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A Scoping Review of the Association between Hemoglobinopathies and Male Infertility

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Abstract

Worldwide, infertility is a prevalent problem that poses a threat to couples, either the male or female partner, or both spouses, may be the cause of infertility. Numerous elements about the patient's general health or way of life may be to blame. Systemic or gonadal dysfunction may be the cause of the patient's health issues. Hematological factors may be one of the systemic reasons. Thalassemia major (TM) and sickle cell disease (SCD) are the two most prevalent hemoglobinopathies that are suspected to be the cause of infertility, particularly male infertility. Through pathophysiological changes, these two hemoglobinopathies result in male infertility. In particular, they change red blood cells' (RBCs') capacity to carry oxygen, resulting in tissue hypoxia that impacts spermatogenesis and the body's natural process of producing new cells, ultimately leading to infertility. Semen analyses and other systemic blood testing can be used to investigate male infertility. Both hemoglobinopathies can be helped by blood transfusions, which can then alleviate male infertility. This paper aims to explore the relationship between hemoglobinopathies (SCD and TM) and their role in contributing to male infertility, in addition to the role of blood transfusions in addressing male infertility by correcting the root cause.

Keywords: Hemoglobinopathies, Male Infertility, Thalassemia Major (TM), Sickle Cell Disease (SCD), Blood Transfusions.

INTRODUCTION

According to the World Health Organization (WHO), infertility is defined as the inability to achieve a successful pregnancy after at least 12 months of regular unprotected sexual intercourse [1]. Infertility extends beyond being only a medical issue; instead, it is a multidisciplinary condition that carries emotional and other social perspectives [2]. Infertility has historically been a stigmatized issue, with blame usually being placed on the woman; however, recent studies have started to explore the causes of infertility related to the male partner [3]. Infertility can also be divided into two categories: primary infertility, which is the inability to conceive at all, and secondary infertility, which is the termination of a successful pregnancy following a prior successful one [4]. It is estimated that between 50 and 80 million cases of infertility occur globally, affecting roughly 10-15% of couples [5]. Approximately 50% of the reasons can be attributed to female partners, 20% to 30% to male partners, and 20% to 30% to causes involving both genders [5]. Numerous causes, including genetic, congenital, acquired, and some idiopathic, can contribute to male infertility [6]. Spermatogenesis quality, which is essential to preserving a man's fertility, might be impacted by the previously stated causes. Spermatogenesis can be impeded by a variety of conditions, such as varicoceles, pituitary diseases, or even congenital anomalies in the male reproductive system that affect the process of sperm transport [7]. It is important to note that several diagnostic tests, including semen analysis and general hematological blood tests, should be performed to detect infertility in men. These tests should look at several aspects of the patient's overall health [8]. The number, shape, and motility of the sperm as well as the patient's semen's viability for assisting his female partner in becoming pregnant are all important aspects of semen analysis [9]. In order to prevent missing hemoglobinopathies like sickle cell disease (SCD) or thalassemia major (TM), blood serum analyses are also essential when looking into male infertility [10]. For example, one study found that moderate to severe hypogonadism and at least one anomaly in a semen analysis parameter are present in 72–100% of SCD

patients [11]. Furthermore, a 2017 study found that 40–80% of TM patients have hypogonadism, which can either cause or worsen male infertility [12]. The effect of hemoglobinopathies, their role in male infertility, and the changes in sexual function parameters before and following blood transfusions will be the main topics of this study.

METHODOLOGY

A literature search was conducted in the Google Scholar, Web of Science, MDPI, and PubMed databases utilizing free text phrases to ensure a comprehensive search approach. "Male infertility," "Hemoglobinopathies," "Sickle Cell Disease," "Thalassemia major," "Semen Analysis," and "Blood transfusion" were among the search terms used. Terms used in free text and only human research were included in the search strategy. As long as the document was entire and not just an abstract piece, the search was not limited by language or time.

Inclusion & Exclusion Criteria

Studies that contained information regarding the pathophysiology or available treatments for the disorders were included if they were related to the primary keywords listed above. Research publications that were (1) incomplete or simply abstracted, (2) published in a different language, or (3) used the same sample in more than one study were not included in our review. Only the article with the earlier publication date was considered if the same sample was utilized in multiple studies.

Outcomes

Our primary outcome in this scoping review is to outline the pathophysiological principles that cause the sequelae of infertility in male partners who are affected by hemoglobinopathies. In this study, we focused only on two hemoglobinopathies, which were Sickle Cell Disease (SCD) and Thalassemia Major (TM). We also looked at the changes within the semen analysis parameters before and after receiving blood transfusions and how could it be promising for future research. We utilized data from 2 published papers that compared the differences in semen analysis before and after blood transfusion. There were a total of 25 patients with SCD and 15 patients with TM which were included.

RESULTS

It is crucial to identify how patients who are affected with SCD and TM will benefit after being transfused with blood and how the semen analysis parameters improved pre and post-blood transfusions. It is important to recall that male patients with SCD and TM are affected by having reduced sperm quality parameters within the semen analysis, in addition to decreased serum levels of reproductive hormones [13–15]. According to one study, patients who were affected with SCD, have shown a clear improvement within 7 days after packed red cell transfusion [16]. It compared two types of RBC transfusion, either as SCD exchange (where the patient's blood was exchanged with new blood) or SCD top-up (whereby two packed RBC units were added with IV access to the patient's blood), and SCD total was an average of both transfusion methods. The data were then compared within the table with all measured parameters and 1 resembled "before transfusion", whereas 2 resembled "after transfusion". The transfusion has improved the hematological analysis, reflected by the positive change in the levels of hemoglobin [16]. Serum Hb levels increased from roughly 8.5 g/dL to 10.5 g/dL [16]. Additionally, sperm motility, morphology, and count all improved about the improvement shown in the semen analytical parameters [16]. The improvement was noticeable when the motility increased from 29.3% to 67.4% and the sperm count increased sharply from 87.4 million/ml to 146 million/ml [16]. Furthermore, the levels of testosterone, FSH, and LH in the serum improved [16]. In terms of numbers, the levels of LH went from 4.4 U/L to 5.7 U/L, FSH went from 5.4 U/L to 6.6 U/L, and testosterone went from 12.3 nmol/L to 14.2 nmol/L [16]. These hormones are essential for the health and quality of the existing sperm at every stage of spermatogenesis. Furthermore, these hormones are necessary to accelerate the last phases of sperm development [17]. The fact that blood transfusions would enhance tissue oxygenation by boosting blood flow in the reproductive tract microcirculation could account for all of these beneficial spermatozoa alterations [16]. A sufficient and efficient blood transfusion would also slow down the progress of ineffective erythropoiesis by lowering iron toxicity and assisting in the regulation of ideal iron levels [16-18]. It's important to remember that iron keeps the semen intact even after ejaculation by supporting the sperm cells within it [18]. Regarding TM patients, the outcomes are nearly identical. One study that examined the effects of transfusion on various semen analysis parameters found that the effects are nearly the same, demonstrating the same degrees of improvement in semen analyses and the increase of important reproductive hormones in the serum [19]. Sperm motility increased from 20.6% to 79.7%, and sperm counts rose from 57.8 million to 166 million/mL [19]. Testosterone rose from 8.7 g/dL to 11.1 g/dL and Hb levels rose from between 16.5 and 20 nmol/L [19].

DISCUSSION

It is critical to comprehend the consensus that this paper focused exclusively on these two hemoglobinopathies. This can be explained by the fact that, despite the possibility of other hemoglobinopathies, the two types chosen for this paper—SCD and TM—remain the most prevalent in terms of prevalence and clinical significance [20]. Knowing the pathogenesis of each is essential. Anomalies in the Beta globin gene on chromosome 11 (11p 15.15) cause both SCD and TM [21]. SCD is caused by a single mutation that replaces an amino acid in the sixth position, whereas TM is caused by a variety of mutations that lead to a quantitative

deficiency of structurally viable beta-globin genes [21]. SCD is caused by a substitution in the sixth position of the beta-globin gene, which occurs when hemoglobin S (sickle hemoglobin) is deoxygenated. This substitution involves the substitution of valine for glutamic acid [23]. This causes these hydrophobic molecules to aggregate and interact with one another, which in turn causes polymerization into bigger molecules that can block blood arteries [23]. In addition to altering the form of red blood cells (RBCs), the polymerization process applies some mechanical force that compromises the integrity of the RBCs' membrane and causes the loss of RBC membrane material [24]. By measuring the concentrations of RBC-derived microparticles in serum, this can be determined [24]. The RBC lifespan deteriorates from what is predicted to be 120 days in healthy individuals to only roughly 5–15 days in those with sickle cell disease [25], as a result of all the previously stated pathophysiological alterations. Many SCD patients get severe anemia as a result of this, which lowers the RBCs' ability to carry oxygen [25]. One of the potential clinical symptoms of rapid hemolysis and altered RBC shape in people with sickle cell disease is priapism [26].

A protracted penile erection that is usually painful and unrelated to sexual activity is known as priapism [27]. Normal blood flow is impeded by sickled cells, which typically induce vaso-occlusion of the tiny arteries of the corpora cavernosa, the penile erectile tissue, as a result of sickling and hemolysis of RBCs in SCD patients [28, 29]. If treatment for this condition is delayed, it may result in tissue hypoxia, irreversible penile fibrosis, and erectile dysfunction [30]. Erroneous globin protein production is the cause of TM, which is also a hereditary condition [31].

The precise pathophysiology, however, has a somewhat different course than SCD. First and foremost, it is important to note that TM is characterized in the literature by its incapacity to produce red blood cells, which leads to chronic anemia [32]. TM is the most prevalent autosomal recessive hemolytic anemia caused by defective hemoglobin production [33]. It is important to remember that two alpha and two beta globin chains are necessary for hemoglobin synthesis. These chains join forces with a heme molecule that contains an iron Fe2+ ion to form a hemoglobin molecule [34]. A flaw in the globin molecule's beta chain, which results in defective hemoglobin, is what defines TM [35]. Thalassemia often manifests in a range of severity, with transfusion-dependent thalassemia (TM), a lifelong anemia, being the most severe [36]. The severity of TM can have a significant impact on the quality of life for those who are affected, and its effects go beyond just severe anemia to include numerous organs and bodily metabolic functions [37]. The iron overload state that results from TM patients' ongoing blood transfusions is typically the cause of organ damage brought on by TM [38]. The liver, heart, and endocrine systems are among the organs that may be impacted; they are all vital for preserving fertility and good sexual behaviour [38]. But it's also important to note that there is another type of thalassemia called non-transfusion dependent thalassemia, which can manifest in a less severe clinical course and may not require blood transfusions [39].

Male infertility may result from either of the two hemoglobinopathies listed above [40, 41]. When attempting to determine what SCD and TM have in common and why they might both contribute to male infertility, the effect of both conditions on male infertility can be summed up in one word: hypoxia [42]. Hypoxia is defined as a drop in oxygen pressure within the organ, which may be brought on by a reduced exchange of oxygen between the vascular bed and the surrounding environment [43]. Since red blood cells are recognized to be the body's oxygen-carrying organs, a defective RBC may have a diminished capacity to carry oxygen [44, 45]. It is commonly known that spermatogenesis, the process by which sperm are created, is one of the many physiological functions of the body where an excess of oxygen is crucial [46, 47]. If the individual is subjected to a certain level of hypoxia, reversible malfunction may marginally impair this process [48]. Reduced sperm count, motility, density, and survival time are specific, measurable characteristics that may be impacted in semen studies of males exposed to hypoxia; these findings demonstrate a decline in sperm quality overall [49]. It is important to note that the primary hypoxic insult in the patient sample from which this result was derived was prolonged exposure to high altitude, which is another way that hypoxia can be generated [49]. The point of bringing up another hypoxic process is to demonstrate that the primary insult that causes sperm function to deteriorate is hypoxia, which can be brought on via the aforementioned mechanism. However, in relation to the subject matter of this paper, it is well known that males with SCD and TM exhibit the similar drop in semen analysis [13]. In addition to the characteristics of their semen analysis declining, patients with SCD and TM also have lower serum levels of reproductive hormones like testosterone, FSH, and LH than people without these conditions [14, 15]. Hypoxia poses a risk because it triggers the Oxidative Stress (OS) process, which results in the generation of Reactive Oxygen Species (ROS) and affects male fertility [50]. It is concerning to note that according to one study, ROS can be detected in the semen samples of 25–40% of infertile men [51]. Due to a variety of factors, including the abundance of polyunsaturated fatty acids in their plasma membranes, which are vulnerable to peroxidation reactions that might harm the spermatozoa's membrane and impair its motility, the sperm cells are prone to being damaged by OS [52]. . In addition to targeting sperm motility, the OS also targets the viability of the DNA contained in the sperm nucleus and speeds up the germ cells' apoptosis [53]. The quality and quantity of sperm gradually decline as a result of this latter injury [54]. Furthermore, it is important to note that spermatozoa

lack the enzymes necessary for repair, therefore even if some bodily cells may repair the damage caused by OS, they are unable to do so [55]. Nevertheless, ROS can play some significant physiological roles in spermatogenesis even though it is known to negatively impact the body's cellular pathways [56]. Treatment for these two hemoglobinopathies must first concentrate on eliminating the insulting agent, hypoxia, which is caused by a defective red blood cell that cannot properly carry oxygen throughout the body and deliver it to spermatozoa [57]. Blood transfusion is the mainstay of treatment for sickle cell disease (SCD) because it lowers the amount of sickle hemoglobin (HbS) and increases the ability to carry oxygen [58].

CONCLUSION

This study investigated the connection between male infertility and hemoglobinopathies, namely sickle cell disease and thalassemia major. Numerous factors influencing spermatogenesis, including genetic, congenital, acquired, and idiopathic causes, have been demonstrated to contribute to male infertility. To diagnose male infertility, evaluate sperm quality, and find underlying medical disorders such hemoglobinopathies, diagnostic procedures including blood and semen testing are crucial. Because sickle cell disease and thalassemia major cause hypoxia, lower sperm quality, and lower levels of reproductive hormones, they can lead to male infertility. Male infertility is caused by the hypoxia that results from impaired RBC function, even though hemoglobinopathies are mostly caused by genetic defects. Hemoglobinopathies can be treated with blood transfusions to enhance hematological parameters and reduce hypoxia. Research has demonstrated that transfusions have a good effect on serum levels of reproductive hormones as well as semen analytical characteristics such sperm count, motility, and morphology.

Blood transfusions promote spermatogenesis and assist control iron levels by improving tissue oxygenation. These results demonstrate the possibility of blood transfusions to improve male infertility linked to hemoglobinopathies and point to the necessity of additional study to address iron excess consequences from transfusions. In the end, this study emphasizes how crucial it is to address the root reasons of male infertility rather than just concentrating on the result.

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