Study of Pregnancy Related Complications in Patients with Systemic Lupus Erythematosus (Retrospective and Prospective Study)

Thesis

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LIST OF ABBREVIATIONS

ACA	Anticardiolipin antibody
ACE	Angiotensin Converting Enzyme
ACR	American College of Rheumatology criterion
ALT	Alanine transaminase
ANA	Ant nucleosom antibody
anti-ds DNA	Anti-double-stranded deoxyneucloprotein
anti-Sm	Anti-Smith antibodies
anti-U_1RNP	Anti-uridaylate-rich ribonucleoprotein
APLA	Antiphospholipid antibod
APS	Antiphospholipid syndrome
ARD	Autoimmune rheumtic disease
ARDS	Adult respiratory distress syndrome
AST	Aspartate aminotransferase
AV time	Atrio Ventricular time
BILAG	Britsh Isles Lupus Assesment
C3	Complement 3
C3a	Complement 3a
C4	Complement 4
C4a	Complement 4a
C5a	Complement5a
CBC	Complete blood count
CD25	Cluster of differentiation 25
CD4	Cluster of differentiation 4
CH50	Complement H50
CHB	Congenital heart block
CK	Creatinine kinase
CMV	Cytomegalo virus
CNS	Central nervous system
CrCl	Creatinine clearance
CRP	C-reactive protein
CS	Cesarean section
CSF	Cerebrospinal fluid
CT	Computed tomography
CTDs	Connective tissue diseases
CVS	Cardiovascular system
DHEA	Dehydroepiandrosterone
DLCO	Diffusing capacity for carbon monoxide
DM	Dermatomyositis
ECLAM	European Community Lupus Activity Measure
ELNT	Euro-Lupus Nephritis Trial
ESR	Erythrocyte sedimentation rate
GBM	Glomerular basement membrane
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GIT	Gastrointestinal tract
HELLP	Haemolysis, Elevated Liver enzymes, Low Platelets
Hgb	Hemoglobin
HPF	High power field
hrs	Hours

HSM	Hepatospleenomegaly
HTN	Hypertension
IgA	Immunoglobulins A
IgG	Immunoglobulins G
IgM	Immunoglobulins M
IL-10	Interleukin 10
IL-4	Interleukin 4
IL-6	Interleukin 6
IUFD	Intrauterine fetal demise
IUGR	Intrauterine growth restriction
IVIG	Intravenous immunoglobulins
LAI-P	Lupus activity index in pregnancy
LDH	Lactate dehydrogenase
MCTD	Mixed connective tissue diseases
MRI	Magnetic resonance imaging
NSAIDs	Nonsteroidal antiinflammatory drugs
PAN	Polyarteritis nodosa
PM	Polymyositis
PNH	Paroxysmal nocturnal hemoglobinuria
PROM	Premature rupture of membranes
RA	Rheumatoid Arthritis
RBCs	Red blood cells
RES	Reticuloendothelial system
Scr	Serum creatinine
SLAM	Systemic Lupus Activity Measure
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus disease Activity Index
SPF	Skin protection factor
SS	Sjögren syndrome
SSc	Systemic sclerosis
TBA	Total body area
Th1	T helper type 1
Th2	T helper type 2
TIA	Transient ischemic attack
TLR 9	Tolllike receptor 9
TTP	Thrombotic thrombocytopenic purpura
UCTD	Undifferentiated Connective Tissue Diseases
UV	Ultra violet rays
UV-A	Ultra violet A
UV-B	Ultra violet B
WBC	White blood cells
WHO	World Health Organization

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic, multisystem autoimmune disease that occurs predominantly in women of childbearing age. Lupus is characterized by autoantibody production and a dysfunctional immune system resulting in organ inflammation and consequent damage ***(Dhar & Sokol, 2006).*** Lupus is a definitive diagnosis when at least 4 of the 11 of the American College of Rheumatology's criteria for lupus are fulfilled ***(Tan et al., 1982).***

Pregnancy is an important clinical setting for disease management in this group of patients. Complications of pregnancy, particularly preeclampsia, can be difficult to distinguish from symptoms of lupus making diagnosis and treatment challenging. Lupus can be detrimental to the pregnancy and may cause adverse fetal outcomes. Conversely, pregnancy can cause flares of lupus disease activity often times necessitating maternal immunosuppressive intervention ***(Dhar & Sokol, 2006).***

Among the reported effects of SLE on the fetus is a greater number of abortions, fetal loss, preterm deliveries and perinatal mortality ***(Meyer, 2004).*** Moreover, the newborn may be affected by the onset of neonatal lupus erythematosus (neonatal LE), manifested as a skin or blood disease, or by the presence of

congenital heart block (CHB). Neonatal LE is intimately associated with the presence of anti-Ro/SSA and anti-La/SSB antibodies ***(Cavallasca et al., 2008).***

Advances in the understanding of the pregnancy-lupus interaction have resulted in better methods of monitoring and treating this clinical situation. As a result, maternal and fetal outcomes have improved over the last few decades ***(Dhar & Sokol, 2006).***

Fetal wastage may result from several factors, including disease activity, hypercoagulability and placental pathology. Renal impairment and hypercoagulability increase the risk for fetal wastage ***(Germain & Nelson-Piercy, 2006).*** Fetal growth is impaired when blood flow through the placenta is restricted by placental pathology. Hypercoagulability can result in placental infarctions and consequent fetal hypoxia. This hypercoagulability could be due to sticky platelet syndrome, pregnancy-induced protein S deficiency, increased inflammatory factors related to lupus disease activity (e.g., factor VIII, von Willebrand factor activity, von Willebrand factor antigen and fibrinogen), hyperhomocystinemia due to folate deficiency, and antiphospholipid antibodies (e.g., lupus anticoagulant, anticardiolipin antibodies and false positive rapid plasma reagin test). Placental pathology in pregnancies complicated by lupus is

characterized by ischemia/hypoxia, decidual vasculopathy, decidual and fetal thrombi, chronic villitis, decreased placental weight and placental infarctions along with deposits of fibrin, IgG, IgM, IgA and C3 in the trophoblastic membrane ***(Ogishima et al., 2000).***

Aim of the Work

This study is a retrospective study of previously pregnant SLE patients and prospective study follow up of recently pregnant SLE patients in order to study pregnancy related complications in patients with SLE.

Systemic Lupus Erythematosus

Systemic lupus erythematosus is a chronic, recurrent, potentially fatal multisystem inflammatory disorder that can be difficult to diagnose ***(Edworthy, 2001).*** The disease has no single diagnostic marker; instead, it is identified through a combination of clinical and laboratory criteria ***(Petri, 1998).*** Accurate diagnosis of systemic lupus erythematosus is important because treatment can reduce morbidity ***(Dammacco et al., 2000)*** and mortality ***(Bellomio et al., 2000).***

Systemic lupus erythematosus most often manifests as a mixture of constitutional symptoms, with skin, musculoskeletal, and hematologic (mild) involvement. However, some patients present with predominantly hematologic, renal, or neuropsychiatric manifestations ***(Schur, 2007).*** Patients with systemic lupus erythematosus appear to be at high risk for coronary artery disease ***(Rahman et al., 1999)***. Infections, especially of the respiratory and urinary systems, also are common in patients with the disease and are difficult to distinguish from flares of lupus activity ***(Schur, 2007).***

The clinical manifestations of systemic lupus erythematosus are fundamentally the same in children and adults ***(Lehman, 2003).***

The Pathogenesis of Systemic Lupus Erythematosus

SLE is not contagious; it is incurable and responds to drug therapy. Lupus presents as three different types: cutaneous lupus, sometimes referred to a discoid lupus; drug induced lupus erythematosus; and the most pathologically involved, SLE. Cutaneous lupus primarily affects the integument. Drug-induced lupus erythematosus is a temporary form of lupus that is precipitated by an interaction with a drug. This type of lupus resolves after the drug is stopped. SLE may cause death if not appropriately managed and treated ***(Childs, 2006).***

As with all autoimmune diseases, a dysfunction in self tolerance precipitates injury/damage to cells and organs by the immune system. Immune system differentiation of self from nonself is referred to as self-tolerance ***(Sommer, 2002).***

Epidemiology

SLE varies among age, race, and sex. Lupus affects both men and women; however, women aged 15–45 years are affected more frequently than men ***(Lash & Lusk, 2004).***

Race-based statistics show a higher incidence in African American women than in White women ***(Childs, 2006).*** Being of Black ethnicity also increases the severity of SLE, leading to greater morbidity and mortality ***(Bongu et al., 2002)***.

Although women are affected more often than men, men who have SLE develop more severe pathophysiologic outcomes related to hematologic, neurologic, renal, and vascular disease ***(Petri, 2005).***

Immunopathogenesis of Systemic Lupus Erythematosus

The main immunologic dysfunction of SLE is the deposition of immune complex in various cells that precipitates inflammation with eventual organ pathology. Vasculopathy and vasculitis are related to the sequelae of endothelial cell damage. The similarities in pathologic responses seen in most organ system dysregulation are abnormality in cellular basement membranes, cellular proliferation, inflammation, and the deposition of immunoglobulins M, G, and A (IgM, IgG, IgA) into cells and tissues. Complement components are also activated. Activated complement consists of membrane and plasma proteins that modify cell membranes and promote inflammation ***(Atkinson & Liszewski, 2001).***

Toxins, tissue trauma, humoral response, exposure to ultraviolet sunlight, and complement activation are known to precipitate the development of SLE ***(Childs, 2006).***