Fetal and Maternal Outcome in SLE Patients Treated with LMWH Three Years Experience (2009-2011)

Thesis

Submitted for fulfillment of Master Degree in
Obstetrics and Gynecology

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2016

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Acknowledgment

First and above all thanks to ***Allah***

I would like to express my endless gratitude and appreciation to my eminent professor, ***Prof. Dr. Raafat Mohamed Riad****, professor of Obstetrics and Gynecology, Cairo University, for giving me the honor to work under his supervision and from whom I did learn a lot, his guidance helped me in all the time of research and writing of this thesis.*

My sincere thanks to ***Dr. Eman Aly Hussein****, Assistant professor of Obstetrics and Gynecology, Cairo University, for her continuous guidance, honest help and endurance that made this study come to light.*

Last but not the least, I would like to thank my family: my mother and to my brother, sister and my husband for supporting me spiritually throughout writing this thesis and my life in general.

List of Abbreviations

ACA	:	Anticardiolipin antibody
ACE	:	Angiotensin Converting Enzyme
ACR	:	American College of Rheumatology
ACS	:	Acute Coronary Syndrome
ANAs	:	Antinuclear antibodies
ANF	:	Antinuclear factor
Anti-Sm	:	Anti- Smith
aPL	:	Antiphospholipid antibody
APS	:	Antiphospholipid antibody syndrome
aPTT	:	Activated Partial Thromboplastin Time
ARDS	:	Acute Respiratory Distress Syndrome
BILAG	:	British Isles Assessment Group
CBC	:	Complete blood count
CHB	:	Complete Heart Block
CNS	:	Central nervous system
CRP	:	C- reactive protein
CT	:	Computed tomography
DRVVT	:	Diluted Russell Viper Venom Test
dsDNA	:	Double stranded DNA
ECG	:	Electrocardiogram
ELISA	:	Enzyme Linked Immunosorbent Assay
EM	:	Electron microscope
ENA	:	Extractable nuclear antigen
ESR	:	Erythrocyte sedimentation rate
ESRD	:	End Stage renal Disease
FDA	:	Food and Drug Administration
GBM	:	Glomerular basement membrane
GFR	:	Glomerular Filtration Rate
GN	:	Glomerulonephritis
GWAS	:	Genome Wide Association Studies
HCQ	:	Hydroxychloroquine
HELLP	:	Hemolysis Elevated Liver enzymes Low Platelets Syndrome
HIT	:	Heparin Induced Thrombocytopenia
HLA	:	Human Leukocyte Antigen
Hpf	:	High power field
HSP	:	Heat Shock Protein
HUS	:	Hemolytic Uremic Syndrome
IF	:	Immunofluorescence

Ig	:	Immunoglobulin
IL	:	Interleukin
IUGR	:	Intrauterine Growth Retardation
IVIG	:	Intravenous immunoglobulin
LAC	:	Lupus anticoagulant
LDL	:	Low Density Lipoprotein
LM	:	Light microscope
LMWH	:	Low Molecular Weight Heparin
MRA	:	Magnetic Resonance Angiography
MRI	:	Magnetic Resonance Imaging
MS	:	Multiple sclerosis
NL	:	Neonatal Lupus
NSAIDs	:	Nonsteroidal Anti-inflammatory drugs
P-ANCA	:	Perinuclear Antineutrophil Cytoplasmic antibody
PCI	:	Percutaneous Intervention
PIGF	:	Placental Growth Factor
PRES	:	Posterior Reversible Encephalopathy syndrome
RBC	:	Red blood cell
SGA	:	Small for Gestational Age
SIRS	:	Systemic Inflammatory Response Syndrome
SLAM	:	Systemic Lupus Activity Measures
SLE	:	Systemic Lupus Erythematosus
SLEDAI	:	Systemic Lupus Disease Activity Index
SnRNPs	:	Small nuclear Ribonucleoproteins
SSA	:	Sjogren's syndrome A
SSB	:	Sjogren's syndrome B
TIA	:	Transient ischemic attack
TTP	:	Thrombocytopenic purpura
UFH	:	Unfractionated Heparin
WBC	:	White blood cell
WHO	:	World Health Organization

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ABSTRACT

Antinuclear antibody is the most sensitive screening test currently available for confirming the diagnosis of systemic lupus when accompanied by typical clinical finding, when three or more typical clinical features are present, such as skin, joint, kidney, pleural, pericardial, hematological, or central nervous system findings. Anti DNA antibody test is the most specific test for SLE, raised titres of antibodies to DNA and low complement usually indicate active disease or lupus flare.

Despite improvement in overall survival rates, patients with SLE still have a death rate that is 3 times that of the general population.

SLE affects pregnancy and its outcome by three main ways. First; SLE increases the risks of late pregnancy losses due to hypertension and renal failure. Secondly it is an important cause of heart block and other cardiac defects in the newborn. This effect may be part of a more general neonatal lupus syndrome. Thirdly, SLE increases the risk of fetal loss independently of hypertension or renal failure. This is usually in the presence of antiphospholipid antibodies.

Key words:

Fetal and Maternal Outcome in SLE Patients Treated with LMWH Three Years Experience

INTRODUCTION

Systemic lupus erythematosus (SLE) is one of the most common autoimmune disorders that affect women during their childbearing years. Typical clinical symptoms of SLE include fatigue, fever, arthritis, a photosensitive rash, serositis, Raynaud phenomenon, glomerulonephritis, vasculitis, and hematologic abnormalities. Flares of SLE are uncommon during pregnancy and are often easily treated ***(Gladman et al., 2010).***

SLE increases the risk of spontaneous abortion, intrauterine fetal death, preeclampsia, intrauterine growth retardation, and preterm birth. Prognosis for both mother and child are best when SLE is quiescent for at least 6 months before the pregnancy and when the mother's underlying renal function is stable and normal or near normal. Lupus nephritis can get worse during pregnancy ***(Madazli et al., 2010).***

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 and Lusk et al., 2004).***

Specific SLE related deaths, such as those due to nephritis, usually occur within the first 5 years of symptom onset. Infectious complications related to active SLE and immunosuppressive treatments are now the most common causes of death in early active SLE. Cardiovascular disease and malignancy, which may be related to chronic inflammation and cytotoxic therapies, are common etiologies of late mortality ***(Magadmi et al., 2004).***

The kidney is the most commonly involved visceral organ in SLE. Although only approximately 50% of patients develop clinically evident renal disease(lupus nephritis), biopsy studies demonstrate some degree of

renal involvement in almost all patients. Glomerular disease usually develops within the first few years after onset and is usually asymptomatic. Acute nephritic disease may manifest as hypertension or hyperlipidemia. Acute or chronic renal failure may cause symptoms related to uremia and fluid overload ***(Gordon et al., 2002).***

Neonatal lupus with skin rashes and congenital heart block can occur in the babies of mothers with antibodies to SSA/RO ***(Asherson et al., 2003).***

The antiphospholipid antibody syndrome (APS) is defined by two major components: presence in the plasma of at least one type of autoantibody known as an antiphospholipid antibody (aPL), and the occurrence of at least one clinical feature from a diverse list of potential disease manifestations. The most common of these clinical manifestations are categorized as venous or arterial thromboses, recurrent fetal loss, or thrombocytopenia ***(Bonnie et al., 2009).***

Risks of pregnancy increase markedly in the presence of lupus nephritis, hypertension, and active disease, especially at the time of conception, and pregnancy is contraindicated until remission can be achieved. Though pulmonary hypertension in lupus is uncommon, in pregnancy it confers to a high risk of maternal death. All women with lupus should receive careful counseling before planning a pregnancy, both in terms of control of the disease and medications potentially toxic to the fetus ***(Gordon et al., 2002).***

The use of exogenous hormones has been associated with lupus flares, suggesting a role of hormonal factors in the pathogenesis of the disease ***(Costenbader et al., 2007).***

The long-term effect of pregnancy in patients with systemic lupus erythematosus (SLE) is unknown. Data from retrospective studies suggest no clinically significant adverse or positive effect of pregnancy on the course of SLE. Currently, more than 50% of all pregnancies in women with lupus have a normal outcome. About 25% of women with lupus deliver healthy babies prematurely. Fetal loss due to spontaneous abortion occurs in fewer than 20% of cases. Patients with SLE may have increased rates of emergency or cesarean delivery secondary to flares of renal disease or preeclampsia. Over the past 50 years, the survival rate in patients with SLE has improved dramatically. In 1955, the 5-year survival rate was only 50%, whereas by the 1990s, the 10-year survival rate was approaching or exceeding 90%, and the 20-year survival rate was approaching 70%. Factors contributing to this improvement include early diagnosis, increased potency of pharmaceutical agents, and improved treatments (eg, dialysis, kidney transplantation).Nonetheless, despite improved survival rates, mortalities among patients with SLE remain 3-5 times greater than those in the general population***(Izmirly et al., 2010)***

A multidisciplinary approach, with close medical, obstetric and neonatal monitoring is essential for optimal outcomes ***(Clowse et al., 2008)***

Aim of the Work

The objective of this study is to highlight the effect of LMWH treatment on pregnant patients suffered from SLE, aiming at improving the fetal and maternal outcome

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is one of the most common autoimmune disorders that affect women during their childbearing years. Typical clinical symptoms of SLE include fatigue, fever, arthritis, a photosensitive rash, serositis, Raynaud's phenomenon, glomerulonephritis, vasculitis, and hematologic abnormalities. SLE increases the risk of spontaneous abortion, intrauterine fetal death, preeclampsia, intrauterine growth retardation, and preterm birth. Prognosis for both mother and child are best when SLE is quiescent for at least 6 months before the pregnancy and when the mother's underlying renal function is stable and normal or near normal. Lupus nephritis can get worse during pregnancy.***(Motha et al., 2009).***

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 and Lusk, 2004).***

More than 90% of cases of SLE occur in women, frequently starting at childbearing age ***(blank et al., 2009)***. The female to male ratio is 9:1 (or greater), as it is predominantly a post pubertal female disease ***(Petri, 2006).***

Worldwide, the prevalence of SLE varies. The highest rates of prevalence have been reported in Italy, Spain, Martinique, and the United Kingdom Afro-Caribbean population. ***(Danchenko et al., 2006)***

The use of exogenous hormones has been associated with lupus onset and flares, suggesting a role of hormonal factors in the pathogenesis of the disease ***(Costenbader et al., 2007).***

The risk of SLE development in men is similar to that in prepubertal or postmenopausal women. Interestingly, in men, SLE is more common in those with Klienfelter syndrome (i.e. genotype XXY), further supporting a hormonal hypothesis. In fact, a study by Dillon et al found that men with Klienfelter syndrome had a more severe course of SLE than women but a less severe course than other men ***(Dillon et al., 2011).***

Pathophysiology:

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by multisystem inflammation with the generation of autoantibodies. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic, epigenetic, ethnic, immunoregulatory, hormonal, and environmental factors ***(D'Cruz et al., 2008)***

Potential mechanisms:

It is important to note that antibodies may be present for many years before the onset of the first symptom of SLE ***(Arbuckle et al., 2003).***

One longstanding proposed mechanism for the development of autoantibodies involves a defect in apoptosis that causes increased cell death and a disturbance in immune tolerance ***(Hahn et al., 2005).*** The redistribution of cellular antigens during necrosis/ apoptosis leads to a cell-surface display of plasma and nuclear antigens in the form of nucleosomes. Subsequently, dysregulated (intolerant) lymphocytes begin targeting normally protected intracellular antigens. The defective clearance of the apoptotic cell debris allows for persistence of antigen and immune complex production ***(Munoz et al., 2009).***

T cells have long been thought to play a central role in SLE pathogenesis, and T cells from patients with lupus show defects in both signaling and effector function. These T cells secrete less interleukin (IL)-2, and one defect in signaling seems to be linked to an increase in calcium influx, possibly due to changes in the CD3 signaling subunits. The following seem to be adversely affected in T cells from patients with SLE: effector activity such as CD8 cytotoxicity; T-regulatory, B-cell help; migration; and adhesion. However, the method by which each of these deficits contributes to the exact clinical syndrome seen in an individual patient is still unknown ***(Cancro et al., 2009).***

Serum antinuclear antibodies (ANAs) are found in nearly all individuals with active SLE. Antibodies to native double-stranded DNA (dsDNA) are relatively specific for the diagnosis of SLE. Whether polyclonal B-cell activation or a response to specific antigens exists is unclear, but much of the pathology involves B cells, T cells, and dendritic cells. Cytotoxic T cells and suppressor T cells (which would normally down-regulate immune responses) are decreased. The generation of polyclonal T-cell cytolytic activity is impaired. Helper ($CD4^+$) T cells are increased. Reports pointing to important roles of interferon-alpha, transcription factors, and signaling variations also point to a central role for neutrophils ***(Bosch et al., 2011).***

***Genetics*:**

There is a clear genetic component in SLE, with a sibling risk ratio 8-fold to 29-fold higher than that in the general population and a 10-fold increase in disease concordance in identical twins. In addition, there is a 24-56% concordance rate in monozygotic twins, compared with a 2-5% risk in dizygotic twins ***(Deng et al., 2010).***