The Clinical Management of Leukocytospermia in Male Infertility: A Narrative Review

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Abstract: A major global health concern, male infertility affects 8–12% of couples globally. Leukocytospermia is a complicated illness that is distinguished from other reasons causing male infertility by having high white blood cell counts in semen. The complex mechanisms behind leukocytospermia's effects on sperm function and fertility are examined in this review. Leukocytospermia induces oxidative stress and reactive oxygen species (ROS) that impair DNA integrity, mitochondrial function, cytoplasmic extrusion, and sperm quality overall. Leukocytospermia is exacerbated by non-infectious factors, such as substance abuse and varicocele, even though genital tract infections are a common cause. The usefulness and dependability of diagnostic techniques range from immunochemistry to direct counting. Although there is still disagreement on the most effective course of action, clinical-care techniques, such as antioxidant supplementation and antibiotic therapy, attempt to address underlying causes and reduce ROS-induced damage. Prospectively, the combination of artificial intelligence with the latest developments in artificial reproductive technologies presents opportunities for more precise diagnosis and customized treatments.

Keywords: leukocytospermia; male infertility; clinical management of male infertility; reactive oxygen species; oxidative stress

1. Introduction

Male Infertility

Infertility is a clinical condition defined as a patient being unsuccessful in establishing a clinical pregnancy after 12 months of regular unprotected sexual intercourse or because of a limitation in an individual's ability to conceive, either as an individual or with his/her partner [1]. Infertility is a significant global health issue, impacting an estimated 8–12% of couples in the reproductive age range [1]. More than 186 million individuals worldwide experience infertility, with a predominant number residing in developing nations [2]. The infertility issue has also been reported to be trending upwards, with studies showing an increase of 0.396% per year for females and 0.293% per year for males between the years of 1990 and 2017 [3]. Infertility is an issue that is most affected by the advanced age of the woman at the time of conception [4], but lifestyle and environmental factors may play a role. Another issue that should not be ignored is the role that male infertility plays in reducing the fertility of a couple.

Male infertility is the sole cause of couple infertility in 20–30% of cases and plays a contributing role in 50% of cases [5]. Male infertility is characterized by a man's incapacity to successfully impregnate a fertile female, persisting for a minimum duration of one year without protected intercourse [6]. The diagnosis of male infertility is largely based on the analysis of semen [7]. Sperm counts in Western populations have reportedly decreased on average by 1.4% per year with an overall decline of 52.4% between 1973 and 2011 [8].

The rising incidence of male infertility and reduced sperm counts can be attributed to a multitude of factors. The causes of this condition can be stratified into three groups that include: congenital, idiopathic, or acquired causes [9]. Congenital causes include inherited medical conditions that occur at or before birth and account for 15% of male infertility cases. Examples of congenital etiologies include bilateral absence of the vas deferens associated with the cystic fibrosis mutation, Kalman syndrome, and chromosomal abnormalities, such as Trisomy 21 [1,9]. The idiopathic causes of infertility in males are not discernable or cannot be attributed to female infertility, and account for 30–50% of cases [10]. Acquired causes of male infertility may include sexually transmitted problems or physical causes, with the most common cause being varicocele, which has a prevalence of 40% in male infertility patients [7,9]. Another area of interest is the role that leukocytospermia may play in decreasing sperm virility in male patients.

Leukocytospermia is a condition in which there are elevated white blood cell counts in the patient's sperm. It is controversial whether this condition truly plays a role in decreasing the fertility of men. However, studies have shown that a correlation exists between leukocytospermia and infertility. Studies done on White European Males, between the years 2010 and 2018, showed that 25% of the patients with infertility showed signs of leukocytospermia [11]. Additionally, studies comparing the sperm of infertile men with leukocytospermia against infertile men without leukocytospermia showed that the leukocytospermia patients had significantly lower total sperm motility [12]. The purpose of this review is to review the current research associated with leukocytospermia to better assess the role that this condition may play in causing male infertility.

2. Methods

Our narrative review collected sources through a general PubMed Database, Google Scholar, and Scopus Medline search. The discovered papers were then cross-referenced with citations. All references cited in the articles that were chosen were also reviewed and analyzed. The authors decided to present the review's findings narratively considering the volume of material that has been published on the topic as a whole and each of the active ingredients in particular. This paper does not provide a systematic or meta-analytical comparison of varied outcomes in measures, population, and methods.

The research strategy included the following keywords: "leukocytospermia", "leukocytes", "leukocyte role in infertility", "reactive oxygen species", "oxidative stress", "genital tract infections", "risk factors", "diagnosis methods", "treatment options", "future studies" accompanied by "male infertility", "sperm morphology", "seminal quality", "azoospermia", and "inability to conceive." Only papers in the English language were included. Randomized-control trials and non-randomized trials were included in the literature review due to the paucity of information available. Moreover, retrospective cohort studies, case-control studies, cross-sectional studies, and prospective cohort studies were also included. We excluded the use of case reports and case series.

2.1. Defining Leukocytospermia

The World Health Organization defines leukocytospermia as a white blood cell concentration of 1×10^6 /mL in patients' semen [13]. While a small number of white blood cells in a semen sample is considered normal, elevated levels may be caused by some underlying condition [13]. Within a sperm sample, granulocytes constitute the highest proportion of white blood cells (50–60%), followed by macrophages (20–30%), and, subsequently, T-lymphocytes (2–5%) [14]. In leukocytospermia, the elevated concentration of white blood cells is generally considered to be due to some form of infection or inflammation of the male genitourinary tract or sex glands [15]. While the infection of the genitourinary tract is a cause of leukocytospermia, several other conditions can lead to elevated white blood cell counts [16]. Noninfectious causes include autoimmune conditions, drugs, alcohol, the presence of varicocele, and environmental exposures [15,17].

2.2. Leukocytospermia Effect on Male Infertility

There are several proposed mechanisms for how leukocytospermia may affect fertility in men. One of the leading theories of how leukocytospermia may play a role in affecting the fertility of sperm is through the production and release of reactive oxygen species (ROS). Phagocytic leukocytes, such as neutrophils and monocytes, employ a process known as respiratory burst as an immune defense against pathogens. When neutrophils encounter a pathogen or receive signals from other immune cells, a respiratory burst is initiated with the activation of the NADPH oxidase enzyme [18]. This enzyme is responsible for reducing molecular oxygen to a superoxide anion (O_2^-), which is a ROS [18]. Superoxide anions can undergo spontaneous or enzymatic dismutation to form the ROS and hydrogen peroxide (H_2O_2), which can be processed by myeloperoxidase (MPO) to become hypochlorous acid [18]. These ROSs play a crucial role in killing pathogens that have been phagocytosed by leukocytes. However, if activated leukocyte concentrations are abnormally high, excessive ROS production can contribute to tissue damage and cause inflammation in certain pathological conditions [18]. When ROS reaches a level that overwhelms the body's antioxidant defense mechanisms, oxidative stress occurs [19]. The release of these ROSs will target the unsaturated fatty acid-rich plasma membrane found in sperm due to the powerful initiation of lipid peroxidation [19]. Patients with higher levels of antioxidants were seen to be able to tolerate higher levels of ROS-producing WBC without suffering sperm damage, while men with lower levels of protective agents may show signs of sperm damage at leukocyte levels as low as 0.6×10^6/mL [20]. Studies done to determine the levels of WBCs associated with oxidative stress in sperm showed that any levels of seminal leukocytes were associated with oxidate damage [21]. Additionally, increasing levels of seminal leukocytes were associated with increasing levels of oxidative stress, even when levels were less than 1×10^6 WBC/mL [21]. This can be explained by the variable ROS scavenger and antioxidant ability of seminal fluid against ROS generated by seminal leukocytes, with ROS scavenger ranges seen from 10% to 100% [20]. Furthermore, a direct link was found between oxidative stress and decreased sperm concentration, motility, and morphology, reinforcing the significant role of ROS in compromising sperm functionality [21].

In leukocytospermia, peroxidase-positive leukocytes are considered the major source of ROS in semen but are not the only source of ROS [22]. A proposed mechanism is the ability of leukocytes to interact with spermatozoa, causing direct or indirect stimulation, which causes an enhanced production of ROS from spermatozoa [22]. The controlled production of free radicals in spermatocytes is essential for the normal physiological function of sperm to complete capacitation and fertilization [23,24]. The cytoplasm of spermatocytes has been seen to contain several enzymes essential in ROS production such as glucose-6-phosphate dehydrogenase and NADPH oxidase-like enzymes [25]. Sperm suspensions that had been isolated from leukocytes or where leukocytes were of an undetectable level still had measurable production levels of ROS [25,26]. The research underscores the significance of ROS production by spermatocytes, as evidenced by studies indicating that women who achieved successful pregnancy through in vitro fertilization (IVF) exhibited notably elevated ROS levels in follicular fluid compared to those who did not conceive [24]. However, high levels of ROS production in male ejaculate samples are linked to poor sperm quality, which shows the importance of producing moderate levels of ROSs for optimal fertility [26].

In leukocytospermia, leukocytes may play a role in enhancing or disrupting the physiological production of ROSs in spermatocytes [22]. Studies comparing pure sperm samples from patients with leukocytospermia and patients without saw a significantly higher level of ROS production from the sample of the patients with leukocytospermia [22]. Additionally, seminal leukocyte concentrations were significantly correlated with increased levels of ROS production by spermatozoa through spontaneous mechanisms and stimulation by phorbol 12-myristate 13-acetate (PMA), a known ROS-production stimulant in spermatozoa [22]. While how this process occurs is unclear, a proposed hypothesis of how seminal leukocytes stimulate spermatozoa is through direct sperm–leukocyte contact or mediated by signal particles released from leukocytes [22]. Another possible mechanism for elevated

ROS generation in pure sperm suspensions from patients with leukocytospermia may be attributed to the increased amount of morphologically abnormal spermatozoa, as compared to non-leukocytospermic samples. Morphologically abnormal spermatozoa, particularly those that retain their cytoplasm, have demonstrated a propensity for producing elevated ROS levels [27].

Spermatozoa possess plasma membranes abundant in polyunsaturated fatty acids, while their cytoplasm contains minimal levels of ROS-scavenging enzymes, which makes them highly vulnerable to ROS-induced damage [28,29]. Additionally, the antioxidant enzymes within spermatozoa are unable to protect the plasma membrane from oxidative damage, making the acrosome and tail vulnerable to ROSs [30]. The limited ability of intra-cellular spermatozoa enzymes to protect against oxidative stress creates a dependence on seminal plasma for defense against ROSs [30]. In patients diagnosed with leukocytospermia, ROS has been seen to decrease the functional integrity of sperm through multiple mechanisms that include decreasing the mitochondrial activity, altering the binding between sperm and egg, disrupting cytoplasmic extrusion, and damaging spermatic DNA [31]. The decrease in sperm motility in oxidative stressed conditions is caused by damage to the mitochondria present in sperm [31]. Mitochondria located in the sperm midpiece are responsible for constantly producing ATP which is necessary for sperm motility. An overabundance of ROS will modify mitochondrial phospholipid membranes, disrupting the membrane selectivity, and inhibiting mitochondrial ATP synthesis [31]. The decrease in ATP production is due to the interruption of the oxidative phosphorylation pathway, which requires the mitochondrial membrane to exhibit selective permeability to maintain an electrolytic gradient across the inner and outer membranes. The electron leakage from the spermatic mitochondrial electron transport chain is considered to be the major source of ROS generation in defective sperm [32]. The loss of the membrane potential in mitochondria and, therefore, a decrease in sperm motility parameters have been associated with a decrease in the fertility of sperm [33].

Spermiogenesis is the final stage in spermatogenesis and is the process by which spermatogonia develops into mature spermatozoa. During the maturation phase of spermiogenesis, the spermatid elongates by shedding excess cytoplasm within the membrane [34]. An impairment in spermatogenesis results in the malfunction of cytoplasmic extrusion mechanisms, leading to the release of sperm cells from the germinal epithelium with an excess of residual cytoplasm [35]. The spermatozoans released with a surplus of cytoplasm are considered to be immature and, therefore, functionally defective [36]. Elevated levels of ROSs, as seen in cases of leukocytospermia, limit spermatozoa's ability to remove surplus cytoplasm from the cell. This inhibition occurs through additional electron transport pathways within the cell's membrane, as well as the presence of unfamiliar oxidases or oxidoreductases that encourage xenobiotic production [37]. Another possible mechanism by which the extrusion of cytoplasm is altered in leukocytospermia is due to damaged Sertoli cells that are essential for sperm maturation [38]. The retention of cytoplasmic droplets in sperm has been negatively correlated with sperm motility and fertility [36].

DNA damage in spermatocytes can be facilitated by the overproduction of ROSs from seminal leukocytes. When artificially produced ROSs were introduced to sperm samples, it resulted in a significant increase in multiple forms of DNA damage, which included the modification of all bases, production of base-free sites, deletions, frameshifts, DNA cross-links, and chromosomal rearrangements [39]. A 25% increase in ROS levels was associated with a 10% increase in DNA fragmentations, with a positive association found between leukocytes, ROSs, and DNA fragmentation levels [40]. ROSs damage DNA through the production of by-products that bind to DNA and cause lipid degradation through the oxidation of DNA bases such as guanine, and direct interaction with DNA, leading to non-specific single- and double-strand breaks [31,35]. DNA damage in spermatozoa is seen to be negatively correlated with successful blastocyte development after fertilization has occurred, with methods such as IVF [41]. Additionally, sperm that was found to have

a higher percentage of DNA double-stranded breaks was significantly increased in men whose wives suffered recurrent pregnancy loss compared to donor sperm [42,43].

2.3. Etiologies and Causes

The etiology of patients with leukocytospermia may be divided into those with and without a genital tract infection. Examination of the semen from infertile patients with asymptomatic leukocytospermia revealed the predominance of gram-positive and gram-negative bacteria, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Streptococcus agalactiae*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* [44–46]. Genital tract infections may affect the urethra, epididymis, testicles, or prostate [19]. Infections of the urethra are generally due to sexually transmitted organisms, most commonly due to *Chlamydia trachomatis*, *Ureaplasma urealticum*, and *Neisseria gonorrhea* [47]. While there is not a significant amount of literature showing the correlation between urethritis and leukocytospermia, studies have shown that past *N. gonorrhea* infections are correlated with elevated white blood cell counts in semen [48,49].

Similar to infectious urethritis, infectious epididymitis in sexually active men aged <35 years is most commonly due to *C. trachomatis* or *N. gonorrhea* [48]. Additionally, sexually transmitted epididymitis is usually accompanied by urethritis [48]. In men >35 years of age, the etiology of epididymitis is mainly due to non-sexually transmitted urinary tract infections caused by Gram-negative enteric organisms, such as *Escherichia coli* [48,49]. Infection of the epididymis is normally accompanied by a co-infection of the testicles, termed 'epididymal-orchitis' [48]. In a study of 400,000 specimens from patients with testicular pathologies, only 0.42% demonstrated isolated orchitis [50]. Research on retrograde infections in rats and mice, where live *E. coli* is administered directly into the seminiferous tubules or through the epididymis or proximal vas deferens, triggers inflammation and the infiltration of leukocytes, notably neutrophils, into the seminiferous epithelium. These infections led to long-term damage of the epithelium and also showed markedly decreased sperm production [51,52].

Infection of the prostate, infectious prostatitis, can present in several forms, including acute prostatitis, chronic prostatitis, and often as a complication of the urinary tract and sexually transmitted infection. Pathogens commonly associated with acute prostatitis include *E. coli*, Enterococcus, and Pseudomonas. Chronic prostatitis in sexually active men is commonly attributed to *C. trachomatis* or *N. gonorrhea* [53]. Chronic prostatitis has a strong correlation with leukocytospermia and studies have established links between the presence of chronic pancreatitis and cytokines and proinflammatory markers associated with T-cell and granulocyte proliferation [54]. In a study consisting of 102 men who met the criteria of leukocytospermia, 68% (70 patients) displayed at least one symptom of prostatitis. Treatment of the underlying prostatitis with antibiotics alone showed resolution of leukocytospermia in 40% of the patients after one month. The addition of frequent ejaculation, to assist in clearing the prostatic gland, along with antibiotics caused leukocytospermia to resolve in 68% of the patients [55]. When comparing chronic prostatitis patients with leukocytospermia to those without leukocytospermia, it was found that ROS levels were significantly higher in prostatitis patients with leukocytospermia, which emphasizes the relevance of elevated leukocytes in chronic prostatitis [56].

While infections of the genitourinary tract play a role in causing leukocytospermia, 80% of leukospermic infertile males show no microbial sign of infection in the sperm analysis [14]. A noninfectious etiology of leukocytospermia is the use of substances, such as cigarette smoking and marijuana and alcohol consumers. After controlling for a history of sexually transmitted diseases, it was seen that the consumption of these substances was associated with an increase in seminal leukocytes [17]. The elevated levels of leukocytes can be attributed to the inflammation caused by the toxic effects these substances have on the genitourinary tract.

There is a well-established association between smoking and leukocytospermia, with a positive correlation established with increasing degrees of smoking [57]. In cigarette smok-

ers, the presence of inhaled radioactive particles has been identified in the testes, which may lead to damage and inflammation, creating an increased leukocyte response [17]. Tobacco metabolites trigger inflammatory responses and stimulate the infiltration of leukocytes into seminal plasma [58]. When examining the ejaculate from smokers and comparing them to those of non-smokers, it was seen that there was a greater percentage of leukocytospermic ejaculates and a higher level of round cells in smokers [59]. Other substances, such as Cannabinoids and chronic alcohol use, are believed to have a direct toxic effect on the germinal epithelium of the testis [17]. In infertile chronic alcoholics, testicular biopsies revealed thickening, hyalinosis, and sclerosis of the lamina propria, along with the presence of mast cells in the interstitial tissue [17,60].

Varicocele is another pathology that may be associated with leukocytospermia in male patients. A varicocele is an abnormal dilation or tortuosity of the pampiniform plexus in the scrotum, and it is reported to be present in 15% of the general male population [61]. By examining the leukocyte subpopulation in semen samples from healthy controls and varicocele patients, it was found that varicocele patients had significantly higher numbers of CD4+ helper T lymphocytes [62]. The elevated levels of CD4+ helper T lymphocytes may be due to the inflammation that is associated with varicocele. When analyzing the patients with varicocele, it was seen that they had a significantly higher mean platelet volume (MPV), a suspected marker for inflammation, when compared to control patients who did not have varicocele [63,64].

An additional acquired condition associated with leukocytospermia is spinal cord injuries. Approximately 60% to 70% of men with SCI are estimated to exhibit elevated leukocyte levels in their ejaculate, leading to adverse effects on sperm motility, viability, morphology, and an escalation in sperm DNA damage [65,66]. In retrograde ejaculates collected from men with spinal cord injuries, they were found to have increased numbers of leukocytes, often secondary to genital tract infections [67]. When comparing urinary tract infections in spinal cord injury patients, it was found that they exhibited significantly higher levels of macrophages and neutrophils compared to control patients with urinary tract infections [65,66].

3. Diagnosing Leukocytospermia

Various methods exist for diagnosing leukocytospermia in patients, each with its advantages. These methods include direct counting of round cells, immunochemistry, seminal granulocyte elastase test, and peroxide staining [19]. Directly counting round cells in a semen sample, the recommended diagnosis process by the American Urology Association (AUA), is a cost-effective procedure, but it is not reliable for diagnosing leukocytospermia due to the difficulty in distinguishing white blood cells from other cells under a microscope [68,69]. This process is completed by using a phase-contrast microscope with a green filter to examine semen samples that have been loaded onto a fixed cell chamber [70]. Round cells seen under microscopy in semen can be either leukocytes, immature germ cells, large anucleate residual cytoplasm, epithelial cells, or *Trichomonas vaginalis* [70]. If a concentration of $\geq 1.0 \times 10^6$/mL of round cells is found in a semen sample, then a test specifically for leukocytes is indicated [70].

Immunochemistry using monoclonal antibodies against the common leukocyte antigens CD45 or CD53 is highly precise and considered the gold standard for diagnosis [68,70,71]. This process can detect granulocytes, lymphocytes, and macrophages from a single semen sample [48]. However, despite the advantages it offers, its practicality in routine medical practice is hindered by the lack of standardization in staining methods and exact monoclonal antibodies to be used [68,70,71]. Additionally, the associated time and cost to complete immunochemistry analysis do not make it as practical compared to the other options [68,71]. Both the American Society for Reproductive Medicine (ASRM) and the AUA recommend immunochemistry as a confirmatory diagnostic test for leukocytospermia [69].

The seminal granulocyte elastase test is used to measure the seminal elastase-inhibitor complex (Ela/α1-PI) levels in seminal plasma [70,72]. Because elastase is a protease released

from activated PMN leukocytes during phagocytosis or disintegration of granulocytes, there is a strong association between elastase and leukocytes [72,73]. The elastase test is done through an immunoassay which detects Ela/α1-PI in seminal fluid, and, if measured at a cut-off level of greater or equal to 230 μg/L, it may be a useful indicator of a genital tract infection [74]. Additionally, the occurrence of elevated seminal Ela/α1-PI levels in infertile males is significantly higher than that seen in fertile males [74]. The levels of granulocyte elastase from semen samples can provide information on the number of granulocytes present in the semen and their inflammatory activation [75]. However, granulocyte elastase enzyme immunoassays are expensive, and routine assessment of PMN elastase in semen and/or serum samples offers limited value as a standalone measure for screening subclinical infection/inflammation in males undergoing infertility investigation [75].

As an alternative, the World Health Organization (WHO) and the European Association of Urology (EAU) suggest peroxidase staining as the preferred method [68,69]. Peroxidases are enzymes that break down H_2O_2 and release O_2, which oxidizes a benzidine derivative in the staining solution, forming a brown precipitate for visualization under light microscopy. Unlike immunohistological staining, peroxidase staining only identifies cells rich in peroxidase, such as polymorphonuclear (PMN) granulocytes and macrophages, which are the predominant types of white blood cells in semen. However, T lymphocytes are not detectable with this staining method; however, they only make up 2–5% of the leukocyte population in semen [14,71]. An additional concern with peroxide staining is the significantly poor performance when compared to immunochemistry. Studies done to determine the prevalence of leukocytospermia in 46 patients detected the condition in 19.6% of patients. However, when the screening was repeated on the same patients using immunochemistry on specific monoclonal antibodies found on leukocytes, it was seen that the prevalence had increased to 41.3% [71].

4. Clinical Management of Leukocytospermia

Debate about whether leukocytospermia is a condition that needs to be treated continues, and if so, what would be the most appropriate treatment for this condition. Organizations such as the AUA, ASRM, and Canadian Urological Association (CUA) have no recommended guidelines for treating leukocytospermia in infertile male patients [76]. Treatment attempts for leukocytospermia focus on addressing the underlying cause of the elevated leukocyte counts or preventing damage that may occur due to the release of ROSs from leukocytes. The EAU guideline recommends the use of antibiotics to treat underlying infections to improve the overall quality of the sperm [69]. However, the use of antibiotics has shown no evidence of reducing the associated inflammatory reaction, and it is still controversial if they play any beneficial role in improving the likelihood of conception [69,77]. Some studies have shown an increase in pregnancy rates with antibiotics-focused therapies [78]. In recent reviews, it was noted that the use of antibiotics showed significant improvement in sperm parameters, resolution of leukocytospermia, and a decrease in the number of seminal bacteria when compared to the untreated groups [77]. However, studies determining the benefit of antimicrobials in pregnancy rates only showed a significant improvement in one out of four trials [79]. Additionally, animal studies studying the effects of antibiotics found that they can arrest spermatogenesis and disrupt sperm parameters, emphasizing caution in the dosing and duration of these drugs [80,81].

Other medications that have been used to treat leukocytospermia include antioxidants, antihistamines, corticosteroids, and non-steroidal anti-inflammatories (NSAIDs). Antioxidant therapy includes vitamin E, coenzyme Q10, and N-acetyl-L-cysteine. Studies using these substances have shown significantly reduced ROSs in leukocytospermia samples and possible improvement in the function of impaired spermatocytes [82–84]. Additional research into the use of the known antioxidant, Quercetin, has shown the further potential benefits that antioxidant therapy may have for leukocytospermia patients [85]. Quercetin is a dietary-derived bioflavonoid. When used in the treatment of infertility patients, it was seen to act as a scavenger for ROSs, and spermatozoa exhibited lower levels of H_2O_2 [85,86].

The use of low concentrations of Quercetin in leukocytospermia patients was shown to have protective effects on sperm from oxidative damage, specifically seen to be protective of sperm mitochondrial DNA and, therefore, sperm motility [85].

After 4 weeks of using the medication ketotifen, an antihistamine, studies found that it was able to moderately improve sperm motility, the percentage of morphologically normal sperm, and a significant reduction in leukocytes. However, the mechanism of how ketotifen had this effect is still unclear [87]. The use of corticosteroids, such as prednisone, for one month at varying doses showed no significant reduction in leukocyte counts. However, it was seen to improve sperm counts and the percentage of forward motility in sperm, but only in oligozoospermia patients [88]. Rofecoxib and valdecoxib are two NSAIDs that are selective Cox-2 inhibitors that have been used as therapeutic agents in leukocytospermia patients. The results of studies showed that Rofecoxib treatment improved sperm motility and morphology, while valdecoxib was only beneficial in improving sperm counts [69]. While there are studies that indicate a possible therapeutic benefit of these substances on male infertility, there has not been enough comprehensive research done to identify a truly effective treatment option in leukocytospermia [69,77]. A summary of clinical interventions in leukocytospermia is outlined in Table 1.

Table 1. Summary of studies that clinically evaluate leukocytospermia.

Study	Year	Sample Size (*n*)	Patient Characteristics	Study Design	Intervention	Study Results
Hamada et al. [78]	2011	34	Patients with diagnosed level of leukocytopsermia who were not previously treated	Retrospective study	Doxycycline	Treatment of low-level leukocytospermia with doxycycline did not significantly change semen parameters but led to a higher resolution rate (56%) compared to historical controls (25%), with a significantly greater natural pregnancy rate (47% vs. 20%) and an odds ratio for pregnancy outcome of 3.7 (95% CI 1.1–11.7; p = 0.04).
Krisp et al. [81]	2003	36	Idiopathic Infertility	Uncontrolled clinical trial	250 mg levofloxacin PO QD for 10 days	Decrease in leucocyte count of 45.8 ± 72.2% compared with a decrease of only 3 ± 109.2% in the untreated group was observed.
Oeda et al. [82]	1997	n/a (semen samples)	Semen samples	Laboratory Study	N-acetyl-L-cysteine (NAG)	Reactive Oxygen Species levels decreased significantly after 20 min incubation with NAG
Oliva and Multigner [87]	2006	55	Idiopathic Infertility	Uncontrolled clinical trial	Ketotifen 1 mg PO BID for 12 weeks	Significant reduction in leukocyte concentration by 4 weeks
Milardi et al. [88]	2017	90	Oligozoospermia with accessory gland inflammation on genital ultrasound	Randomized, uncontrolled clinical trial	Prednisone 5 mg, 12.5 mg, or 25 mg PO QD	Improved sperm count and percent with forward motility but no significant differences within leukocytospermia within the groups
Lackner et al. [89]	2006	56	Abacterial Leukocytospermia	Prospective nonrandomized study	Valdecoxib 20 mg PO QD for 14 days	Significant reduction in leukocyte concentration after treatment
Gambera et al. [83]	2007	47	Idiopathic infertility	Uncontrolled clinical trial	Rofecoxib 25 mg PO QD for 30 days	Significant reduction in leukocyte concentration after 30 days of treatment; Pregnancy rate of 15.8%

Abbreviations: BID: twice a day, PO: per os, QD: every day.

5. Future Directions

With the growing number of leukocytospermia patients and the increasing number of male infertility patients, there is a growing concern about finding a truly curative option for leukocytospermia. The advent of artificial intelligence and artificial reproductive technologies (ARTs) presents an opportunity. Over the last 25 years, computer-assisted semen analysis (CASA) has emerged as a viable alternative to traditional semen analysis, offering more dependable and objective outcomes [90,91]. While CASA is able to analyze round cells, it cannot provide accurate information on the white blood counts in sperm samples; it is currently limited to analyzing the parameters of sperm, such as motility, concentration, and morphology [92]. A software designed to analyze sperm through dark-field microscopy, Software such as SpermQ (v0.1.7) can be used as a better diagnostic tool for researchers evaluating leukocytospermia [92]. Additionally, men with medical issues that could affect their future fertility are frequently advised to have their sperm cryopreserved. This offers a potential avenue for combating leukocytospermia from progressing and provides patients with an alternative solution. Future studies are needed on the impact of cryopreservation on fertility rates in patients with leukocytospermia [76].

6. Conclusions

In conclusion, the issue of male infertility, which impacts 8–12% of couples globally, highlights the need to comprehend diseases like leukocytospermia. This study clarifies the complex pathways by which male fertility is impacted by leukocytospermia, a condition marked by high white blood cell counts in semen. Leukocytospermia adversely impacts sperm function, mitochondrial activity, cytoplasmic extrusion, DNA integrity, and, ultimately, reproductive potential through the formation of reactive oxygen species (ROS) and consequent oxidative stress. Leukocytospermia has noninfectious causes as well, such as substance abuse and varicocele, even though genital tract infections are a significant etiology. Identification can be achieved by a variety of diagnostic techniques, from immunochemistry to direct counting; however, their applicability and dependability vary. Clinical-care methods, including antioxidant supplementation and antibiotic therapy, attempt to address underlying causes and the reduce damage caused by ROS, although agreement on the best ways to treat the condition is still elusive. Future developments in artificial reproductive technologies and artificial intelligence present exciting opportunities for more precise diagnostics and customized treatments.

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