The Effects of Maternal Systemic Lupus Erythematosus on the Developing Fetus

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Abstract

Systemic lupus erythematosus (SLE) is a systemic inflammatory autoimmune disease which can affect multiple systems of the human body. SLE can have a wide range of negative effects on a person’s health that vary from patient to patient. Typically SLE affects the integumentary and musculoskeletal systems as well as the developing fetus. The underlying cause of SLE is not fully known, however, genetics, heredity, and environmental features are associated with the severity and outcome of the disease. Due to the wide range of deleterious effects associated with SLE, pregnant women diagnosed with SLE are especially sensitive to SLE-associated inflammatory responses. Currently, a concerted effort is underway to determine the mechanism(s) by which SLE affects fetal development. Maintenance of the autoantibody levels in the mother's blood is vital and a key method in sustaining the health of the fetus by preventing the likelihood of maternal-fetal exchange of SLE-associated autoantibodies. However, these autoantibodies may cross the placenta and enter the fetus. When SLE autoantibodies enter the fetal circulation the fetus can potentially form neonatal lupus erythematosus (NLE). NLE is a rare developmental disorder that results in cardiac, dermatologic, hepatic disorders and hematologic abnormalities in some infants. One of the more prominent abnormalities is the formation of congenital heart block (CHB). This review will focus on the mechanisms that permit maternal-fetal autoantibody exchange and regulate SLE-mediated congenital heart block as well as current therapies used to prevent autoantibody exchange.
Introduction

Systemic Lupus Erythematosus and Neonatal Lupus Erythematosus

Lupus is a group of autoimmune diseases named for the occurrence of a distinctive butterfly rash, resembling the bite of a wolf that appears across the bridge of the nose. This multifaceted disease can present in four forms which include: cutaneous lupus, systemic lupus erythematosus, drug-induced lupus, and neonatal lupus. In this review, we will focus on systemic lupus erythematosus (SLE) and specifically how SLE affects fetal development in pregnant females. SLE is a systemic autoimmune disease with major inflammatory responses (Matsushita, Higashino et al. 2002). Studies have shown that SLE is ten times more prevalent in women than men and two to three times more prevalent in African-Americans and persons of Latin American descent than Caucasians (McCarty, Manzi et al. 1995; Tincani, Danieli et al. 2006; Smyth and Garovic 2009; Borchers, Naguwa et al. 2010).

To date, no cure has been found for this chronic disorder. SLE can affect any area of the human body, including dermatologic, neurologic, renal, cardiologic, hematologic, and other systems (Matsushita, Higashino et al. 2002; Izmirly, Llanos et al. 2010). Some common symptoms of SLE are fatigue, arthalgia, arthritis, fever, skin rashes, anemia, edema, pleurisy, facial rash, photosensitivity, alopecia, Raynaud's phenomenon, seizures, and mouth or nose ulcers (Khamashta 2006). The requirements for diagnosis are assessed through patient history, hematologic tests—including complete blood counts and autoantibodies as well as physical examination. Individuals who present 4 of the 11 American College of Rheumatology Classification Criteria for SLE, simultaneously or within the same observed time period, can be
considered positive for SLE (Table 1.). However, individuals who have less than 4 may still be diagnosed with SLE. Treatment of SLE includes a combination of physical activity, rest, medications, and healthy eating habits. The regimen for therapy varies from patient to patient depending on the systems affected by the disease.

**Table 1: 1997 American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus**

| 1. | Malar Rash |
| 2. | Discoid Rash |
| 3. | Photosensitivity |
| 4. | Oral ulcers |
| 5. | Nonerosive arthritis |
| 6. | Pleuritis or Pericarditis |
| 7. | Renal Disorder |
| 8. | Neurologic Disorder |
| 9. | Hematologic Disorder |
| 10. | Immunologic Disorder |
| 11. | Positive Antinuclear Antibody |

Table 1. Summary of classification criteria for Systemic Lupus Erythematosus

The higher prevalence of SLE in women has potential detrimental effects in pregnant females such as increased frequency of miscarriages, still births, preterm birth, neonatal lupus, and perinatal mortality (Buyon, Clancy et al. 2009). A pregnant female with SLE may pass autoantibodies to the fetus across the placenta which may cause developmental abnormalities. Furthermore, the presences of these antibodies can result in NLE and ultimately CHB, a major complication of NLE (Clancy and Buyon 2004).

NLE is a maternally acquired disease of the fetus that is associated with the cross-placental transfer of anti-Ro/SS-A and/or anti-La/SS-B autoantibodies, which are highly prevalent in individuals with SLE. The Ro/SS-A antigen is a small nucleocytoplasmic RNA protein complex (Ben-Chetrit, Gandy et al. 1989; Chan, Silverman et al. 1999). The function of the Ro/SS-A antigen is not completely known, although it is hypothesized to function in the
ribosomal RNA discard pathway (O'Brien and Wolin 1994). The La/SS-B antigen consists of a 48-kDa protein and serves as a termination factor for RNA polymerase III (Rinke and Steitz 1982; Stefano 1984; Gottlieb and Steitz 1989). The presence of these autoantibodies in the fetal circulation can lead to CHB.

Clinical manifestations of NLE include photosensitive rash and hematologic abnormalities (AlSaleh, Jassim et al. 2008; Walling and Sontheimer 2009). Some symptoms of NLE are temporary with the passing of maternal antibodies in the fetal circulation after birth however others are considered major. A major complication which occurs in 2% of fetuses of SLE-affected mothers is CHB (Jing-Bin, Ying-Long et al. 2009). CHB also referred to as atrioventricular block is an irreversible condition which causes scarring of the cardiac tissue and eventually affects the functionality of the heart (Nussinovitch and Shoenfeld 2007).

**Normal Fetal Heart Development**

Normal heart development of the fetus starts to occur at 15-16 days of gestation. The stages of heart development include five basic steps. These five basic steps give rise to the fundamental architecture and function of the heart. The initial step in development of the heart and associated cardiac structures is the migration of cardiac stem cells to the myocardial plate (site of cardiac development). After these stem cells arrive at the myocardial plate the neonatal heart is formed by initiating cardiac looping, the process of developing the future cardiac chambers. Following formation of the cardiac chambers, atrioventricular valves (AV valves) are formed. The AV valves permit blood flow from the atrial (upper, blood receiving) chambers of the heart to the ventricular (lower, blood pumping) chambers of the heart in the fully developed heart. Once all chambers and valves have been completed, the cardiac conduction system as well
as the cardiac vasculature is established (Moorman and Christoffels 2003; Dunwoodie 2007; Mitchell, Sander et al. 2007).

Cardiac development begins with migration of pre-cardiac stem cells following gastrulation (formation of the germ layers) to the site of cardiac formation. The initial heart cells arise from pre-cardiac stem cells that form along the midline of the developing embryo. These stem cells then migrate to the thoracic cavity and begin heart development. The second major phase in heart development is the actual shaping of the heart inside the thoracic cavity. After establishing the shape of each chamber of the heart, it must then be formed and defined. The heart must define the four chambers that comprise the heart. Defining and forming these chambers is known as cardiac looping. The heart contains four chambers that are separated by septa, connective tissue that forms the cross formation associated with the heart. The four chambers of the heart are the right ventricle and right atrium as well as the left ventricle and left atrium (Figure 1).

*Figure 1. Diagram of the Adult Heart divided into 4-chambers. Gray arrows indicate the flow of deoxygenated blood and black arrows indicate the flow of oxygenated blood.*
As the chambers continue to form, valves that permit blood to flow from the atrial chambers to ventricular chambers must form. These valves, known as atrioventricular valves, also prevent the backflow of blood into the atrial compartments of the heart. In CHB, cardiac tissue formation is disrupted with the introduction of scar tissue on the atrioventricular valve, which affects the successful circulatory flow of blood through the heart and the development of the fetal heart (Miranda-Carus, Askanase et al. 2000).

Another major problem observed in NLE associated CHB is disruption of the developing cardiac conduction system NLE (Michaelsson and Engle 1972; Watson, Lane et al. 1984; Buyon 1998; Buyon, Hiebert et al. 1998). The cardiac conduction system requires that cardiac myocytes produce and propagate the electrical impulses that are required to establish and maintain the heart’s rhythm (i.e. heartbeat). The cardiac myocytes responsible for the formation of the cardiac conduction system develop and are located in the right atrium adjacent to the ventricle (Christoffels and Moorman 2009). At this location in the right atrium electrical impulses, due to calcium influx into the cardiac myocytes, necessary to cause heartbeats are generated. Specifically, this area of the right atrium is referred to as the atrioventricular node (AV node). The production of an electrical impulse at the AV node promotes ventricular contraction and the pumping of blood from the ventricle. However, this system is prevented from completely forming in severe cases of NLE- associated CHB (Michaelsson and Engle 1972; Watson, Lane et al. 1984; Buyon 1998; Buyon, Hiebert et al. 1998). The immune response of the fetus to the maternal autoantibodies increases inflammation of the developing cardiac tissues, block calcium influx in cardiac myocytes, and prevents the appropriate formation of the cardiac conduction system (Garcia and Campos-de-Carvalho 2000).
**Congenital Heart Block**

There are three categories of congenital heart block—first degree, second degree, and third degree heart blockage (Brucato, Cimaz et al. 2002). First-degree and second-degree heart blockage can progress to third degree heart blockage, irreversible CHB, without treatment. According to the National Heart, Lung, and Blood Institutes Disease and Conditions index, first degree heart block constitutes decreased movement of electrical signals travelling through the heart. Second degree heart block occurs when the movement of these signals is decreased on a larger level. In addition to slowed movement of electrical signals in second degree heart blockage, some electrical signals may not arrive at the ventricles. The blockage of signal results in the non-contraction of ventricles and their inability to pump blood throughout the body (Tincani, Rebaioli et al. 2005). Third degree heart blockage occurs when none of the electrical signals reach the ventricles. This degree of heart block is the most severe form of heart blockage and is associated with increased morbidity and lack of reversibility of the disorder in the fetus (Buyon, Clancy et al. 2009; Reynolds, Buyon et al. 2009). Importantly, there are no standard treatment measures to prevent CHB during gestation. Treatment after birth for babies diagnosed with NLE-associated CHB consists of pacemaker implantation or steroid treatment of newborn infant (Mevorach, Elchalal et al. 2009).

**Discussion**

**Systemic Lupus Erythematosus, Pregnancy and Medical Management**

SLE can affect individuals of all ages; however, it disproportionately affects women of childbearing years (McCarty, Manzi et al. 1995). Generally people with SLE can experience a
wide array of symptoms which can affect any system of the body, including the reproductive system housing a developing fetus. The fertility rate in patients with SLE is relatively normal compared to the general population; however, fetuses born to mothers with SLE may face major complications (Mok and Wong 2001). These complications range from spontaneous abortion to stillbirths (Mok and Wong 2001). Although certain studies suggest that SLE-associated flares increase during pregnancy, other studies show no change in the number of disease flares during pregnancy (Mok and Wong 2001). These differences likely occur because of a discrepancy in the definition of lupus flares and how disease activity is assessed within each study (Mok and Wong 2001). Common characteristics exhibited during pregnancy may be misread as lupus flares. These lupus-like symptoms include palmar erythema (reddening of the palms), temporary facial blush, increase in protein in urine due to an increase in glomerular filtration rate, and postpartum alopecia (hair loss) (Buyon 2009). However, some of the conditions mentioned above, specifically postpartum hair loss is common in all pregnancies; therefore, it is difficult to determine whether or not certain SLE-associated conditions are truly exacerbated by pregnancy. It has been suggested that different measures to evaluate SLE symptoms are needed to decipher between pregnancy and SLE-associated symptoms (Smyth and Garovic 2009). A specific timeframe of when SLE flares will occur in pregnancy has not been definitively described in the literature thus complicating diagnosis. When SLE flares do occur, it often presents itself as skin and joint inflammations. Women with a pre-existing diagnosis of SLE, who are planning to become pregnant, are highly advised to have a six month period without SLE disease flares before becoming pregnant (Khamashta 2006). Studies, demonstrate, that during this timeframe, pregnant SLE females have an increased risk of premature labor, and those with active lupus nephritis increase the likelihood of fetal mortality (Clark, Spitzer et al. 2005; Khamashta 2006).
Once pregnant, women diagnosed with SLE are to be considered high-risk and should be frequently monitored to maintain the health of the mother and the fetus (Mok and Wong 2001). SLE pregnancies are considered high risk because there is an increased risk of spontaneous miscarriage, pre-eclampsia, intra-uterine growth restriction, fetal death, and pre-term delivery (Khamashta 2006). When these high-risk pregnancies are identified, a team of doctors from a variety of disciplines, such as obstetrics/gynecology, internal medicine and rheumatology is advised to monitor the progress of the pregnancy.

Since treating SLE during pregnancy may present dangers to the developing fetus, these treatments must be closely monitored. Any treatment during pregnancy should be evaluated for their teratologic effects on the fetus. Drugs such as prednisolone, azathioprine, cyclosporine A and hydroxychloroquine help in preventing flares during pregnancy and can be maintained (Esplin and Branch 1997). However, medications such as methotrexate, mycophenolate mofetil, and cyclophosphamide have been found to be teratogens (Esplin and Branch 1997). It is advised to stop these medications three months prior to becoming pregnant (Khamashta 2006). Management of the disease is extremely important, while monitoring the type of drugs used for their possible toxic affects to the mother and/or the unborn fetus (Khamashta 2006). An additional concern that physicians have for pregnant mothers with SLE is whether lupus will be passed through maternal antibodies to the developing fetus. Recent studies demonstrate that a subset of females with SLE may pass on the disease causing maternal autoantibodies to the developing fetus (Lee 2005). These data suggest that approximately 3% of the pregnant mothers with SLE pass the disease on to their babies (Lee 2005).
Neonatal Lupus Erythematosus and Congenital Heart Block

Neonatal lupus erythematosus (NLE) is a fetal autoimmune disease suggested to be acquired by the passage of autoantibodies anti-Ro/SS-A and/or anti-La/SS-B from the mother to the fetus through the placenta (Oshiro, Derbes et al. 1997; Lee 2004). The exact mechanism as to how this autoantibody exchange occurs remains unknown and is the focus of current lupus research (Wahren-Herlenius and Sonesson 2006). The major condition associated with NLE is CHB; however, NLE has other associated fetal disorders. Skin lesions similar to those in SLE, hypo pigmentation (abnormal reduction of skin color), hepatitis (inflamed liver), and thrombocytopenia (reduced platelet count) are additional conditions that have been associated with NLE. These non-cardiac disease manifestations are typically temporary and symptoms are non-existent once maternal autoantibodies have exited the fetal circulation (Lee and Jarrett 1990).

CHB is a rare disease in the absence of heart structure irregularities occurring in 1 out of 15,000 to 1 out of 20,000 in the general population (Wahren-Herlenius and Sonesson 2006). Thirty-one percent (31%) of the children with CHB die, and 71% of them die in the first month of life. In children who survive, 67% require lifelong pacemakers (Yang, Chen et al. 2005). Individuals with SLE have an increased prevalence of high titers of Ro/SS-A and La/SS-B autoantibodies. These antibodies have been found to be associated with the development of CHB (Buyon, Rupel et al. 2004). This leads to a concern for pregnant SLE females because of the potential of these antibodies to cross the maternal-fetal barrier. The transmission of autoantibodies occurs during the middle of the second trimester (13-27 weeks). When these proteins begin to circulate through the fetal blood they can influence inflammation of the atrioventricular node and myocardial tissues in the neonate’s heart (Jaeggi, Fouron et al. 2004).
On a molecular scale, researchers are examining potential molecular mechanisms that may regulate the transmission of autoantibodies and participate in the formation of CHB.

CHB can be a lethal disorder, and therefore is important for early detection to reverse the effects of cardiac scarring caused by the initiation of apoptotic cardiac cells. In mothers with Ro/SS-A autoantibodies, 2-5% of neonates have been found to have complete CHB, which develops during the 18-24 week gestation period (Salomonsson, Sonesson et al. 2005). Salomonsson and colleagues proposed a model for the mechanism of the development of congenital heart block in fetuses of mothers with Ro/SS-A autoantibodies (2005). They have identified Ro/SS-A antigens that contain specific proteins which are pathogenic and promote CHB. Specifically, the Ro52 protein, a Ro/SS-A antigen has been discovered in mothers with fetuses diagnosed with complete CHB (Salomonsson, Sonesson et al. 2005). Salomonsson and colleagues propose the following model: Maternal autoantibodies, Ro/SS-A cross the placental barrier and enter the fetal circulation and bind to Ro/SS-A antigens on the surface of the cardiomyocyte (2005). This binding is very specific in pathogenicity, in that CHB was found to be associated with Ro/SS-A antibodies with the p200 epitope (Salomonsson, Sonesson et al. 2005). This highly specific antibody-antigen interaction has been associated with cases of third degree heart block and resulting in NLE-associated CHB. Upon binding to the Ro/SS-A antigen on the cardiomyocytes, calcium dysregulation and intracellular accumulation is induced in the affected heart cells (Salomonsson, Sonesson et al. 2005). Calcium (Ca\(^{2+}\)) is the leading regulator in the heart’s development of pacemaking and contractibility. An increased concentration of Ca\(^{2+}\) in heart cells disrupts the functionality of these two processes. Furthermore, the irregularity in calcium in the cells eventually leads to apoptosis of the cardiomyocytes (Salomonsson, Sonesson et al. 2005). This in turn can lead to a buildup of apoptotic cells in the cardiac muscle
tissue leading to potential scarring and fibrosis. It is this scarring and fibrosis that subsequently results in the formation of CHB (Figure 2). However, this model does assume that antigens necessary to elicit interaction with anti-RO/SS-A maternal antibodies are somehow released from their intracellular components and made available as targets for the maternal autoantibodies. To date no literature exists to address this physiological assumption.

**Figure 2.** Maternal Anti-SSA/Ro autoantibodies cross the placental barrier and bind the SSA/Ro antigens on the surface of cardiomyocytes. The binding of the antibodies signals apoptosis of the affected cardiomyocytes.

**Alternative model of the development of NLE-associated Congenital Heart Block**

In the previous sections the widely accepted mechanism for the development of NLE-associated CHB describes cardiomyocyte apoptosis as a result of the anti-Ro/SS-A maternal autoantibodies attacking the developing fetal heart and promoting calcium dysregulation leading to an accumulation of calcium and apoptosis. However, the above mechanism assumes antigens necessary for interaction with the maternal autoantibodies are made available on the cell surface
of developing fetal cardiac cells. However, the alternative mechanism that opposes this well accepted mechanism described previously, utilizes physiological apoptosis that occurs during normal fetal heart development to expose antigens to the maternal autoantibodies. More importantly, this alternative mechanism of NLE-associated CHB addresses the glaring assumption made in the previously described model, that anti RO/SS-A antigens are released from intracellular components and made available to maternal autoantibodies.

Typically during normal fetal heart development, apoptosis is a normal physiological event which functions in part as a “sweeping away” of unused cardiac cells (Pexieder 1975). This form of apoptosis occurs in the developing fetal heart in areas such as the endocardial cushion, developing conduction system and AV node. Physiological apoptosis during endocardial cushion formation permits the development of the septum between the atrium and ventricles. This alternative mechanism of NLE-associated CHB is thought to be regulated by a signal that utilizes apoptosis associated with the normal development of the heart and specifically cardiomyocytes. During fetal heart development, extra cardiomyocytes are made and are not used. In order to remove these additional cardiomyocytes, apoptosis occurs. It is this apoptosis that is believed to promote cell degradation and release of anti-Ro/SS-A antigens. After the release these antigens from intracellular compartments, these antigens are now free to interact with neighboring cardiac cells utilizing a paracrine cell signaling mechanism. Once released an attached to neighboring cells, these antigens are presented to anti Ro/SS-A maternal autoantibodies that are circulating in the fetal blood system and this interaction promotes fetal cardiac apoptosis (Figure 3). This increase of apoptotic events leads to fibrosis, pathologic accumulation of connective in the heart organ that can eventually lead to NLE-associated CHB.

This model is supported by the work of Tran and colleagues, where they found apoptosis
in the fetal conduction system of the heart and tested for the presence of Ro/La (La, also referred to as SS-B, an alternate version of the SS-A antigen) antigens on the surface of the cardiomyocytes once cells underwent normal apoptosis during development (2004). High levels of the antigens were detected and the apoptotic cells presented intracellular La antibodies on the cell surface. Additionally, anti-Ro/La maternal autoantibodies were found to be aggregated with human IgG in apoptotic cells in the areas such as the atrium, endocardial cushions and the AV node (Tran, Macardle et al. 2002; Tran, Ohlsson et al. 2002). More importantly this study utilizes an \textit{in vivo} model of anti-Ro/La antibody binding to the surface of apoptotic cells (Tran, Ohlsson et al. 2002). Other groups have proposed a similar model of NLE-associated CHB (Miranda, Tseng et al. 1998; Mazel, El-Sherif et al. 1999; Rosen and Casciola-Rosen 1999; Miranda-Carus, Askanase et al. 2000).

\textbf{Figure 3.} \textit{Alternative mechanism for the development of NLE-associated CHB.} A. Cardiomyocytes with intracellular anti-Ro/SS-A anti-Ro/SS-B antigens surrounded by anti-Ro and anti-La antibodies, B. Physiological apoptosis occurs; intracellular antigens are translocated to the cell surface. C. Neighboring cells become apoptotic due to signals sent by initial apoptotic cell. Apoptosis is accelerated due to the antibody-antigen interaction.
**Treatment of NLE-associated Congenital Heart Block and Development of Diagnostic Markers**

Due to the complete irreversible nature of CHB, identifying at risk mothers and administering preventative treatment is imperative in improving the survival of the neonate and possibly preventing the progression of first degree heart block to third degree heart block (referred to as CHB). There are several methods of prophylactic treatment for CHB. These treatments can include fluorinated glucocorticoids, immunosuppressants, intravenous immunoglobulin, and plasmapheresis (Yang, Chen et al. 2005). Ro/SS-A specific proteins are considered to be a potential marker of CHB in the fetus who progresses to complete CHB. Identifying a marker for NLE-associated CHB is important since not all mothers with Ro/SS-A and La/SS-B antibodies pass these antibodies to the fetus causing cardiac defects (Jaeggi, Fouron et al. 2004; Mevorach, Elchalal et al. 2009).

A fetus with NLE-associated CHB, can present with bradycardia, abnormally slow heartbeat, typically less than 50 beats per minute (Matsushita, Higashino et al. 2002). A normal fetal heart rate is between 110-180 beats per minute. As a method of treatment to improve the fetus’ heart rate, researchers have studied administering dexamethasone and β-sympathomimetic in-combination or individually to the mother (Jaeggi, Fouron et al. 2004). Jaeggi and colleagues concluded that the administration of dexamethasone did not revert effects of CHB; however, it improved the outcome of the fetus by circumventing other associated diseases from manifesting (2004). Additionally, Jaeggi and colleagues present evidence that demonstrates combining dexamethasone with β-sympathomimetic treatment to treat CHB-associated bradycardia significantly improves the outcome of the fetus (2004). Additional studies support the finding that administration of β-sympathomimetic increases the fetal heart rate (Matsushita, Higashino et
In other case reports salbutamol, terbutaline (β-sympathomimetic), and ritodrine, respectively, were successful in managing CHB (Groves, Allan et al. 1995; Koike, Minakami et al. 1997; Chan, Silverman et al. 1999). Further studies have found beneficial effects of the utilization of corticosteroids in reducing the immune-initiated damage to the developing fetal heart (Ostensen 2004; Hussain and Parke 2006; Tincani, Danieli et al. 2006; Jazwinska-Tarnawska and Niewinski 2008). Although these treatments have favorable results to the fetal outcome, long-term side effects of the medications can increase morbidity (Tincani, Danieli et al. 2006). For example, administration of high dose corticosteroids during pregnancy can lead to premature rupture of the membranes, intrauterine growth retardation, gestational diabetes, hypertension, osteoporosis, and avascular bone necrosis (Mok and Wong 2001).

After evaluating two possible models of CHB, I suggest a synthesis of the two models that focuses on apoptosis as a target for possible therapy. In each model, either by physiological occurrence or calcium dysregulation, the end result is apoptosis of the cardiomyocytes which exposes the intracellular antigens that could be identified with antibodies in maternal circulation. A possible pharmacological model for treatment would involve developing a drug that inhibits antibody binding to specific Ca\(^{++}\) channel which continues to be operationally functional. This chemical could possibly bind to a specific region on the antibodies which would prevent it from binding to their appropriate antigens despite interacting with these antigens. Because maternal Anti-Ro/SSA antibodies are innate to the maternal circulatory system and are key factors in both models, pinpointing this immunological structure would be pertinent to discovery of a treatment. A hypothetical drug would need to be administered to the gravid female during the critical phases of fetal cardiac development. Extensive pharmacological research testing would be needed to investigate the possibility of teratological effects on the fetus. In addition, molecular
and biochemical techniques such as electron microscopy and protein analysis should be utilized to identify the specific site the antibody that can be affected by the drug and to characterize the complete structural components of the antibody, respectively.

**Conclusion**

Systemic lupus erythematosus is an autoimmune disorder in which its symptoms can be exacerbated in affected pregnant females. The increase in symptoms in the female can negatively affect the health of the fetus, and it is imperative to closely monitor these at-risk pregnancies. This risk is due to the ability of maternal autoantibodies to cross the placenta and initiate pathogenesis of the fetus. One of the most severe SLE-associated conditions is the formation of congenital heart block and can develop as a result of the passage of maternal autoantibodies. Research has been initiated to examine the mechanisms of SLE-associated congenital heart block, and generate potential therapies to prevent the affects of maternal autoantibodies. To date two differing models of NLE-associated exist, however, with the current information available it is difficult to determine which model more precisely describes the mechanism regulating the formation of NLE-associated CHB. Since both models describe the formation of NLE-associated CHB result in cardiac apoptosis, it is plausible that both models present a part of the entire mechanism(s) and thus do not preclude either model. Specifically, it is possible that the “alternative mechanisms” is a precursor to the widely accepted model of maternal autoantibodies attacking developing fetal cardiac tissue and vice versa.

Understanding the molecular pathways of systemic lupus erythematosus, neonatal lupus erythematosus, and congenital heart block are all necessary in finding an effective treatment and possibly a cure. Research in these areas would be increasingly beneficial to the scientific community and helpful in improving the quality of life of individuals affected by SLE.
Additionally, as CHB associated with maternal lupus status is highly correlated with the ethnic background of the mother, these studies also offer the opportunity to examine a developmental model of health disparities.
**Bibliography**


