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Lupus and the Effects on Pregnancy

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Abstract

Systemic Lupus Erythematosus is a disease that manifests in many different ways. The cause of lupus still remains elusive. However, many of the pathologies associated with the disease as well as the disease process have been described. The pathophysiology of the disease as well as its effects on specific patient groups will be discussed below. More specifically, Systemic Lupus' effect on pregnancy with current diagnostic and treatment modalities will be the focus of this paper.

Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune disease that is common and affects around 400 per 100,000 people in certain populations. SLE mainly affects African or Hispanic women, especially during their reproductive years. The telltale sign of SLE is the production of autoantibodies, specifically antinuclear antibodies (ANAs). The most common method for detecting these ANAs is indirect immunofluorescence, which can recognize antibodies that bind to nuclear antigens, such as DNA, RNA, and proteins. Besides ANAs, patients with SLE have a variety of other autoantibodies that fight against red blood cells, platelets, and lymphocytes. The causes of SLE, like most autoimmune diseases, are unknown. However, genetic, environmental, and immunological factors seem to play a role (Kumar, et. al. 2018). Fatigue, joint pain, and rash are the most common symptoms of SLE. SLE is unique because of the disease's ability to appear and disappear called flares. Flares are known to occur during rapid hormonal changes, as occurs in pregnancy. For women with SLE, pregnancy is a major concern. Pregnancy is a high-risk time for SLE patients because flares during pregnancy may be related to increased irreversible organ damage (Ateka-Barrutia, Khamashta, 2013). The risk of flare during pregnancy depends on the disease activity 6-12 months before conception; the risk is higher in those who have had repeated flares preconception. Therefore, women living with SLE who are thinking about conceiving should consult their rheumatologist prior to conceiving, so that they can monitor disease activity to ensure the best outcome for mother and baby.

Methods

The data in this paper was compiled using Pubmed, ProQuest, and Google Scholar. PubMed and Proquest were accessible through Touro College's Online Library system. Key terms used to search were: "SLE pregnancy", "SLE", "hydroxychloroquine", and "autoimmune diseases".

Discussion

Pathogenesis of Systemic Lupus Erythematosus

The principle deficiency in SLE is the failure of the mechanisms that maintain self-tolerance. Although the cause(s) of the lack of self-tolerance remains unknown, there are several genetic, environmental, and immunological factors that seem to play a role.

There is a lot of evidence that suggests a genetic predisposition to SLE. Family members have a higher risk of developing SLE, and even twenty percent of uninfluenced first-degree family members have autoantibodies. The concordance of SLE in monozygotic twins is twenty-five to fifty percent and around five percent in dizygotic twins, which suggests that genetic factors play a crucial role in the predisposition of SLE (Kumar, et. al. 2018). The above said indicates a polygenic inheritance of the disease- it is approximated that at least 4 susceptibility genes are required in order to develop SLE (Schur, 1995).

Studies reveal that SLE susceptibility involves human leucocyte antigen (HLA) class II gene polymorphisms. In patients from different backgrounds, a relation between HLA DR2 and DR3 with SLE is a regular finding with an odds ratio for developing SLE of roughly 2 to 5 (Pisetsky, 1997). Which means, a person with HLA DR2 and DR3 are two to five times more likely to develop SLE than a person without HLA DR2 and DR3. HLA class II genes have also been linked to the presence of some autoantibodies, for example: anti-Sm, anti-Ro, anti-La, anti-nRNP, and anti-DNA antibodies. HLA class III genes, specifically those "encoding complement components C2 and C4", are major contributors in the development of SLE. Patients with homozygous C4A null alleles, regardless of their background, have a higher risk of having SLE. Additionally, SLE is connected to inherited deficiencies of C1q, C1r/s, and C2 (Mok, Lau, 2003). A reduction in complement activity could encourage SLE susceptibility by damaging the neutralization and removal of foreign and self-antigens. "When the antigen burden overwhelms the clearance capacity of the immune system, autoimmunity may ensue" (Mok, Lau, 2003). Other polymorphic genes have been linked to SLE such as: tumor necrosis factor alpha, interleukin six, the T cell receptor, CR1, Fc gamma RIIA and Fc gamma RIIIA, immunoglobulin Gm and Km allotypes, and heat shock protein seventy (Sullivan, 2000). Nonetheless, in majority of cases, consistent results were not reported in studies of patients from different ethnic backgrounds.

Although genetic factors play a crucial role in regard to the predisposition towards SLE, the start of the disease stems from environmental triggers. Infectious agents, such as bacterial DNA/endotoxins and retroviruses, may cause particular reactions by molecular imitation and disrupt immunoregulation. Viruses might set off or induce a flare in lupus by harming tissues to release autoantigens,

triggering B cells, and inducing SLE by molecular imitation. But, viral findings have not been consistent in the tissues of people with lupus (Herrmann, et. al. 1996). Therefore, there is not enough evidence to defend that any one infectious agent causes SLE. Certain diet choices, like alfalfa sprouts and high intake of saturated fats, influences the making of inflammatory mediators. Alfalfa sprouts contain L-canavanine which has been associated with the development of SLE-like symptoms (Prete, 1985). Procainamide, hydralazine, chlorpromazine, isoniazid, phenytoin, and penicillamine are drugs that alter "cellular responsiveness and immunogenicity of self-antigens" (Mok, Lau, 2003). Procainamide and hydralazine are aromatic amines or hydrazines, and they can cause an SLE-like disorder (Adams, Mongey, 1994). Ultraviolet light may aggravate SLE in many patients. UV light can trigger inflammation, promote cellular apoptosis, and induce tissue damage. Exposure to the sun's light causes and aggravates SLE. Exposure of skin to ultraviolet light changes the location and/or chemistry of DNA, Ro, and nRNP antigens, and also amplifies their immunogenicity. Recent studies have shown that ultraviolet light causes the apoptosis of human keratinocytes, which brings about the development of clusters on the exterior of dying cells, that hold nuclear and cytoplasmic antigens. This supplies a method for the exposure of self-antigens to the immune system and evokes autoimmunity (Mok, Lau, 2003).

To summarize: UV light and other environmental factors cause the apoptosis of cells. Insufficient removal of the nuclei of these cells leads to a large burden of nuclear antigens. Underlying abnormalities in B lymphocytes and T lymphocytes are accountable for flawed tolerance, and, as a result, self-reactive lymphocytes live on and stay functioning. Said lymphocytes are activated by nuclear self-antigens, and antibodies are made to fight the antigens. Complexes of the antigens and antibodies stick to Fc receptors on dendritic cells and B cells and might be engulfed. The nucleic acid elements engage toll-like receptors (TLRs) and trigger B cells to create more autoantibodies. TLR stimuli also trigger dendritic cells to make interferons and other cytokines, which intensifies the immune response and induces more apoptosis. The overall result is a "cycle of antigen release and immune activation resulting in the production of high-affinity autoantibodies" (Kumar, et. al. 2018).

Autoantibodies

The number one hallmark, and the number one concern, of lupus is the production of autoantibodies. These antibodies attack the patient's own molecules found in the cytoplasm, nucleus, cell surface, and soluble molecules like coagulation factors and IgG. Antinuclear antibodies are found in more than ninety five percent of SLE patients; anti-double stranded DNA (ds-DNA) and anti-Sm antibodies are specific for SLE and not found in patients with other autoimmune diseases, making them very important in the diagnosis (Tan, et. al. 1982). ANAs can be divided into 4 groups: antibodies to DNA, antibodies to nucleolar antigens, antibodies to nonhistone proteins bound to RNA, and antibodies to histones. Additionally, many other autoantibodies are found in patients with SLE. These autoantibodies attack lymphocytes, platelets, and red blood cells. Thirty to forty percent of SLE patients have anti-phospholipid antibodies. These patients have complications secondary to excessive clotting (Kumar, et. al. 2018).

Symptoms of SLE

SLE is a chronic disease, meaning that the disease is long lasting, in this case specifically, the disease waxes and wanes. The symptoms and the effects on daily life of SLE vary, however, there are some that were seen in nearly all patients. A group of patients were selected from 6 rheumatology practices that were spread across the United States between May and July 2014. These patients were between the ages of eighteen and seventy-five and had a clinical diagnosis of lupus. Ninety eight percent of patients reported they felt fatigue, ninety three percent reported joint pain, eighty eight percent reported a rash, eighty percent reported swelling of feet, legs, fingers, or hands and joint stiffness. Because SLE is chronic it has major effects on a patient's daily life and activities. Sixty one percent of those interviewed had difficulty with housework, thirty nine percent had difficulty driving and sleeping, and twenty two percent had difficulty caring for children. Sixty two percent of the patients who participated in this study were not working outside the home; ninety one percent said that this was caused by SLE (Mathias, et. al. 2018).

Hormonal Effects on SLE

Lupus is primarily a female disease; it is "characterized by a 9:1 female to male ratio of disease incidence" (Weckerle, Niewold, 2011). Generally, SLE occurs between puberty and menopause, the reproductive age range (15:1 ratio). Occurrence of SLE before puberty and after menopause is uncommon. Furthermore, patients with a hypergonadotrophic disorder, namely Klinefelter's Syndrome, are prone to lupus as well. From these observations, it is assumed that endogenous sex hormones play a major role in lupus (Mok, Lau, 2003).

Epidemiological studies show a connection between the use of exogenous estrogens and the emergence of

lupus. The Nurses' Health Study revealed that hormonal replacement therapy and the use of oral contraceptive pills have an association with an increased chance of developing SLE (Sanchez-Guerrero, et. al. 1997). Lupus improvement was observed in patients who had gone through menopause or an oophorectomy. Conversely, lupus flares mainly occur during hormonal changes, such as pregnancy, exogenous estrogen administration, puerperium, and ovulation during IVF (Mok, Wong, 2001). Many patients exhibit disease flares during the second half of their menstrual cycle, this has been attributed to the mid-cycle estrogen surge. Additionally, patients who develop lupus after the age of fifty were reported to have a milder disease and less significant organ involvement. All these observations are helpful in explaining and understanding why pregnancy for SLE patients is extremely difficult.

Pregnancy and SLE Pregnancy

Healthy, normal pregnancy causes the body to go through many physiological changes; these changes may influence rheumatic disease expression. Most organ systems go through some level of change during pregnancy. The glomerular filtration rate goes up by fifty percent during a normal pregnancy. Subsequently, women with preceding proteinuria might be expected to have a noticeable rise in urinary protein excretion in the 2nd and 3rd trimesters. There is also an expected thirty-fifty percent elevation in intravascular volume; women who have cardiac or renal compromise might not endure this well. Additionally, blood counts are usually different during pregnancy. Anemia is usual due to hemodilution, and in eight percent of uncomplicated pregnancies there is an occurrence of thrombocytopenia. The chance of venous thromboembolism increases by fivefold during normal pregnancy, because of the prothrombotic state that pregnancy creates along with compression by the expecting uterus and venous stasis (Sammaritano, 2016).

In normal pregnancy, the mother's immune system is altered in order to ensure fetal health and survival: immunoglobulin secretion rises, cell mediated immunity decreases, and pregnancy-specific proteins work to inhibit lymphocyte function (Branch, Wong, 2014). General immunosuppression would reduce maternal resistance against infection, so instead, there is an activation in the maternal immune system during pregnancy of immune-modulatory molecules and immunocompetent cells (Ostensen, Clowse, 2013). Cytokines and chemokines manage these immunocompetent cells with T helper cells; cytokines are an important factor in supporting successful pregnancy. The Th1/Th2 cytokine shift is a crucial immunological change that occurs during pregnancy. Th2 includes numerous interleukins which trigger antibody synthesis and humoral immunity. In pregnancy a prevalence of the Th2 response might be anticipated, and since lupus is predominantly a Th2-mediated disorder, aggravation of the disorder is more likely (de Jesus, et. al. 2015).

Pregnancy is high-risk for women with SLE, because disease flares during pregnancy have been linked to organ damage. Therefore, it is recommended that every woman with lupus should receive a preconception evaluation which should assess organ damage related to lupus, medications, and disease activity. If a patient is taking medications for lupus that have adverse effects on pregnancy, it is suitable for the patient to change to a lower risk medication (Flint, et. al. 2016). Additionally, for the best pregnancy outcome and for the mother's safety, it is advised that women with SLE should conceive during a time of inactive disease. Disease flares during pregnancy have been linked to disease activity six to twelve months before conception. Lupus flare within 6 months prior to conception has been linked to a significant rise in the chance of flare during pregnancy and a fourfold increase in pregnancy loss (Clowse, 2007).

Pregnancy for women with lupus has been linked to: risk of flare, preeclampsia, hypothyroidism, stroke, preterm birth, hypertension, pre-gestational diabetes, caesarean section, placental deficiencies leading to intrauterine growth restriction (IUGR), pregnancy loss, and even death. The Danish National Registry stated that maternal complications were found in fifty percent of lupus pregnancies (Jakobsen, et. al. 2015). A recent study observed thirteen thousand five hundred and fifty-five SLE pregnancy deliveries. Twenty five percent of SLE pregnancies were delivered preterm, meaning the pregnancy was shorter than thirty-seven weeks (Yan Yuen, et. al. 2008). Six to thirty five percent of babies were born small for gestational age. One in five lupus pregnancies ended in pregnancy loss (compared with one in ten from controls), with a four to six-fold increased likelihood of stillbirths compared with controls (Clark, et. al. 2003). Disease activity within six months before conception has been linked to an increased rate of fetal loss. Patients with anti-dsDNA antibodies have the highest risk for preterm birth and pregnancy loss. Patients with lupus have a three to four-fold increased chance of developing preeclampsia. Antiphospholipid antibodies are found in thirty-forty percent of SLE patients and have been linked to negative obstetric outcomes. Women with aPL antibodies have an increased chance of developing IUGR, preeclampsia, preterm birth, and fetal loss (Smyth, et. al. 2010).

The PROMISSE study observed three hundred and eighty five women with lupus and found that fifteen percent of

them experienced a mild flare, whereas five percent experienced an extreme flare. Sixty percent of women with active SLE prior to conception experienced flares during pregnancy, however, only ten percent of women with inactive SLE prior to conception experienced flares during pregnancy (Buyon, et. al. 2015). A study conducted in Sweden observed five hundred and fifty one first singleton births to patients with lupus and assessed their outcomes in comparison to the general population. This study included twelve thousand eight hundred and forty seven normal pregnancies, one hundred and ninety eight pre-lupus women, sixty five women who were first diagnosed with lupus zero-two years after giving birth, and one hundred and thirty three women who were diagnosed two-five years postpartum. Compared to those who were diagnosed with lupus two-five years after their first pregnancy, those with lupus during their first pregnancy, or diagnosed soon after, had the highest risk of poor clinical outcomes. Twenty six percent of women who were diagnosed with lupus zero-two years after giving birth had preeclampsia during pregnancy, thirteen percent of women who were diagnosed two-five years after giving birth had preeclampsia during pregnancy, and sixteen percent of women who had lupus while pregnant had preeclampsia; while only approximately five percent of women without lupus had preeclampsia (Arkema, et. al. 2016).

Over the last forty years some of the adverse pregnancy outcomes have improved. A study compared lupus pregnancies from forty years earlier to their current pregnancy group, which consisted of eighty three pregnant women. The rate of pregnancy loss decreased dramatically from forty percent to seventeen percent, compared with the general population rate of sixteen percent. On the other hand, the preterm delivery rate did not change dramatically. It only dropped from thirty seven percent to thirty two percent versus nine to twelve percent preterm delivery rate of the general population (Clark, et. al. 2005). A Norwegian study analyzed pregnant women with connective tissue diseases, including lupus, over the last four decades. Although maternal and fetal complications were more prevalent in lupus patients compared to the general population, the number of births did increase and the rate of C-sections, low birth weight infants, and preterm births decreased (Wallenius, et. al. 2015).

Effects of SLE on the Baby

Complications during pregnancy can impact fetal and neonatal outcomes. There is an increased chance of preterm delivery, preeclampsia, fetal loss, and low birth weight babies in women with lupus. When maternal autoantibodies, aPL antibodies, anti-Ro/SS-A and anti-La/SS-B antibodies are present there are more precise risks. The presence of aPL antibodies has been commonly linked to prematurity and intrauterine growth restriction. Anti-Ro or anti-La antibodies are found in around thirty percent of SLE patients. These autoantibodies can cross the placenta by active transport between the sixteenth and thirtieth weeks of pregnancy. Babies who are born to women with anti-Ro/SS-A and anti-La/SS-B antibodies have an increased risk of having neonatal lupus erythematosus (Sammaritano, 2016). These autoantibodies have been linked to the development of congenital complete heart block and noncardiac neonatal lupus erythematosus expressions such as: transaminitis, reversible thrombocytopenia, and photosensitive rash (Brito-Zero'n, et. al. 2014).

Congenital complete heart block is the most serious condition linked to anti-Ro/SS-A and anti-La/SS-B antibodies and occurs in approximately two percent of babies born to mothers with these antibodies. If the mother previously had a child with congenital heart block, then the risk for the second child having it increases to eighteen percent; if the mother previously had two children with congenital heart block then the risk increases to fifty percent (Brucato, et. al. 2001). In more than eighty percent of children with congenital heart block the mother had anti-Ro or anti-La antibodies. Typically, congenital heart block develops between sixteen and twenty four weeks of pregnancy, and it can be recognized by low fetal heart rate which is less than sixty beats per minute. Anti-Ro and anti-La antibodies attack the myocardium and fetal atrioventricular node. This causes immune mediated inflammation and fibrosis in tissues that are affected, resulting in various levels of heart block or cardiomyopathy (Llanos, et. al. 2012). The risk of death for babies affected is around ten-twenty percent and most of those who survive require a permanent pacemaker.

Various treatments for congenital heart block have been tried. Because of their capability to diffuse across the placenta, fluorinated steroids are used for cases that involve myocarditis, hydrops, or incomplete heart block due to its potential to reverse the affects (Friedman, et. al. 2009). Exposure to hydroxychloroquine throughout pregnancy might lower the chances of development of congenital heart block (Izmirly, et. al. 2012).

Treatments/Management of SLE Pregnancy

Firstly, patients with lupus who are considering pregnancy should be closely followed by their rheumatologist and obstetrician. Lupus should be quiescent, and the patient should be on medications that are low risk for approximately 6 months before conception. Recent studies show that antimalarial medications are beneficial for the

mother and baby and have few side effects, and therefore should be taken throughout pregnancy. In one study of one hundred and eighteen lupus pregnancies, poor pregnancy outcomes were dramatically reduced in the women who were taking hydroxychloroquine. "Preterm delivery rates were 15.8% in that group versus 44.2% in untreated patients, and rates of IUGR were 10.5% versus 28.6%" (Leroux, et. al. 2015). In a different study, women who stopped taking hydroxychloroquine suffered remarkably more lupus activity than women who continued hydroxychloroquine (Clowse, et. al. 2006). The use of hydroxychloroquine throughout pregnancy in patients with lupus minimizes the number of flares and hypertensive disorders. Hydroxychloroquine is safe to use during pregnancy, and there have been no "reported malformations, growth restriction and ocular, auditory, or neurological toxicity in exposed fetus" (Ruiz-Irastorza, Khamashta, 2011). Hydroxychloroquine is secreted in breast milk; however, there were no reports of negative effects in children who were breastfed.

In the case of disease reactivation during pregnancy, corticosteroids are usually used. Since fluorinated corticosteroids diffuse across the placenta, they should not be taken during pregnancy. On the other hand, non-fluorinated corticosteroids, (prednisone, prednisolone, methylprednisolone, hydrocortisone) are broken down by placental 11 beta-hydroxysteroid dehydrogenase, and only ten percent of drug dosage crosses the placenta. That said, non-fluorinated corticosteroids are connected to various complications such as diabetes, preeclampsia, and hypertension; therefore, low doses are recommended (prednisone<7.5 mg/day) (Ruiz-Irastorza, et. al. 2012). A dose of above ten mg/day of prednisone has been linked to a higher chance of developing dyslipidemia, arterial hypertension, maternal hyperglycemia, and fluid retention. Non-fluorinated corticosteroids are only slightly passed into breast milk and is permitted during breastfeeding. However, if the dose is high then women should wait four hours after taking the corticosteroid to breastfeed.

Most immunosuppressive medications are stopped during pregnancy and breastfeeding, except azathioprine in doses up to two and a half mg/kg/day, cyclosporin, and tacrolimus. Although cyclosporin has been deemed safe to use during pregnancy, it has been linked to an increased chance of preeclampsia, hypertension, and gestational diabetes (Ateka-Barrutia, Khamashta, 2013). Mycophenolate mofetil, methotrexate, and cyclophosphamide are not safe to use during pregnancy and should be switched to safer drugs.

NSAIDs are overall safe to use throughout pregnancy if they are limited to short term usage. However, long term use of NSAIDs have been linked to cardiac and renal failure, fluid overload, and hypertension in the mother, and renal disorders and oligohydramnios in the fetus. The use of these medications should only take place at the end of pregnancy, after thirty weeks of gestation (Ostensen, et. al. 2006).

Antiplatelets and anticoagulants are also used to treat lupus. The use of low-dose aspirin (75-100 mg/day) and dipyridamole is safe to use during pregnancy. Aspirin can be used even throughout labor or epidural anesthesia to decrease the chance of hemorrhagic issues. Since heparins do not diffuse across the placenta, they are safe to use throughout pregnancy and breastfeeding. However, warfarin is damaging to the fetus during organogenesis (the first six-ten weeks of pregnancy) and therefore should not be taken during this timeframe (Ostensen, et. al. 2006). Patients taking these medications should be switched to heparin when pregnancy is confirmed.

Conclusion

Systemic Lupus Erythematosus is a disease with varying severity in the population, but one that can have devastating effects on mother and baby. Advances in the understanding of the disease as well as treatment and prevention of flare ups have allowed women with lupus to have successful and healthy pregnancies with favorable outcomes. It is imperative however, that women with lupus seek guidance from their rheumatologist and obstetrician and focus on prenatal care for the best possible outcome for mother and baby.

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