of males born from IVF or ICSI has also been studied. In addition to the study of semen parameters, the hormonal profiles of fathers have been studied to determine the subsequent hormonal profiles of sons born from IVF or ICSI. In the following section, we aim to describe the literature on parental subfertility and the history of fertility treatments' effect on male offspring (see Table 2).

Table 2. Summary table of studies investigating parental subfertility and reproductive health in male offspring.

Author, Year	Aim	Study Design	Exposed Group	Control Group	Outcome	Main Findings	Strengths	Weaknesses
Jensen, 2006	The association between maternal fertility treatment and reproductive health in offspring	Cross-sectional	Young men whose mothers had received fertility treatment N = 47	Young men conceived without fertility treatment N = 176	Semen quality Hormone assay	Men whose mothers had received fertility treatment had lower sperm concentration and count, smaller testicles, and fewer motile and morphologically normal spermatozoa compared to control group. No significant differences in hormone assay.	Semen analysis was conducted blindly and with an external quality program.	The article does not distinguish between different types of fertility treatment. No information on paternal fertility. One semen sample
Ramlau-Hansen, 2008	The association between parental subfertility and reproductive health in offspring	Cross-sectional	Sons of couples with a TTP > 7 months N = 67	Sons of couples with a TTP < 5 months N = 244	Semen quality Hormone assay	Parental TTP was inversely correlated to semen volume and total sperm count in sons.	Provides insight on hereditary factors.	One semen sample
Belva, 2016	Reproductive health of males conceived by ICSI for male factor infertility	Cohort study	Young men conceived by ICSI ("ICSI men") N = 54	Young men conceived spontaneously N = 57	Semen quality	ICSI men had lower median sperm concentrations, total sperm counts, and motile sperm count in comparison to the men who were spontaneously conceived Sperm concentration and motile count in fathers did not correlate with corresponding values in their sons	Differences persisted after adjustment for factors related to decreased semen quality. No self-reported data.	The control group were friends of the exposed group and recruited at college and university campuses, which might not be representative of the background population No information on paternal male factor infertility. One semen sample

Table 2. *Cont.*

Author, Year	Aim	Study Design	Exposed Group	Control Group	Outcome	Main Findings	Strengths	Weaknesses
Arendt, 2021	Reproductive health of men conceived by couples with a long time to pregnancy, with medically assisted reproduction or IVF/ICSI	Cohort study	Sons of couples with 1) TTP >12 months, 2) conceived by MAR or 3) by IVF/ICSI N = 245	Sons of couples with a TTP < 5 months N = 632	Semen quality Hormone assay	No associations between long TTP and semen quality on offspring. Sons conceived after IVF or ICSI had 30% higher estradiol levels	Detailed information on prenatal factors (TTP, type of MAR) and various confounders.	Low participation rate (19%) Not enough statistical power to distinguish between IVF or ICSI. No information on the cause of prolonged TTP. One semen sample
Catford, 2021	The reproductive health of men conceived by IVF/ICSI compared to men conceived naturally	Cohort study	Men conceived by IVF/ICSI N = 120	Men conceived without assisted reproductive technology N = 356	Semen quality Hormone assay	Mean total and progressive sperm motility were lower in men conceived with IVF/ICSI than the control group. Men conceived with IVF/ICSI had lower mean serum FSH and LH levels than control group. They had higher mean serum testosterone levels.	Men conceived without ART were unbiased.	Clinical significance of the findings in sperm motility and morphology is unclear. Recruitment of volunteers for studies requiring semen is very low and vulnerable to participation bias. One semen sample

8. Effects on Semen Quality

To our knowledge, the first study to address the semen quality of adult sons who were conceived after fertility treatment was a Danish cohort study conducted in 2007 [122]. The study included data from a sub-cohort of men who had provided a semen sample as part of a physical examination to determine their health status prior to recruitment for military service (n = 1925). Based on questionnaire data, the mothers were asked whether they had undergone fertility treatment to achieve pregnancy and, if yes, they had the chance to specify what form of treatment they had received. The open-ended answers were hereafter categorized into "receipt of hormone treatment" (n = 25) or "no receipt of treatment" (n = 22). The semen quality of sons who had been conceived by mothers who had undergone fertility treatment (n = 47) was compared to a random sample of men within the same cohort whose mothers had conceived without fertility treatment (n = 176). Multiple linear regressions were performed to adjust for potential confounders. The findings showed a significant decrease in sperm concentration, where young men of mothers who had not undergone fertility treatment had a median sperm concentration of 48 million/mL, whereas young men of mothers who had undergone fertility treatment had a median sperm concentration of 33 million/mL. The paper also reported a decrease in the median total sperm count when comparing young men who were conceived without fertility treatment (152 million) to young men who were conceived with fertility treatment (129 million). Moreover, the study found that fertility treatment was associated with fewer motile spermatozoa (mean percentage 65.5 (SD 13.0) in young men conceived without fertility treatment vs. 61.8 (SD 18.7) in young men conceived with fertility treatment) and morphologically normal spermatozoa (mean percentage 10.5 (SD 4.5) in young men conceived without fertility treatment vs. 8.6 (SD 5.2) in young men conceived with fertility treatment). However, the latter findings were not statistically significant. After adjustment for type of fertility treatment (receipt of hormone treatment vs. no receipt of treatment), they observed a more statistically significant decrease in sperm concentration (−58.7% 95%CI [−76.1; 28.5]) and count (−58.6% 95% CI [77.2; 24.7]) in the 25 young men whose mothers had received hormonal fertility treatment to conceive compared to the young men whose mothers had not received fertility treatment to conceive.

The first study to prospectively evaluate the semen quality of adult men who had been conceived by ICSI for male infertility was a Belgian cohort study from 2016 [123]. Data from this study are part of a larger initiative investigating the cardiometabolic profile and reproductive status among young ICSI adults who are now eligible for research, given that ICSI treatment was implemented in 1991. Thus, the men included in this study were conceived between 1992 and 1996 after the transfer of fresh cycle embryos through ICSI treatment using freshly ejaculated sperm. Of the 215 eligible ICSI families with male offspring, the follow-up data included 54 ICSI adult men whose semen quality was compared with the semen quality of spontaneously conceived peers within the same age group (n = 57). Men who were conceived by ICSI had a statistically significantly lower median sperm concentration (17.7 million/mL), lower median total motile count (31.9 million), and lower median total motile sperm count (12.7 million) compared to spontaneously conceived peers (37.0 million/mL, $p = 0.004$; 86.8 million, $p = 0.001$; and 38.6 million, $p = 0.0002$, respectively).

Both studies [124] suggest that fertility treatment (with or without hormonal treatment), as well as intracytoplasmic sperm injection (ICSI), is associated with lower sperm concentration, sperm count, and sperm motility. However, the studies fail to elucidate the etiology behind the decreased semen quality, specifically regarding whether it pertains to the reproductive technique employed or hereditary factors transmitted across generations. Further, the studies do not investigate whether the observed lower semen quality in men

conceived after assisted reproduction translates into lower fertility, as these outcomes were not available.

To help clarify the etiological uncertainty, a Danish cohort study from 2008 compared the semen quality of sons born to subfertile parents, who had not undergone fertility treatment but who had a prolonged "time to pregnancy" (TTP) categorized as 7–12 months (n = 33) or >1 year (n = 34), respectively, with the semen quality of sons born to fertile parents (n = 244) [123]. The results from this cohort study demonstrated that the adjusted sperm concentration was 22% lower in sons of parents whose TTP was >1 year (45 million/mL, 95%CI [28; 68]) compared to sons of parents whose TTP was 0–6 months (58 million/mL, 95%CI [45; 74]). However, this was not statistically significant (p = 0.15). The same trend was observed for the percentage of morphologically normal sperm, where this was 23% (p = 0.19) lower in sons of parents whose TTP was >1 year (4.0%, 95%CI [2.6; 5.9]) compared to sons of parents whose TTP was 0–6 months (5.2%, 95% CI [4.1; 6.5]). The adjusted total sperm count was 152 million (95% CI [84; 240]) and 210 million (95% CI [157; 274]) for men conceived by parents with TTP >1 year and 0–6 months, respectively. By comparing the results from these studies [123–125], there might be an association between parental in- and subfertility and the semen quality in the male offspring. These findings indicate that maternal and paternal hereditable factors may be partly, but not necessarily completely, responsible for the association of decreased semen analysis components.

In contrast to the above-mentioned findings, two recent studies found no or little association between parental subfertility or fertility treatment and semen quality in offspring [125,126]. More specifically, a study from 2021 investigated the semen quality in a sub-cohort of sons whose mothers had participated in the Danish National Birth Cohort (DNBC) while pregnant [127]. The DNBC was established between 1997–2007 and includes comprehensive questionnaire data on different parental exposures, as well as data regarding fertility treatment. The results were based on 1058 semen samples collected between 2017–2019. The parental fertility history was stratified into several groups, including couples who had conceived spontaneously but with a TTP > 12 months, couples who had conceived by intrauterine insemination (IUI) or ovulation induction, and couples who had conceived by IVF or ICSI. The results did not show any statistically significant differences in semen parameters in any of the mentioned groups compared to sons born by parents with a TTP < 5 months. The overall findings did not support an association between inherited infertility or that the semen quality in sons is affected by fertility treatment. Another cohort study from 2021 investigated the semen quality and reproductive hormones of young men conceived by couples who had undergone either IVF or ICSI at IVF fertility treatment centers in Melbourne between January 1994 and January 2000 (n = 120) [126]. Due to this, it was possible to divide study participants into two subgroups based on the parental infertility factor: severe paternal spermatogenic failure (STF) or obstruction. Semen quality was compared to young men aged 18–22 years who were born without assisted reproductive technology (ART) and found through the Western Australian Pregnancy Cohort Study (n = 356), where 2900 women were included in early pregnancy, resulting in 2868 (1454 males) children included in the cohort.

The study found that the mean total and progressive sperm motility were lower in men conceived with IVF or ICSI (55.3% (SD 11.6) and 44.7% (SD 12.9), respectively) compared to young men born without ART (60.6% (SD 16.9) and 53.9% (SD 18.6), respectively). However, the clinical relevance of this finding is unclear. They found no correlation between the semen parameters of young men conceived with ICSI and their fathers, and the investigation of semen quality in subgroups did not show any differences either, indicating that differences in semen quality may be related to the procedure rather than the underlying paternal STF.

9. Effects on Reproductive Hormonal Profile

In addition to the semen parameters reviewed above, few studies have investigated the association between hormonal profiles and parental infertility or subfertility. Likewise, the published studies have contradictory findings. The Danish study from 2007 analyzed the hormonal profiles of young men conceived with or without fertility treatment, respectively. One blood sample was drawn before 12 p.m., around the time of inclusion, and centrifuged and analyzed. The study observed a decrease in testosterone levels in men conceived with fertility treatment (21.7 nmol/L (SD 6.1)) compared to men whose mothers did not receive fertility treatment to conceive (23.1 nmol/l (SD 7.0)), which is a difference at −1.4 nmol/L (95%CI [−3.6; 0.8]). In accordance with this, they observed a lower free-androgen index in men whose mothers had received fertility treatment as well (84 (SD 37)) compared to the control group (86 (SD 32)). In terms of testosterone level and free-androgen index, this difference became less significant after adjusting for the time of blood sampling [127]. Contrary to this finding, the Danish cohort study from 2021 found a higher free-androgen index (15%, 95%CI [0; 32]), as well as 30% (95% CI [7; 57]) higher estradiol levels in men conceived by IVF or ICSI compared to men conceived spontaneously [123]. The study from 2008 compared the hormone levels in young men born by parents with a long TTP with the young men born by couples with a short TTP and found no differences between FSH, Inhibin B, and testosterone levels between the two groups [126]. The Australian cohort study from 2021 compared the reproductive profile of young men whose parents underwent IVF or ICSI to conceive with the young men whose parents did not receive ART and found lower mean serum FSH (3.3 IU/L, 95% CI [3.0; 3.7] vs. 4.2 IU/L, 95%CI [3.9; 4.4], respectively) and luteinizing hormone (LH) (3.9 IU/L, SD(1.4) vs. 11.0 IU/L, SD(3.6), respectively) in men conceived by IVF or ICSI, as well as higher mean serum testosterone levels (19.1 nmol/L, SD(5.3) vs. 16.8 nmol/L, SD(5.3), respectively) [125].

In summary, most of the reviewed studies regarding hormonal trends only collected one semen sample from the study participants [123,125,127]. This is a limitation, as it is well known that sperm quality varies over time in the same man [126]. It might be considered a strength that two of the included studies offered a second semen sample to the study participants. However, only one participant delivered a second semen sample in total in one of the studies [128]. For the other study, of the men conceived with IVF or ICSI, only those with an abnormal semen sample result were offered a second sample [124]. This means that both studies only used results from the first semen sample in their analysis.

Two of four studies found increasing testosterone levels in men conceived by fertility treatment or IVF/ICSI compared to young men who conceived spontaneously, whereas one of four found no changes in serum testosterone. In terms of FSH and free-androgen index, the results are more contradictory, where none of the studies included have identified a consistent trend. To this, the studies included in this article had included a relatively small number of men available for analysis, which results in high statistical uncertainty. Furthermore, it decreases the representability of the study population and increases the risk of selection bias. However, a common denominator is that the study participants are young men, which lowers the chance of them knowing their semen quality prior to study participation. All studies have included study participants using national cohorts, which minimizes selection bias.

While research has been completed to elucidate the associations regarding sperm quality or reproductive hormonal aberrations following birth from a parent(s) with infertility, the findings remain contradictory, and final conclusions cannot currently be drawn.

10. Conclusions

The genetic landscape of male factor infertility is complex. While several discoveries have been made, a full understanding of the various etiologies of male factor infertility from a genetic standpoint is still incomplete. Klinefelter Syndrome, genetic rearrangements and mutations, autosomal anomalies, and epigenetic factors have been described in the literature as contributing to male factor infertility. These discoveries have allowed men to be eligible for various work-up and treatment options, thus opening the opportunities for men to participate in ART and successful conception. Future research in genomic and exome sequencing will likely lead to additional genetic discoveries in the complex process of spermatogenesis.

Existing research on the impact of parental subfertility and ART on the reproductive health of male offspring, particularly semen quality and hormonal profiles, has yielded inconsistent findings. While some studies suggest a potential association between fertility treatments or subfertility and reduced semen parameters, others find no significant differences. Similarly, investigations into hormonal profiles have produced conflicting results, with no clear trends emerging across studies. Limitations such as small sample sizes, reliance on single semen samples, and potential selection bias contribute to the uncertainty. Further well-designed studies with larger cohorts and standardized methodologies are required to clarify these associations and determine their clinical significance.

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