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Review

Plasmapheresis in Neonatal Lupus

Mark Sharobim [1,2], Angelica S. J. Scribner [1] and William N. Rose [1,2,*]

[1] School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI 53792, USA
[2] Department of Pathology and Laboratory Medicine, University of Wisconsin Hospitals and Clinics, Madison, WI 53792, USA
* Correspondence: wrose@uwhealth.org

Abstract: About 2% of mothers with Sjögren's syndrome and about 1% of mothers with systemic lupus erythematosus deliver a baby with a congenital heart block (CHB). This is thought to be as a result of the maternal autoantibodies that cross the placenta and cause congenital lupus in the fetus/neonate. Among patients with a 2nd or 3rd degree atrioventricular block, the mortality rate in the neonatal period is about 10%, and most neonates who survive require a pacemaker into adulthood. Despite the compelling mortality and morbidity, the data on the optimal preventive treatments are meager and not well-established. In addition to pharmaceutical therapy, one potentially effective therapy is plasmapheresis. Plasmapheresis is safe in pregnancy, well tolerated, and is effective in removing the offending substances in the serum which may cause disease. We review this literature, in order to educate the reader and to motivate interest in studying this condition in the future.

Keywords: Sjögren syndrome; cardiac neonatal lupus; systemic lupus erythematosus; congenital heart block; plasmapheresis

1. Introduction

Antibodies are complex proteins involved in the immune response for protection from invading pathogens [1,2]. The antibody creation is random in order to cover the full spectrum of antigens that are presented to the immune system throughout life. If antibody producing cells evade normal biological quality control processes, an autoimmune disorder may arise as the body's natural immune elements mounts an attack against host structures and tissues. Thus, a pathological autoimmunity is an inappropriately overactive response to self-antigens with both humoral and cellular phases.

The defective processes involved in a dysregulated immune response develops at sites of normal immune development, such as thymus, bone marrow, and secondary lymphoid tissues [3]. Therapeutic interventions in affected individuals are typically concentrated on mitigating the dysregulated overactive immune responses by using conventional agents, such as anti-inflammatory, steroid, or immune-modulating drugs [4]. Less common methods aimed at decreasing the levels of pathologic autoantibodies in certain autoimmune conditions, include intravenous immunoglobulins (IVIG) and plasmapheresis.

Autoimmune antibodies underly the pathogenesis of two diseases common in the general population: Sjögren's syndrome (SS) and systemic lupus erythematosus (SLE). Pregnant mothers affected by these conditions harbor autoantibodies which confer increased risks of complications in offspring, most notably congenital heart block (CHB). CHB is one consequence amongst a spectrum of signs and symptoms in fetuses that develop neonatal lupus (NL) and subsequently cardiac neonatal lupus (CNL) [5]. While the etiology of antibody mediated cardiac damage in CNL leading to CHB is relatively well understood, the data is limited on the clinical effectiveness of methods used to remove the circulating pathologic antibodies, such as plasmapheresis in mothers with affected fetuses. Thus, this review will aim to describe the pathogenesis of neonatal and cardiac neonatal lupus, as it occurs in Sjögren syndrome (SS) and systemic lupus erythematosus (SLE), and the published reports on the efficacy of plasmapheresis in cardiac neonatal lupus.

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1.1. Sjögren's Syndrome and Systemic Lupus Erythematosus

Sjögren's syndrome (SS) is a complex autoimmune disorder that presents with autoinflammatory destruction of oral and cervical mucosal glandular tissue, with long-term sequelae including (but not limited to) chronic infection, organ dysfunction, and hematologic neoplasia. Primary SS (pSS) refers to the clinical manifestations that occur in the absence of another autoimmune condition, while secondary SS (sSS) is associated with an additional systemic autoimmune connective disease. These can include rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and polymyositis.

Both pSS and sSS present with clinical manifestations such as dry mouth (xerostomia) and eyes (keratoconjunctivitis sicca), as well as parotid gland enlargement, fatigue, musculoskeletal symptoms, and skin rash. pSS is estimated to be present at varying levels of severity in 0.2 to 1% of the general population [6]. The condition can affect people of any age, but the symptoms manifest in middle age, frequently between the ages of 45 and 55. As with many autoimmune diseases, there is a strong female predominance, as females develop this syndrome at an almost 10 to 1 rate to males [7].

Systemic lupus erythematosus (SLE) is characterized by a syndrome of chronic autoimmune and inflammatory pathophysiology, that mostly affects women of childbearing age. In the disease course, the multisystemic involvement leads to a wide clinical spectrum of presentation [8]. Due to variable presentations and long-term outcomes, management requires routine clinical monitoring and laboratory testing, to guide therapy and assess disease response [9].

Although both conditions are characterized by multisystem involvement, SLE uniquely may affect virtually every organ of the body. Patients initially present with mild symptoms, such as joint pain, skin involvement with a characteristic malar rash, and photosensitivity, and then a more severe and occasionally life-threatening pathology, such as kidney and bone marrow failure, as well as the central nervous system involvement, most commonly in the form of encephalitis [10]. SLE is prevalent at a level of 20 to 150 cases per 100,000 in the USA. Due to improved understanding and detection, the incidence is up 3-fold in the last few decades [11,12]. As with SS, an increased frequency among females is well-established and is evident in any global demographic. A systematic review of global SLE epidemiology showed that incidence is highest in Afro-Caribbean populations and lowest in Caucasians, while intermediate in Asian and Hispanic individuals [13]. It is most prevalent in the North and South American countries, while relatively less widespread in Europe, and even less in Asia and Africa [11,14].

1.2. Plasmapheresis

Derived from the Greek "aphairesis", meaning to "separate, takeaway by force, remove", apheresis describes the process by which the components of blood are removed from the body [15]. Any component of whole blood, such as plasma, red blood cells, white blood cells, platelets, and stem cells, may be removed, and a suitable replacement is returned to the patient. Most commonly, venous whole blood is removed from the patient and separated in components by centrifugation, and then the plasma component is removed and discarded while simultaneously infusing a replacement fluid [16]. This process is reviewed in extensive detail, conceptually, by Reeves et al. [17], and Osman et al. [18] illustratively. Plasmapheresis differs from dialysis, which is primarily a diffusion-based method that utilizes a concentration gradient between whole blood and dialysate, across a membrane filter with selected pore sizes [19]. In plasmapheresis, the pathologic substances may be immune complexes, autoantibodies, paraproteins, cholesterol-laden lipoproteins, and endogenous or exogenous toxins.

In contrast to plasmapheresis, in a general sense, the term plasma exchange, also called therapeutic plasma exchange (TPE), is sometimes reserved as a more specific term for a therapeutic plasmapheresis that uses allogeneic plasma, as the replacement fluid instead of albumin and/or saline. The usual indication to use plasma is to replenish the substances that the patient lacks, such as the clotting factors or regulatory proteins that are

present in normal donor plasma [20]. This term is not used consistently to signify the use of plasma as the replacement fluid, as many authors use plasmapheresis and plasma exchange as synonyms.

The Apheresis Applications Committee of the American Society for Apheresis (ASFA) describes four different categories by which therapeutic plasmapheresis may be indicated for certain diseases [21]. Category 1 and 2 disorders are those by which first-line treatment or second-line treatment, in addition to standard of care, includes therapeutic apheresis, respectively. Categories 3 and 4 delineate diseases for which evidence is lacking for benefit from therapeutic apheresis, and in some cases, apheresis may pose harm and thus needs individualized ethics approval on a single-institution basis.

An example of a condition in which plasmapheresis is first-line therapy, is thrombotic thrombocytopenic purpura (TTP). In TTP, the defective clearance of the von Willebrand factor (VWF) multimers by the autoantibodies raised against ADAMTS13 results in the consumption of the host platelets and multisystemic thrombotic vascular effects. This can be life-threatening without ready access to plasmapheresis [22]. Common autoimmune conditions included in category 1 include acute inflammatory demyelinating polyradiculoneuropathy/Guillain–Barre syndrome, myasthenia gravis, N-methyl D-aspartate receptor (NMDA) antibody encephalitis, and chronic inflammatory demyelinating polyradiculoneuropathy.

For plasmapheresis to have optimal benefit, the targeted substance must have a sufficiently long half-life that is not more efficiently removed by the patient's own endogenous clearing systems. For example, serum IgG has a half-life of about 21–23 days [23]. Theoretically, halting the production of autoimmune IgG with therapy would still mean significant antibodies will be circulating for days to weeks after intervention. Some additional, often overlooked, implications of plasmapheresis are that a 1-plasma volume exchange replaces 63% of the patient's plasma, while most clotting factors require only 15–20% activity for normal hemostasis, and their levels recover to the baseline within 2–3 days after plasmapheresis [24]. Thus as an example, plasmapheresis can be performed on a Monday, Wednesday, and Friday schedule using albumin without the need for routine monitoring of the patient's coagulation factors or hemostasis status unless the procedure is performed daily or the patient has a known coagulopathy independent of plasmapheresis [24].

1.3. Development of the Neonatal Immune System

The development of the neonatal immune system takes place in utero with the progressive evolution of the neonatal immune response to foreign and self-antigens. This process is affected by genetic as well as environmental factors in both the fetal and neonatal periods. The development of immune competency is tightly linked to organogenesis, as hematopoiesis and subsequently immune system maturation takes place in the fetal yolk sac, liver, spleen, lung, bone marrow, peripheral lymph nodes, and thymus [25]. Indeed, the first wave of fetal hematopoiesis occurs in mesodermal derived tissues of the fetal yolk sac [26]. Primitive granulocytes, macrophages, and erythroid cells can be detected in this tissue, as early as 3–4 weeks [27]. By the second trimester, and as fetal hematopoiesis moves to sites such as the liver, thymus, and spleen, the fetus has enough maturation of cellular and organ elements to mount innate and adaptive responses [28].

Neonatal autoimmune conditions are exceedingly rare and almost invariably due to the passive transfer of maternal autoantibodies to the fetus. Primary autoimmune disease of the fetus, in which no autoimmune condition can be attributed to maternal factors, is virtually not encountered in most clinical practice [29]. Neonatal lupus is the most common presentation of the autoimmune pathology in the newborn [30]. Discussed in more detail in later sections, this is thought to be due to the high-titer antibodies that are present in mothers with SLE or SS that readily cross the placenta. In some cases, the autoantibodies are specific enough to cause an isolated disease in the fetus, such as in cases of cardiac neonatal lupus.

The Ro/Sjögren's-syndrome-related antigen A (Ro/SSA) and La/Sjögren's-syndrome-related antigen B (La/SSB) are two proteins associated with connective tissue disorders, especially SS and SLE, that commonly have self-directed autoantibodies created against them, often in response to environmental stressors [31].Ro/SSA is an extractable nuclear antigen that is present in cytoplasm but may translocate to the nucleus in proinflammatory states. In addition, Ro/SSA binds with RNA to form protein-RNA complexes called Ro-ribonucleoproteins (Ro-RNPs), though the biological significance of these interactions is incompletely understood [32]. The function of La/SSB is better understood; it is a protein that binds to the 3′ poly(U) terminus of nascent tRNAs, preventing the endogenous exonuclease digestion and promoting natural folding and maturation [33].

Anti-SSA and anti-SSB antibodies can also be found in individuals without these associated autoimmune disorders and can lead to similar fetal complications. Studies have explored the correlation between anti-SSA and anti-SSB antibodies and negative pregnancy and fetal outcomes, through the retrospective observation or various related treatments in patients with and without clinically detectable symptoms of autoimmunity [34,35]. These autoantibodies have, however, most commonly been associated with neonatal lupus, which can manifest as transient neonatal skin rash, liver abnormalities, thrombocytopenia, and spontaneous abortion in children born to mothers with SLE.

One of the most common fatal in utero presentations associated with the presence of maternal anti-SSA and SSB antibodies is fetal congenital heart block (CHB), another clinical manifestation of neonatal lupus. Due to the passive vertical transference of the maternal antibodies, fetuses undergo autoantibody-mediated cardiac damage, leading to CHB, while in utero, with a 30% overall mortality rate and associated irreversible complications [36]. The condition is also associated with hydrops fetalis, myocarditis, and late gestational age [37].

1.4. Neonatal Autoimmune Syndromes and Neonatal Lupus

Fetal immunoglobulins are almost entirely derived from the mother, except for trace IgA and IgM. At the third trimester, IgG crosses the placenta and rises until the time of delivery [38]. Fetal autoimmune diseases are caused by passively transmitted maternal autoantibodies which enter the fetal circulation and cause disease. In the fetus, autoimmune disease is most commonly due to passively derived maternal SLE autoantibodies [30]. The pathognomonic serological markers for disease with SLE include high titer autoantibodies, collectively referred to as antinuclear antibodies (ANAs). Specific types of ANAs seen in SLE are raised against double stranded DNA (dsDNA), Smith antigen and ribonucleoproteins (Sm-RNP), and Sjögren syndrome autoantigen types A or B (SSA/Ro and SSB/La) [39].

Neonatal lupus (NL) is an autoimmune disease in which SSA and SSB autoantibodies cross the placenta resulting in a fetal and neonatal pathology. The most common manifestations are seen in the cardiovascular system and skin. SSA and SSB autoantibodies are present in 20–30% of patients with SLE and are exceedingly more common in patients with Sjögren's syndrome [40,41]. Of note, less than 2% of healthy pregnant women with no clinically detectable disease may have SSA and SSB autoantibodies [42]. Uniquely, anti-SSA/Ro antibodies are specific to four different protein antigens with similar epitopes which may have a molecular weight of 45, 52, 54, and 60 kDa. Only anti-SSA/Ro52 and SSA/Ro60 are clinically significant [43]. Large-scale studies show patients with SLE may be positive only for anti-SSA/Ro60, while patients with pSS are more likely to have a combination of anti-SSA/Ro52 and SSA/Ro60 [44,45]. While all three antibodies (anti-SSA/Ro52, anti-SSA/Ro60, and anti-SSB/La) maybe present in patients with NL and subsequently CHB, over 95% of mothers had at least a positive titer to just anti-SSA/Ro52, while anti-SSA/Ro60 and anti-SSB/La were present only in about 60% of patients [46].

At the time of the birth of an infant with neonatal lupus, the maternal manifestations of SLE may range from asymptomatic in over a third of cases, to SLE with multisystemic involvement, to SLE with associated Sjögren's syndrome. It is important to note that since

there maybe high titer SSA and SSB antibodies in mothers with Sjögren's syndrome alone, these patients may have fetuses and neonates with cardiac neonatal lupus without ever being diagnosed with SLE [47].

Due to a relatively low incidence, pathogenesis is thought to be a multi-step immune mediated process. Though it is not completely understood, two leading hypotheses describe the mechanism of the myocyte damage in an advanced congenital heart block. One model suggests that the maternal autoantibodies damage the L- and T-Type calcium channels found on cells of the sinoatrial (SA) and atrioventricular (AV) nodes [48]. In both autopsy studies and animal models, histopathologic analysis shows fibrosis and calcification of AV node sections, as well as antibody deposition and lymphocytic infiltration of pacemaker cells in affected hearts [48]. The autoimmune damage of both SA and AV nodes is consistent with cardiac conduction abnormalities in affected fetuses that are affected by sinus bradycardia and QT-prolongation, in addition to an atrioventricular block, more conventionally (discussed further below). A similarly related hypothesis suggests that the antigens harboring epitopes recognized by SSA and SSB antibodies translocate to the surface of the cardiac myocytes in utero [49]. Through antibody-mediated binding and signalling, these cells normally undergo physiologic remodelling then aberrantly apoptosis and do not regenerate. This suggests that a limited window and minimum threshold of myocyte damage is necessary for irreversible disease. Indeed, mouse models of the L-type calcium channel gene knockouts show the rescue of function when targeted calcium channels are exogenously overexpressed, even when exposed to anti-SSA/Ro and anti-SSB/La, after critical periods of development [50].

1.5. Cardiac Neonatal Lupus

The diagnostic criteria for neonatal lupus include maternal or fetal seropositivity for SSA and SSB, and one or more fetal/neonatal manifestations of atrioventricular heart block, skin rash typical of SLE, hepatobiliary complications, such as elevated aminotransferases, hepatomegaly, and cholestasis, or hematological abnormalities, such as cytopenias [51]. Of the organs affected, sequalae of hepatobiliary and hematolymphoid damage are generally two of the least commonly encountered [52]. A generalized summary of the affected organ systems, by frequency, is discussed below Neonates born to mothers with high titer SSA and SSB antibodies more commonly have cardiac manifestations such as an atrioventricular heart block which often cannot be completely reversed. Cardiac neonatal lupus (CNL) is most frequently seen as a first-, second-, or third-degree heart block with a majority progressing to a third-degree block. Since mothers with high-titer antibodies to SSA and SSB are more likely to have offspring with NL, the routine screening of at-risk mothers throughout pregnancy is recommended [53].

Though the passive transfer of maternal antibodies begins as early as the 12th week of gestation, it peaks in the second to third trimester, and thus regular screening begins starting at the end of the first trimester. Serial sonography with transabdominal ultrasound and echocardiography in patients with high-titer antibodies ($\geq$50 U/mL) is warranted. Recommendations from the American Heart Association suggest serial routine echocardiography be performed beginning at 16 weeks gestation and continued until week 28 [54]. Echocardiography has been shown to detect up to 90% of severe heart blocks even in low-risk populations [55]. Postnatally, any neonate with a heart block of any degree that was not previously identified or explained by cardiac structural abnormalities should have subsequent testing of the maternally derived autoantibodies to SSA and SSB. A positive test in either the mother or fetus establishes a causal diagnosis in such cases.

Epidemiologic surveillance suggests 1–25% of cases of mothers with SLE and SSA and SSB autoantibodies result in a cardiac manifestation, with increased risk for mothers with a previously affected child [36,47]. Overall however, older estimates suggest this is only 1–2% of mothers with the offending autoantibodies [56]. Despite this, only 85% of fetuses with a congenital heart block without structural abnormalities due to another cause have the passive maternal transfer of SSA or SSB antibodies [57]. This points to a combi-

nation of maternal, genetic, fetal, and environmental factors which contribute to develop these syndromes.

Other less common cardiac manifestations include sinus bradycardia, QT-interval prolongation, cardiomyopathy, congestive heart failure, myocarditis, and structural abnormalities such as patent foramen ovale, patent ductus arteriosus, and pulmonary stenosis [58]. In utero, patients with an advanced heart block often present with fetal bradycardia with a normal atrial rate and a slowed ventricular rate, while neonates present at birth with a heart rate of fewer than 100 beats per minute [59]. Though most often not present, the signs of heart failure or volume overload may occur, such as peripheral edema, diaphoresis, jugular venous distension, and pulmonary edema. About 5–10% may proceed to fulminant dysfunction in the form of heart failure or cardiomyopathy [60]. The SSA and SSB autoantibody-mediated cardiac dysfunction in fetal and neonatal patients results in significant mortality. Overall mortality approaches 30% [59]. The mortality rate by postnatal day 90 is about 15%, and patients with endocardial fibroelastosis or cardiomyopathy are at highest risk [61].

Therapeutic interventions are guided by the presentation of CHB as there is no consensus on the age and symptomatic status of patients that received typical treatment for a heart block, which is pacemaker therapy. Some physicians routinely implant pacemaker systems in the first month of life while others agree it is only required after a patient reaches 15 years of age [62]. While this type of approach is directed at those who have already developed the clinically detectable disease, some authors have suggested the transient immunological environment encountered in utero may pose a potential for preventive treatment. Indeed, a mainstay of treatment in utero is steroid therapy, which is presumed to reduce the inflammatory mediators that damage the fetal cardiac conduction systems [63].

1.6. Treatment of Congenital Heart Block

Treatments that have been studied for preventing or mitigating the severity of a congenital heart block in patients with autoimmune disorders, such as Sjögren syndrome and SLE, include immunoadsorption, corticosteroids, intravenous immunoglobulins (IVIG), and plasmapheresis, but none have been fully proven efficacious for a CHB [64]. Trials of steroids alone have been shown to reduce a 2nd degree block, increase the heart rate, and decrease the need for cardiac pacing at birth [65]. The use of steroids must take into consideration the risk of prolonged use in pregnancy, which may include increased chance of preterm delivery and low birth weight in the fetus, and increased risk of infection and persistent high serum glucose in the mother [66].

As a proof of concept, a small study by Tonello et al. showed that in 10 patients who started plasmapheresis immediately after being diagnosed with a fetal CHB and continued weekly throughout the pregnancy, a statistically significant reduction varying from 2- to 35-fold in antibody titers were achieved in 80% of patients [67]. No significant side effects were reported during any treatments in all patients. Of note, the AFSA guidelines on the use of plasmapheresis in cardiac neonatal lupus designate a grade 2C or category III for this treatment modality, which is a weak recommendation due to the limited evidence [21].

The first study that suggested the use of plasmapheresis to deplete the pathologic autoantibodies contributing to a fetal CHB in mothers with SLE and SS during pregnancy was by Herreman et al. in 1985 [68]. The authors described using plasmapheresis, aziothioprine, and steroids to mitigate the syndrome after the detection of high-titer autoantibodies. This was carried out after a previous pregnancy to the index mother and resulted in the birth of a fetus with a CHB. Though this was the first description of plasma exchange as a potential therapeutic, the second fetus born to the treated mother still developed a CHB [68]. Subsequently, case reports have shown that the combination of IVIG, steroids, and plasmapheresis, have effectively diminished the antibody titer levels of anti-Ro/SSA and anti-La/SSB, though many have not demonstrated the prevention of the development of the neonatal onset of a CHB after initially being diagnosed with the in utero disease [69–72]. One study followed six pregnant individuals with a diagnosed fetal con-

genital heart block throughout their pregnancies. The individuals were given a combination therapy of plasmapheresis, IVIG, and corticosteroids, and it was found to be a safe and effective treatment in reducing the progression of the heart block [73]. Another similar study [67] followed 10 pregnant individuals diagnosed with a fetal CHB, treating them with steroids, IVIG, and plasmapheresis. This study found that plasmapheresis was effective in removing anti-SSA and anti-SSB antibodies and the second-degree blocks reverted following treatment; however, but the third degree blocks remained, likely due to the development of permanent cardiac damage at this stage [74]. A more recent study compared the use of steroid, IVIG, and weekly plasmapheresis, as opposed to just single agents, in pregnant mothers. The combination therapy showed a significantly lower progression from a 2nd to 3rd degree block at birth, an increase in heart rate, and a lower need of implants after birth [75]. The largest study to date with a control arm was by Rufatti et al. in 2022 [75]. In this study, the patients were given either steroids, IVIG, and random plasma exchange, as opposed to the same regimen in the treatment arm, except with routine, multiple weekly exchanges throughout the pregnancy. In the treatment group, there was a statistically significant reduction in the likelihood of progressing from a 2nd degree heart-block diagnosed in utero, and the need for a pacemaker in the post-partum interval for the neonate. A statistically significant increase in the likelihood of increased heart rate after birth (all endpoints $p \leq 0.01$) was observed. As with previous studies, once a fetus developed a 3rd degree heart block, there was no statistically significant reversal seen with any treatment modality. A summary of all the relevant studies in the literature to date is found in Table 1.

These studies indicate that plasmapheresis is a safe and potentially effective treatment for a CHB, especially if started in pregnant individuals before a critical period in utero, when cardiac damage can take place. Due to the small sample size of most studies, a crucial next step would be to conduct larger-scale studies to analyze the clinical benefit of such treatments. It is unclear, however, what is the contribution of each of the three therapeutics in preventing the development of a CHB. Furthermore, relatively larger studies have not demonstrated the consistent prevention with these treatment modalities, as single agents. Additionally, while it is confirmed that plasmapheresis may deplete circulating autoantibodies known to cause CHB, it is unclear if removal of offending agents also influences non-cardiac manifestations of NL. The clinical spectrum of presentation in NL is summarized in Table 2.

Additional investigation into single and double agents show varied data; small to medium sized studies describing the use of plasmapheresis and IVIG in at-risk pregnant mothers have been performed. Combination treatments with IVIG and steroids alone have at least been shown to revert the clinically diagnosed in utero CHB in a case report [76]. As single agents, plasmapheresis, IVIG, and immunoadsorption are presumed to decrease serum SSA and SSB antibodies that can cross the placenta to the fetus. Immunoadsorption, or the removal of specific antibodies from the serum, reduces the SSA/SSB antibodies in pregnant mothers, but has been inconclusive in definitively reducing the likelihood of CHB [35].

Plasmapheresis as a single agent to prevent CHB however, to our knowledge, has only been described once in a study Miyakata et al. in 2001 [77]. The authors demonstrated the use of plasmapheresis in patients with clinically detectable SSA and SSB antibodies, but not necessarily a fetal CHB. This is the first study to date to describe the reduction of serum antibodies after plasmapheresis, however in terms of the therapeutic potential, one fetus developed a CHB, which is consistent with the overall population risk in seropositive mothers.

Table 1. Summary of studies describing plasmapheresis in pregnant mothers with cardiac neonatal lupus.

Authors	Plasmapheresis Single Agent or in Combination	Study Design and Methods	Notes/Outcomes
(1) Herreman et al. 1985 [68]	Combination with steroid and plasmapheresis	- Case report, n = 1 - Combined plasmapheresis and steroids in a mother with a history of prior pregnancy with an isolated complete heart block following an otherwise uncomplicated pregnancy - The fetus had severe bradycardia at 23 weeks gestation and the mother tested positive for antinuclear antibodies	- Plasmapheresis and steroid treatment did not reverse the heart block, the live infant was born otherwise without complications
(2) Barclay et al. 1987 [69]	Combination with steroid and plasmapheresis	- Case report, n = 1 - Combined plasmapheresis and steroids in a mother with a history of prior pregnancies which resulted in early neonatal death, due to a CHB - anti-SSA/Ro titer was present at a level of 1:20 at 20 weeks gestation	- Outcome resulted in the live birth of the infant without clinically demonstrable CHB
(3) van der Leij et al. 1994 [70]	Combination with steroid, azathioprine, and plasmapheresis	- Case report, n = 1 - Multiple agents in a mother with a history of prior pregnancy which resulted in early neonatal death, due to a CHB - anti-SSA/Ro and anti-SSB/La levels were monitored throughout the pregnancy and diminished with treatment	- Outcome resulted in the live birth of the infant without clinically demonstrable CHB
(4) Miyakata et al. 2001 [77]	Single agent	- Prospective, n = 15 - All pregnant mothers received single agent plasmapheresis if positive anti-SSA/Ro or anti-SSB/La titer	- One case of CHB was found after plasmapheresis - No significant side effects or pregnancy complications
(5) Zemlin et al. 2002 [71]	Combination with steroid and plasmapheresis	- Case report, n = 1 - A mother with primary Sjoegren's syndrome was treated with steroids and plasmapheresis in four singleton pregnancies	- One pregnancy resulted in miscarriage, one with fetal CHB, and two normal births by Caesarean section

Table 1. *Cont.*

Authors	Plasmapheresis Single Agent or in Combination	Study Design and Methods	Notes/Outcomes
(6) Yang et al. 2005 [72]	Combination with steroid and plasmapheresis	- Case report, n = 1 - A mother with systemic lupus erythematosus and a positive anti-SSA/Ro antibody titer was given steroids, immunosuppressants, and plasmapheresis in her second pregnancy, after previously giving birth to a child with a CHB	- Though no in utero CHB was detected in the second pregnancy, the patient's pregnancy resulted in an otherwise uncomplicated birth by Caesarean section
(7) Makino et al. 2007 [78]	Combination with steroid	- Prospective, n = 24 - All pregnant mothers who had positive anti-52-kDa SSA/Ro and anti-48-kd SSB/La antibodies or elevated titers of anti-SSA/Ro antibody (> 1:512), were treated with steroid only or steroid in combination with plasmapheresis	- Most cases of CHB developed in patients whose mother was taking neither steroids or plasmapheresis - One case developed in a patient whose mother took both treatments
(8) Rufatti et al. 2012 [73]	Combination with steroid, IVIG, and plasmapheresis	- Prospective cohort, n = 2 - Pregnant mothers had an in utero diagnosis of fetal CHB by echocardiography	- Congenital heart block was reversed in both fetuses - No recurrence of CHB was detected at the 8 and 29 month follow up
(9) Di Mauro et al. 2013 [79]	Combination with steroid, IVIG, and plasmapheresis	- Case report, n = 1 - Multiple agents in an incidentally detected fetal CHB in uter,o detected by fetal echocardiography	- Mother was asymptomatic for the autoimmune disease prior to and after the fetal CHB presentation - High-titer anti-Ro/SSA was found
(10) Rufatti et al. 2016 [80]	Combination with steroid, IVIG, and plasmapheresis	- Prospective cohort, n = 12 - Pregnant mothers had an in utero diagnosis of fetal CHB by echocardiography - All fetuses had a 2nd or 3rd degree heart block and were diagnosed in the 20th week of gestation or latter - All mothers showed progressively decreased antibody titers throughout pregnancy	- Two fetuses with a second degree heart block reverted to 1st degree, and one reverted to normal atrioventricular conduction - All six fetuses with a 3rd degree heart block remained stable throughout pregnancy
(11) Hou et al. 2020 [76]	Combination with steroid, IVIG, and plasmapheresis	- Prospective cohort, n = 2 - Pregnant mothers had an in utero diagnosis of fetal CHB by echocardiography at 24 and 28 weeks gestation	- Congenital heart block was reversed in one fetus and persisted in the other

Table 1. *Cont.*

Authors	Plasmapheresis Single Agent or in Combination	Study Design and Methods	Notes/Outcomes
(12) Rufatti et al. 2022 [75]	Combination with steroid, IVIG, and plasmapheresis	- Non-randomized control study, n = 35 - Control arm: n = 19, treatment arm: n = 16 - Control arm: steroids alone or steroids + IVIG + random plasma exchange - Treatment arm: steroids + IVIG + weekly plasma exchange - Both groups began therapy after detection of a 2nd or 3rd degree CHB in utero - Mothers with a diagnosis of SLE, SS, or other connective tissue disease with a positive anti-SSA/Ro and/or anti-SSB/La titer	- Weekly plasmapheresis in the mother of the affected fetuses significantly reduced the likelihood of progressing from a 2nd degree block diagnosed in utero ($p = 0.01$), increased heart rate at birth ($p < 0.01$), and the likelihood of pacemaker implantation ($p < 0.01$) - No difference in the regression from a 3rd degree block was seen

CHB = congenital heart block; IVIG = intravenous immunoglobulin; SLE = systemic lupus erythematosus; SS = Sjogren's syndrome.

Table 2. Clinical manifestation of neonatal lupus by the organ system.

Integumentary—Common [81]
- Erythematous macules and patches
- Petechial hemorrhages
- Discoid lesions
- Cutis marmorata
Cardiac - Common [82]
- 1st, 2nd, or 3rd degree heart block
- Sinus bradycardia
- Prolonged QT-interval
Pulmonary—Occasional to less common [83]
- Pulmonary hypertension (self-limiting)
Hepatobiliary—Less common [84]
- Asymptomatic liver enzyme elevation
- Cholestasis
- Hepatitis
- Mild hepatosplenomegaly
Hematolyphoid—Less common [85]
- Cytopenias common in SLE: anemia, neutropenia, thrombocytopenia
- Aplastic anemia
Central nervous system—Rare [86]
- Hydrocephalus
- Macrocephaly
Musculoskeletal—Rare [87]
- Chondrodysplasia punctata (stippling of the bones and cartilage on radiography), self-limiting

SLE—systemic lupus erythematosus.

2. Discussion

Maternal Sjögren's syndrome autoantigen types A or B (SSA/Ro and SSB/La) autoantibodies pose a significant risk to the fetus. A congenital heart block (CHB) resulting from the passive transfer of maternal antibodies can present in utero and persist into adult years. A heart block is often irreversible and presents with clinical signs such as bradycardia without significant symptomatology, but may progress to a fulminant disease, such as in the form of cardiomyopathy and heart failure. Treatment can be invasive as some institutions chose to implant pacemakers in early life. The immune-mediated nature of the pathogenesis suggests there is some role for mitigating the pathologic autoimmune response. This is complicated by the fact that it is unclear at which stage in utero these events occur beyond an irreversible threshold.

Additionally, the inflammatory events that occur after the specific targeting of the cardiac myocytes by the autoantibodies are not well elucidated. These are reflected in the evidence showing that the methods to reduce the autoantibodies such as plasmapheresis, IVIG, and immunoadsorption clearly show reduction in the SSA and SSB titers without definitively reducing CHB risk. This further suggests that there is a critical window of development in which the cardiac damage occurs and is thereafter sustained even with the removal of the offending antibodies.

In terms of the therapeutic effect of plasmapheresis on CHB in patients born to mothers with SLE or SS, it appears that it is best used as an adjunct to steroids and/or IVIG. Indeed, multiple studies have confirmed at least some mitigation of CHB signs and symptoms at birth and into early years. This, combined with its favorable safety profile, suggests that plasmapheresis has some role in reducing pathological antibody levels and presumably diminishing the likelihood of cardiac toxicity. Given the variable onset and severity of cardiac neonatal lupus, the optimal timing and treatment regimen that will give the most benefit are still unclear. In terms of therapeutic effect, trials of plasmapheresis in combination with other agents have demonstrated modest reductions in the degree of heart block, but longer-term follow-up studies are needed to determine the mortality benefit.

Potential useful future directions to help elucidate mechanisms and interventions to reduce CHB will invariably need to gather larger patient cohorts. Due to its relatively rare nature and propensity to be treated in tertiary care centers, multicenter studies may be helpful. These studies may include investigating whether the successful prevention or mitigation of CHB with combination therapy, including plasmapheresis, correlates with replicable reduction in serum levels of the offending antibody. This is presumably in line with the limited data that shows the lower titer of maternal autoantibodies pose less of a risk of fetal and neonatal CHB.

Past studies have additionally not been large enough to properly determine if SSA and SSB antibodies, seen in SS alone or in SLE, pose a greater risk. For example, patients with SLE may have SSA and SSB in the serum, but this is just one of the many nuclear autoantibodies found in these patients. The additional fluctuation between those and other more common serum markers in SLE may mean that mothers may have a greater risk at different stages in their disease. This is contrasted with SS, where SSA and SSB is consistently and commonly present in the circulation. The correlation between chronic and acute seropositivity and the risk of CHB, is yet to be determined.

3. Conclusions

The most common congenital fetal autoimmune syndrome is a heart block. This is thought to arise from passively transferred maternal autoantibodies commonly seen in patients with Sjögren's syndrome and Systemic Lupus Erythematosus. Morbidity and mortality can be high, especially when advanced levels of heart block develop. Due to the immune-mediated nature of this disease, a balance between the opportune timing and effective depletion of the autoantibodies is key. To date, therapy aimed at blunting the immune and inflammatory response when a clinically detected fetal heart block is present has been shown to reduce the magnitude of the disease. Newer treatment modalities,

such as plasmapheresis, when used in combination with other immunomodulators are promising. Larger scale studies are needed to determine an effective role for such therapy.

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