MATERNAL AND FOETAL OUTCOMES OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS ADMITTED TO THE MATERNITY WARD AT GROOTE SCHUUR HOSPITAL: A RETROSPECTIVE STUDY

by

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Contents

Declaration

I, **Lindisa Mbuli**, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Background:

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease commonly affecting females of child-bearing age, hence hormonal changes in pregnancy are thought to play a role in disease activity – often necessitating changes in immunosuppression therapy. SLE is common in Cape Town, however, the effect of pregnancy on SLE and vice versa has not been well characterised. The aim of this study is to report on the pregnancy outcomes of patients with SLE presenting to the maternity department of Groote Schuur Hospital, Cape Town.

Methods:

This study was designed as a retrospective review of records of pregnant women known with SLE and followed up at the maternity section of Groote Schuur Hospital. The duration of the survey was from 1 January 2003 to 31 December 2013. Records were identified using the attendance registers in the relevant departments.

Results:

There were 61 pregnancies reviewed in 49 patients; 80.3% of the pregnancies were in patients of mixed ancestry and the rest (19.7%) in black African patients. The mean age at presentation of the current pregnancy was 27.2±5.0 years. Mean gestational age at presentation and delivery was 13.0 ± 6.0 weeks and 28.9 ± 9.8 weeks respectively and 47.5% of the pregnancies were in patients with lupus nephritis (LN). Thirty-nine (63.9%) pregnancies reached the third trimester and 11.5% of all pregnancies ended in the first trimester. There was a lower number of live births to mothers of African ancestry than to those of mixed ancestry (p=0.001).

In 55.7% of the pregnancies, no flare was reported while a renal flare was reported in 23%. Pregnancies in patients with LN had higher frequencies of flares (58.6% vs 31.3%; p=0.032), pre-eclampsia (34.5% vs 12.5%; p=0.041), longer stay in hospital (12.0 ± 9.1 days vs 6.1 ± 5.1 days; p=0.004) and low birth weight babies (1.94 ± 1.02 kg vs 2.55 ± 0.95 kg; p=0.046) than in patients without LN. Only 36 (59%) of the neonates were discharged home alive and of these 2 (5.6%) were to mothers of black African ancestry (p=0.001).

Conclusion:

Increased lupus activity in pregnant SLE patients may account for the increased deaths of neonates born to SLE mothers. Patients of black African descent and those with LN tend to have a poorer outcome. A multi-disciplinary approach to the management of SLE patients (of child-bearing age or pregnant) needs to be further evaluated.

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Figures and Tables

Chapter 1:

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List of abbreviations

- GSH: Groote Schuur Hospital
- UCT: University of Cape Town
- SLE: Systemic lupus erythematosus
- LN: Lupus nephritis
- Non-LN: Non-lupus nephritis
- CKD: Chronic kidney disease
- MDGs: Millennium Development Goals
- HIV/Aids: Human immunodeficiency virus/ acquired immune deficiency syndrome
- ACR: American College of Rheumatology
- ANA: Antinuclear antibody
- SLICC: Systemic Lupus International Collaborating Clinics
- ISN/RPS): International Society of Nephrology – Renal Pathology Society
- SLEDAI: Systemic Lupus Erythematosus Disease Activity Index
- BILAG: British Isles Lupus Assessment Group Index
- ECLAM: European Consesus Lupus Activity Measurement
- SLAM: SLE activity measure
- DVT: Deep vein thrombosis
- TH1: CD4+ T-helper cells have type 1 cells
- TH2: CD4+ T-helper cells have type 2 cells
- TH17: CD4+ T-helper 17 cells
- TREG: Regulatory T-helper cells
- IFN γ: Interferon gamma
- TNF α: Tumor necrosis factor alpha
- IL: Interleukin
- TNFR: TNF receptors ,
- I IL-R: Interleukin receptors
- TGFβ1: Transforming' growth factor beta 1
- PIBF: Progesterone-induced blocking factor
- NF-AT: Nuclear factor of activated T cell
- DNA: Deoxyribonucleic acid

- HELLP syndrome: Haemolysis, elevated liver enzymes and low platelet count syndrome
- MAHA: Microangiopathic haemolytic anaemia
- APS: Antiphospholipid syndrome
- LAC: Lupus anticoagulant
- ACL: Anticardiolipin antibodies
- Anti-β2GP1: Anti-beta 2 glycoprotein 1
- HIT: Heparin-induced thrombocytopenia
- ACE-I: Angiotensin Converting Enzyme Inhibitors
- Anti-ds-DNA: Anti-double stranded deoxyribonucleic acid
- LDH: Lactate dehydrogenase
- ALT: Alanine aminotransferase
- AST: Aspartate aminotransferase

Chapter 1: Literature Review

1.1. Background:

Recently Dr. Graca Machel, the widow of former president Nelson Mandela, argued that Africa may not be able to achieve some of its targeted Millennium Development Goals (MDGs) by the end of 2015.(1) Goal 4 of the MDGs aims to reduce child mortality by two thirds whereas Goal 5 aims to improve maternal health through the reduction of maternal deaths and to achieve universal access to reproductive health. These goals are one of the most important and measurable promises that the international community has pledged to women and children. In South Africa, almost one third of all childhood deaths are neonatal.(2) Immaturity accounts for almost 45% of all early neonatal deaths, however, some progress has been made globally with reduction in early childhood mortality from 12.4 million in 1990 to 8.8 million in 2008.(2,3)

Obstetric haemorrhage and high blood pressure cause more than 50% of pregnancy and childbirth deaths globally. In South Africa, non-pregnancy related infections (for example, tuberculosis in HIV-positive women) alone account for 40%, obstetric haemorrhage 14% and hypertension 14% of all maternal deaths.(2) Although auto-immune conditions were reported to account for 2.8% of overall maternal mortality in South Africa, the use of acute and chronic medications, especially immunosuppressive therapy in patients with auto-immune diseases and disease flares during pregnancy, can confound or even contribute to the major causes of mortality in these patients.(2)

Systemic lupus erythematosus (SLE) is an auto-immune disease of unknown aetiology and is characterised by multi-system involvement associated with variable clinical manifestations and disease course characterised by pathogenic auto-antibody formation, immune complex deposition, and end organ damage.(4). This disease is a manifestation of complex interplay between genetic factors, hormones, auto-antibodies and environmental factors.(5) Like most auto-immune diseases it affects mostly women of child-bearing age (up to 90% at diagnosis) but all genders, ages and ethnic groups are susceptible.(6,7)

Women with SLE not treated with alkylating chemotherapeutic agents like cyclophosphamide have normal fertility as autoimmune ovarian failure is rare and therefore, pregnancy is often uncomplicated in these patients. However, pregnancy in SLE patients is regarded as “high risk” as it may increase SLE activity with adverse short-term and long-term maternal outcomes: maternal death, stroke, hypertension, pre-eclampsia or eclampsia, nephritis with accelerated end organ damage requiring dialysis.(8) SLE also has adverse outcomes on pregnancy and foetal outcomes characterised by pregnancy loss, preterm birth, low birth weight, intrauterine growth retardation and neonatal death. In the United States of America (USA) it is estimated that there are 3 200 to 4 500 SLE pregnancies per year, and these are associated with a significantly increased rates of hypertensive disorders, higher risk of Caesarean delivery and longer hospital stays compared with the general obstetric population.(8, 9) Estimates of pregnancy and its effects on SLE and vice versa are not readily available in Africa.

1.2. Systemic Lupus Erythematosus

1.2.1 Epidemiology of disease and clinical features:

SLE is a chronic multi-organ, auto-immune, inflammatory disease which predominantly affects adults with propensity for women of child-bearing age of between 20 to 40 years, but may affect all age groups and both sexes with only 8% to 15% of SLE cases occurring in children.(10) Table 1 summarises the incidence in different countries both in the developed and developing countries.

Table 1: Data of the estimated incidence of SLE in different countries

COUNTRY	Author (Year) [REF]	INCIDENCE
USA[#]	ernknopf et al (2011) (10)	2 - 7 per 100 000 persons per annum
United Kingdom	Johnson et al (1995) (11)	3.8 per 100 000 persons per annum
South Africa	Jessop et al (1973) (12)	2.4 per 100 000 persons per annum
India	Kumar A (2002) (13)	3 per 100 000 persons per annum
China (Hong Kong)	Mok et al (2008) (14)	6.7 per 100 000 persons per annum

 # United States of America

The prevalence of SLE ranges from 14.6 to 68 cases per 100 000 persons in the USA; the paucity of data from Africa makes the true prevalence of SLE difficult to ascertain in Africa.(10) It has been suggested from published reports that women of African descent are up to four times more likely than Caucasian women to develop the disease. In South Africa, SLE has been reported to be more common in women of mixed ancestry than in Africans (12,15). However, whether the ongoing epidemic of HIV/Aids (common in black Africans) plays a modulating effect on this disease, presentation has not been critically assessed.

Five- and 10-year survival for patients with SLE in the developed world has been reported to be about 88% - 96% and 75% - 95% respectively. (10) This has been attributed to the earlier diagnosis and more effective treatment options available in developed countries, which have effectively increased the 20-year survival rates to an estimated 80%.(10) Studies from South Africa show a 10-year survival rate of less than 40%; although this figure is compounded by a high rate of loss of follow-up of patients. (5)

1.2.2 Classification criteria:

Over the years there has been a concerted effort for development of a tool or criteria that is easy to apply and adapt for the diagnosis and classification of SLE. Siegel and Lee described early criteria in 1962 in an effort to standardise diagnosis and classification of SLE, and subsequently 14 criteria were selected in 1971 by the American College of Rheumatology (ACR) as a classification criteria, with only four criteria needed to make a diagnosis.(16) In 1982 the ACR criteria were published and included the ANA test and reduced to 11 criteria. In 1997 the ACR criteria were revised by the committee and included anti-phospholipid antibodies as one of the criteria as proposed by MC Hochberg and the item “LE preparation” was

deleted.(16,17) The attempt has always been to ensure a consistent definition of SLE for purposes of research and surveillance of the disease.

The 1982 ACR criteria have been validated, but the subsequent revised criteria of 1997 have not been validated. The Systemic Lupus International Collaborating Clinics (SLICC) group, an international group of investigators dedicated to SLE clinical research, had undertaken to revise the SLE classification criteria to address multiple concerns that have arisen since the development of the 1982 ACR criteria. A formal assessment of the important clinical manifestations of SLE and the limitations of the 1982 ACR criteria, conducted by the SLICC group, was published in 2004, highlighting possible duplication of highly correlated terms relating to cutaneous lupus such as malar rash and photosensitivity. The need to use new standards in the quantification of proteinuria; limitation to seizures or psychosis without any other cause for neurological manifestation of SLE and omitting many other neurological manifestations of SLE; immunological manifestation omission of low complement levels and new information regarding anti-phospholipid antibodies and the inclusion of patients who did not satisfy any of the criteria for immunological disorder, being classified as having SLE.(17)

In 2012 the SLICC criteria were published with 17 criteria. Refer to appendix 1(17).
The proposed classification rule is as follows:

"Classify a patient as having SLE if he or she satisfies four of the clinical and immunological criteria used in the SLICC classification criteria, including at least ***one clinical criterion and one immunological criterion,*** *OR if he or she has a biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-ds DNA antibodies."*

The SLICC classification criteria have been validated in studies involving multi-centre population sample versus the 1997 revision of the ACR criteria which were never validated, but it should be noted that the SLICC criteria, as is the case with the original revised ACR criteria, have not been tested for purposes of diagnosis.(17)

Lupus nephritis is present if an SLE patient is shown to have proteinuria more than 500mg/day or when the cellular casts in the urine and/or histologically proven.(17,18) Urine abnormalities raise the suspicion of nephritis but confirmation requires renal biopsy. Lupus nephritis is histologically categorised into six classes according to the International Society of Nephrology – Renal Pathology Society (ISN/RPS) classification as shown in Table 2. The presence of proliferative forms of LN has been demonstrated to be a predictor of poor outcome in SLE patients.

Table 2: International Society of Nephrology – Renal Pathology Society (ISN/RPS) Classification of Lupus Nephritis (19)

LN class	Histological description
Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis (<50% glomeruli)
III (A)	Active lesions
III (A/C)	Active and chronic lesions
III (C)	Chronic lesions
Class IV	Diffuse lupus nephritis (>50% glomeruli)
	Diffuse segmental (IV-S) or global (IV-G)
IV (A)	Active lesions
IV (A/C)	Active and chronic lesions
IV (C)	Chronic lesions
Class V	Membranous lupus nephritis
Class VI	Advanced sclerosing lupus nephritis
	(≥90% globally sclerosed glomeruli without residual activity)

1.2.3 SLE disease activity assessment:

Since SLE is a chronic disease, its characteristics are of continued disease activity and natural history of progressive accumulation of injury of the same organ at diagnosis, or further involvement of new organ systems over its chronic history even with appropriate management. Three patterns of disease activity have been recognised:

- Remitting relapsing pattern (flare)
- Chronically active disease with persistent disease symptoms and clinical or laboratory signs
- Long quiescence or remission.

The use of clinical evaluation, laboratory investigations and standardised disease activity tools (for example, SLEDAI (20), BILAG (21), ECLAM (22), SLAM (23)) can be employed to differentiate between the different disease patterns of SLE.

The SLICC/ACR Damage Index measures cumulative organ damage after the diagnosis of lupus and is updated yearly; and has been validated and proven reliable to determine cumulative damage of SLE over the determined time period or years in patients with the disease. Poor prognosis has been associated with higher damage scores early in the disease with associated high mortality. The SLICC/ACR Damage Index tool, together with the disease activity indices, complement each other to determine/predict or prognosticate outcomes of SLE patients. (24)

1.2.4 SLE and pregnancy:

A female patient with SLE who becomes pregnant faces a potential risk to her health and that of her foetus. SLE can have a severe disease flare which may be potentially life-threatening and other drugs used to control the disease may be teratogenic and foetotoxic. Pregnancy seems to be a risk factor for SLE flare with

estimated two- to three-fold increase in SLE activity during pregnancy and puerperium. The estimation is 35- to 70% of all SLE pregnancies will have a flare but with a lower risk of moderate to severe flare, being 15- to 30%.(8) Most flares are mild, cutaneous and joint disease being the most common manifestations. Pregnancies in patients with SLE and underlying chronic hypertension, renal disease, anti-phospholipid antibodies, and anti-SSA (Ro) and anti-SSB (La) antibodies are high risk for adverse outcomes.(25-29)(30) In general, women with SLE uncomplicated by hypertension or renal impairment prior to conception, usually have successful pregnancies, and pregnancy does not have an adverse effect on the progression of renal disease.(31) SLE in remission for at least six months prior to conception minimises the risk of flares during pregnancy and the discontinuation of hydroxychloroquine before or during pregnancy is associated with significant higher risk of SLE flares.(32) It is likely that therapy changes may also have major influence on pregnancy risk, therefore fetotoxic drugs, eg Mycophenolate mofetil, angiotensin converting enzyme inhibitors/ angiotensin receptor blocker, cyclophosphamide and methotrexate should be avoided.

The understanding of SLE and advancement in management has seen the disease no longer a contraindication for pregnancy with the exception of organ-system complications like pulmonary hypertension and advanced chronic kidney disease being a relative contraindication to falling pregnant. According to Clark et al (33), in the past 40 years there has been a decrease in the rate of pregnancy loss rates in patients with SLE and this has been attributable to disease management and recognition that inactive disease in contrast to stable disease is an important consideration in reducing both maternal and foetal morbidity. The rate of loss in SLE

pregnancies over the past 40 years decreased from a mean of 43% between 1960 and 1965 – to 17% between 2000 and 2003.(33)

Also, SLE carries a two- to three-fold risk of foetal loss compared to the general population and the risk is increased in mothers with high disease activity, anti-phospholipid antibodies and active lupus nephritis.(25) SLE pregnancies have poor outcomes compared with non-SLE pregnancies even after adjusting for modifiable risk factors like obesity, tobacco smoking, and alcohol or drug abuse during pregnancy. Diabetes mellitus and hypertension is a common co-morbid diagnosis attributable to disease and treatment complications which places SLE pregnancies at higher risk than other women. Pregnancy complications like Caesarean section, pre-term labour, intrauterine growth restriction, pre-eclampsia and eclampsia are two- to four-fold higher in women with SLE than the non-SLE population as summarised in Table 3 below.(25)

Table3: Pregnancy complications in SLE pregnancies (25)

Pregnancy complications	**Percentage of SLE deliveries with the complication**	**Percentage of non- SLE deliveries with the complication**
Caesarean section	36.6%	25.0%
Pre-term labour	20.8%	8.1%
Intrauterine growth restriction	5.6%	1.5%
Pre-eclampsia	22.5%	7.6%
Eclampsia	0.5%	0.09%

SLE pregnancies have high maternal mortality rate ranging from 325-1100/100 000 live births in the USA, a rate that is more than 20 times higher than the mortality rate

for the non-SLE population.(25) Clowse et al have shown in their study that compared to the general population, SLE pregnancies had higher risk of medical complications like thrombotic complications (10-fold higher), infectious complications caused both by disease-related immune dysregulation and immunosuppressive therapy (five- to eight-fold higher) and haematological complications as summarised in Table 4 below.

Table 4: Medical complications in SLE pregnancies (25)

Medical complications	Percentage of SLE deliveries with the complication	Percentage of non-SLE deliveries with the complications
Thrombotic Complications		
Stroke	0.32%	0.03%
Pulmonary embolus	0.4%	0.04%
DVT*	1.0%	0.01%
Infectious complications		
Sepsis	0.5%	0.1%
Pneumonia	1.7%	0.2%
Haematological complications		
Transfusion	2.7%	0.5%
Postpartum haemorrhage	4.5%	3.3%
Antepartum bleeding	2.0%	0.4%
Anemia at delivery	12.6%	6.8%
Thrombocytopenia	4.3%	0.4%

*Deep vein thrombosis

1.2.5 Physiological changes in pregnancy that can mimic SLE:

Certain physiological changes that occur in pregnancy can sometimes mimic symptoms of SLE. These changes sometimes can make the diagnosis or flare of SLE difficult. Increased blood volume in pregnancy (up to 50% increase) can cause anaemia and also be responsible for thrombocytopenia in 5- to 10% of pregnant women.(8)

Also, changes in the urinary system such as the increased renal blood flow and dilatation of the collecting system can cause proteinuria and haematuria through an increase in glomerular filtration rate that occurs in early pregnancy and bleeding from small venules in dilated collecting system, respectively.

Musculoskeletal changes such as muscle and joint pain commonly seen in pregnancy may be a mimic of some of the musculoskeletal features of SLE.

During pregnancy, complement C3 and C4 may rise by 10- to 50% secondary to increased liver protein synthesis, and thus a flare with complement activation may occur despite apparently normal levels of C3 and C4.(34) Conversely, C3 and C4 may be low in the absence of SLE flare, probably due to synthetic defects. However, the drop of C3 or C4 levels by more than 25%; is reasonable to be attributed to disease activity.(35)

1.2.6 Pregnancy, cytokines and disease activity in SLE

1.2.6.1 Hormones and cytokines in normal pregnancy:

Pregnancy introduces a unique situation where genetically different individuals co-exist in a single body for up to an average of between 38 and 40 weeks, which has

initiated a lot of research to understand the mechanism of tolerance. Hormones are produced by the corpus luteum and trophoblast with complex alterations the hypothalamus-pituitary-adrenal axis with profound influence in functioning of the innate and adaptive immunity from proliferation, distribution and functioning of immune cells.(36) The interaction of myeloid dendritic cells which are antigen presenting cells results in activation of T cells under the influence of cytokines facilitated by chemokines. Cytokines and chemokines regulate T-helper cells function, which are effector cells in immune response. T-helper cells are involved in interactions with antigen presenting cells and with the B cells which form the antibodies, via specific signalling pathways and cytokine production. Interplay between hormones, cytokines and effector T-helper cells is important for a successful pregnancy.(36) The CD4+ T-helper cells have type 1 cells (TH1) which are involved in the cell mediated immunity, while the type 2 (TH2) cells are involved with humoral (antibody) mediated immunity. Tom Wegmann in 1993 proposed that successful pregnancy was a TH2 process with suppression of TH1 cell response.(37) TH1 cells produce different cytokines (interferon gamma (IFN γ), tumor necrosis factor α (TNF α), interleukin-12 (IL-12) and interleukin 2(IL-2)) and TH2 produce interleukin 4 (IL-4), interleukin 10 (IL-10) and interleukin 13 (IL-13). Uncomplicated successful pregnancies are associated with suppression of TH1 response and TH 1 type response in reproductive failures.(38)(36) TNF-α and IFN-γ are necessary in early pregnancy for successful implantation and development of placenta and may be detrimental in late pregnancy. (36, 39, 40) The placenta increases the production of IL-10 during late pregnancy which down regulates the production of pro-inflammatory cytokines by TH1 cells and macrophages, hence cytokine expression at the feto-maternal interface is regulated according to the stage

of pregnancy to create optimal conditions for foetal development.(41) There are other subset of CD4+ T-helper cells which are T-helper 17 cells (TH 17) which are pro-inflammatory and are defined by production of interleukin-17 (IL-17); and regulatory T-helper cells (TREG) which are key cells type to self-regulate against attacks and destruction of own. TREG suppress CD4+ and CD8+ T-cell proliferation and also antigen presenting cells through production of interleukin-2 (IL-2). There is a close relation for differentiation of T cells either to TREG or TH 17 cells, which is dependent on the presence of transformation growth factor β1(TGFβ1). Presence of TGFβ1 favours TREG while in the co-presence of IL-6 predominant differentiation into the TH17 subtype occurs.(42) Properly functioning TREG are important for successful healthy pregnancy, they are critical for maternal immune tolerance both locally in the uterus, and in the systemic circulation.(43) (44,45) According to Tower et al, the generation of TREG seems to be controlled by FOXP3 enhancer element and they recognise the paternal antigens and have inhibitory effect on maternal immune effector cells.(43) TREG cells increase in the first trimester, peak in the second trimester and dip post-partum.

In uncomplicated non-SLE pregnancy there is increase in regulatory molecules that have modulator effect on circulating cytokines and cytokine actions. These are soluble interleukin receptors which block binding and uptake of certain cytokines in cells. Among them are TNF receptors (TNFR), interleukin 1 receptors (IL-1Ra) which buffer the biological effect of both the TNF-α and IL-1β, and interleukin 6 receptors (IL-6R). (41) The IL-Rs have been shown to increase in pregnancy especially in the second and third trimester in women with healthy pregnancies. In healthy pregnancies the secretion of cytokines by peripheral lymphocytes and monocytes changes with diminished pro-inflammatory response over the course of pregnancy.

(36,46) There is decrease in TNF-α, IL-1β and IL-6 with progression of pregnancy, while IL-4 and IL-10 remain stable.(47) Progesterone induces the expression of the immune-modulatory protein, progesterone-induced blocking factor (PIBF) by the peripheral lymphocytes. PIBF is associated with an increase of IL-10 production which has an anti-inflammatory effect. (36,48,49) Oestrogen has multiple effects on the immune system, it can up-regulate multiple genes like bcl-2 gene on B cells, blocking tolerance induction on naïve B cells and enhance transitional B cells' resistance to apoptosis expanding the population of marginal zone B cells. Thus oestrogen may facilitate the differentiation and maturation of pathogenic naïve auto reactive B cells.(50,51) Oestrogen can influence T cells by increasing the expression of calcineurin, a calcium/calmodulin-activated protein phosphate enzyme playing a key role in regulating the transcription factor (nuclear factor of activated T cell – NF-AT) during T cell activation which in turn upregulate the expression of IL-2 which stimulates the growth and differentiation of T cell response and production of other cytokines.(52, 53) Oestrogen has also been shown in vitro to reduce apoptosis of peripheral mononuclear cells and to reduce TNF-α; and it can activate dendritic cells while prolactin has inhibition effect. (54) In viewing all the data and evidence, pregnancy is a well-balanced immunological environment that doesn't favour one immunological state over the other, but a milieu that changes with each stage of pregnancy to favour successful pregnancy outcomes.

1.2.6.2 Hormones and cytokines in pregnant SLE patient:

In diseases like SLE and other connective tissue diseases there is both T cell signalling and cytokine level derangement, thus generation of high-affinity auto-antibodies and cell mediated tissue damage.(55) The immune system's capacity to self-regulate via T cells is also compromised in SLE.(43, 56) Pro-inflammatory TH 17 cells are usually found in high numbers in inflammatory sites in SLE and conditions like pre-eclampsia and recurrent pregnancy loss.(43) IL-17 is a cytokine capable of stimulating the inflammatory response through chemokines and cytokine production, and proliferation and recruitment of neutrophils, macrophages and lymphocytes.(42) As mentioned above, TREG cells increase in the first trimester, peak in the second trimester and dip post-partum. The TREG are lower in women with SLE compared to healthy women and this persists through the whole pregnancy; with a lower capacity to activate TGFβ1 in women with SLE.(43) This could suggest impaired pregnancy tolerance in SLE patients, which may explain increased pregnancy risks in this cohort of patients.

Prolactin has dual effect, pro-inflammatory as oestrogen and also inhibitory to the immune system. High levels of prolactin can break tolerance of high-affinity DNA-reactive B cells and T cell dependent autoreactive follicular B cells.(57) In small human and animal studies bromocriptine an anti-prolactin has been shown to reduce clinical activity of SLE par to hydroxychloroquine, which may be proof that increase prolactin may be a driver of disease flare in pregnancy and pueperium.(54,57-59)

These immunological changes in pregnancy may be useful in explaining some of the adverse events that occur in SLE patients.

1.2.7 Medical conditions in pregnancy that make diagnosis SLE flare difficult:

Thrombocytopenia, while potentially a marker of SLE activity can occur in pregnancy as a physiological phenomenon but levels less than 70 x 10^9 /L are in keeping with a pathological process. Common pathological causes of thrombocytopenia during pregnancy are:

•Pre-eclampsia, eclampsia HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count) associated peripheral consumption in microangiopathic haemolytic anaemia (MAHA)

•Foetal demise

•Antiphospholipid syndrome (APS)

•Heparin therapy, heparin-induced thrombocytopenia (HIT) caused by formation of abnormal antibodies that activate platelets that can predispose to thrombosis.

Thrombocytopenia, anaemia are also a features of normal pregnancy, pre-eclampsia, eclampsia with HELLP syndrome and active SLE. Lymphopenia (1,000/mm^3 at least once) and direct Coombs' test in the absence of haemolytic anemia are features in keeping with active SLE.

The discontinuation of angiotensin converting enzyme inhibitors (ACE-I) in pregnancy can precipitate increase in proteinuria, but the increase of greater than double of baseline would indicate either worsening lupus nephritis or pre-eclampsia. Proteinuria, haematuria and rising creatinine is also of feature of pre-eclampsia and severe eclampsia, which might be difficult to distinguish from active lupus nephritis. An active urinary sediment with rising or positive anti ds-DNA antibodies with low C3 and C4, proteinuria with UPCR greater than 2g/ml or 2g/24 hour urine is more in keeping with active lupus nephritis. It should also be noted that the development of proteinuria or the rise of in chronic kidney disease of whatevere cause may be a feature of kidney damage. Hyperuricaemia and abnormal liver function tests are

unusual in lupus flare and more indicators of pre-eclampsia. (60) Table 5 below has summarised the different clinical scenarios or conditions which might make diagnosis of SLE difficult during pregnancy.

Table 5: Differential diagnosis between physiological pregnancy, lupus flare, pre-eclampsia and HELLP syndrome (60)

Signs and symptoms	**Physiological pregnancy**	**Active SLE**	**Pre-eclampsia**	**HELLP syndrome**
Anaemia	Haemolytic anaemia unusual	Haemolytic anaemia with positive direct Coomb's and associated leucopenia	Usually absent	MAHA: high LDH> 600UI/ml Schistocytes at peripheral blood smear
Thrombocyopenia	>70 x 10^9/L	Normal or low	Normal or low in severe pre-eclampsia	<70 x 10^9/L
Serum creatinine	low	Normal or high	Normal or high	Normal
Proteinuria	≤ 300mg/24h	Normal or ≥ 2g/24h	Normal ≥300mg but usually ≤ 2g/24h	Normal or rising
Blood pressure	Low to normal	Normal or rising	>140/90	>140/90
Liver functions tests	Normal	Normal or high	Normal	High ALT & AST > 1000UI/ml
Complement C3 & C4	Rising	Normal or low	Normal	High levels of split C3a & C5a
Anti-ds DNA antibodies	Negative	Positive or rising	Negative	Negative

1.2.8 Lupus nephritis and pregnancy outcomes:

A number of issues arise in the pregnant patient with lupus nephritis (LN):

1. Pregnancy may increase lupus flares with adverse short and long term effects on renal function and potentially leading to accelerated end-stage renal disease

2. Active LN and advanced chronic kidney disease (CKD) are relative contraindication to conceive because of increased risk for maternal and foetal complications, including spontaneous miscarriage and premature delivery, IUGR, and pre-eclampsia.

Almost 40 to 60% of SLE pregnancies will experience some flare during the course of pregnancy, but renal involvement is not more common in pregnancy as compared to non-pregnant patients with SLE although lupus nephritis may manifest for the first time in pregnancy.(42) Although pregnancy itself in patients with LN or the occurrence of LN flare during pregnancy may not have a long term deleterious on renal function, baseline creatinine or stage of CKD, it can however influence the prognosis of the renal disease in these pregnancies. The presence of anti-phospholipid antibodies during pregnancy has been associated with increase in diagnosis of LN and nephritis flares with increased premature births.

Some studies have reported poor clinical outcomes in patients with LN (both active and inactive disease) with pregnancy; losses up to 60% have been reported in patients with active LN while lower rates of pregnancy loss of 8- to 36% in cohorts have been shown in LN patients with inactive disease.(30) The high percentages and variations are largely attributed to study designs which are mostly retrospective and having small number of patients; different definitions, statistical methods, bias and outcomes. Recent studies though have shown better outcomes of 13 to 27 %

pregnancy loss (excluding induced termination of pregnancy) in pregnancies of LN patients that might be a reflection of better understanding of LN and changing clinical environment with emergence of new therapies.(29,30,61)

In a systemic review and meta-analysis of pregnancy outcomes in patients SLE and LN, Smyth et al (2010) found that lupus flare which was 25.6% and accounted for almost a quarter of all maternal complications. Lupus flare was one of the severe complications associated with maternal death occurring in 1 % of all maternal complications others included opportunistic infections, sepsis and renal impairment from other causes. Meta regression analysis showed statically significant association between active LN and maternal complications of hypertension and foetal complications of premature birth; history of nephritis and maternal hypertension and pre-eclampsia. The same study showed that there was no statically significance in LN histological subtypes between foetal and maternal complications. (30)

The available evidence shows that renal flare is more likely to occur in women with active disease at conception and active LN seems to increase both maternal and foetal pregnancy adverse outcomes especially when associated with APA in pregnant SLE patients. There is limited evidence of different LN histological subtypes associated with adverse foetal and maternal outcomes. Restriction on use of fetotoxic medications also infuences the pregnancy outcomes in LN.

1.2.9 Pregnancies in SLE patients versus pregnancies in the general population:

According to Clark et.al in the past 40 years there has been a decrease in pregnancy loss rates in patients with SLE attributable to disease management and recognition that inactive disease in contrast to stable disease is an important consideration in

reducing both maternal and foetal morbidity.(33) Recent published data in the developed countries show favourable pregnancy outcomes with live birth rates in 85- to 90% of pregnancies.(30) Smyth et.al in their meta-analysis of 37 papers which included 2 751 pregnancies showed that almost one quarter of pregnancies were unsuccessful, and almost 39.4% of all live births were premature.(30) The poor predictor was mostly active lupus nephritis which was associated with premature births and gestational hypertension. This finding is in congruence with the only study in South Africa of SLE and pregnancy outcomes showed 77% success rate of pregnancy in patients with SLE and 39% of these births as premature.(62) The differences between these studies may be a reflection of access to better clinical resources including new therapeutic options, or this discrepancy in pregnancy outcomes may be a reflection of heterogeneity of study designs, populations included in the studies and perhaps the different prevalence of complications like lupus nephritis. The risk of early pregnancy loss or miscarriage (less than 20 weeks gestation) in SLE population is not markedly higher than the general population. It is estimated that 20% of pregnancies will end in miscarriage compared to almost 15% of clinically known pregnancies for the general population.(8)(63)

1.2.10 Anti-phospholipid antibody syndrome (APS) in pregnancy:

APS is a form of acquired thrombophilia mediated by auto-antibodies with resultant recurrent vascular (venous or arterial) thrombosis and/or recurrent pregnancy losses in the presence of auto-antibodies against phospholipid binding plasma proteins, mainly apolipoproteins β2 glycoprotein 1 (anti β2GP1) and prothrombin, and the other group of antibodies called lupus anticoagulant (LAC) and anti-cardiolipin antibodies(aCL)(64) The manifestation of APS can be primary or secondary if it occurs with other auto-immune diseases like SLE, scleroderma, Sjőgren's syndrome,

dermatomyositis and rheumatoid arthritis. These auto-antibodies have prevalence of 1- to 5% in the general populations especially common with progressive age and can be up to 37% in patients with SLE.(64)(65)

The pathogenic mechanism of presence of antiphospholipid antibodies and adverse pregnancy outcomes is still not fully understood. The presence of placental thrombosis and infarction has been reported but thrombotic events don't fully explain antiphospholipid antibodies mediated foetal loss.

The presence APA has been shown to have positive association with poor outcomes in pregnancy including induced and spontaneous miscarriages, hypertension in pregnancy (pre-eclampsia and eclampsia) and premature birth.(66) The recurrence of miscarriage without underlying medical condition is not uncommon in the general population, being recorded in 1/100 or 1/200 women, but foetal deaths, after the 10th week of gestation, are infrequent in the general population.(67) A history of habitual spontaneous miscarriages (recurrent three or more pregnancy losses before 20 weeks) is rare in the absence of conditions like genetic, hormonal or uterine abnormalities, but more common with anti-phospholipid antibody syndrome.(67,68) Factors like the previous miscarriage, or foetal death are the strongest predictor of further complications in women with APS. Anti-cardiolipin antibodies and LAC are important causes of foetal death and they increase the risk of foetal loss in pregnancy with a hierarchy of effect. Their presence even in the absence of renal disease is one of the predictors for development of pre-eclampsia.(69,70) The anti-cardiolipin antibodies may be present in up of 50% of SLE patients as shown in the Greek study.(30,71) Presence of aCL antibodies in high titres has a direct predictive outcome of pregnancy with IgG-aCL associated with both early miscarriage and late foetal loss. The presence of LAC is also associated low birth rates with overall live

births of 73% and a prematurity rate of 37% even with different treatment modalities employed to improve outcomes.(72) LAC is strongly associated with recurrent foetal loss before 24 weeks as highlighted by in study by Guillermo Ruiz-Irastorza et al, with an odds ratio of 7.79.(25) Anti-β2GP1 are more predictive of early and severe pre-eclampsia and eclampsia as highlighted in several studies, with general anti-phospholipid antibody syndrome carrying 20- to 50% risk of early and severe pre-eclampsia and eclampsia.(68) The presence of APS in the best setting of First World management has the pregnancy success rate of 75- to 80% and high risk of complications like hypertension/pre-eclampsia, prematurity, or thrombosis that can take place during pregnancy and the puerperium.(29)

1.3 Summary:

Systemic lupus erythematosus is a complex disease of unknown aetiology and with variable mode of presentation. It is an illness that predominantly affects females of child-bearing age. Changes in the hormone profiles of females with SLE during pregnancy may contribute to a flare (worsening activity) of disease and could potentially be associated with maternal and foetal morbidity and mortality. The presence of kidney disease in lupus has generally been shown to be a poor prognostic factor and could therefore be an important predictor of pregnancy outcome for the mother and her foetus. The ACR guidelines have therefore recommended that women of child-bearing potential with active or prior LN receive counselling regarding pregnancy risks conferred by the disease and its treatments.(18)

The outcomes of SLE mothers and their foetuses are not known at Groote Schuur Hospital – and whether the presence of kidney disease or other demographic factors in SLE affects pregnancy outcomes in this group of patients is not known.

A retrospective study of pregnant SLE patients presenting and treated at the maternity department of Groote Schuur Hospital will be carried out. This study will therefore broadly enable us to identify factors that are associated with poor maternal and foetal outcome and specifically factors that can be modified by us in order to reduce maternal and foetal morbidity and mortality of our patients with SLE (with or without nephritis).

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Chapter 2: Journal-ready manuscript

Lupus Nephritis: A Significant Predictor of Maternal and Foetal Outcomes in SLE Pregnancies in Cape Town

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Abstract

Background:

Systemic lupus erythematosus (SLE) is a multi-system auto-immune disease commonly affecting females of child-bearing age, hence hormonal changes in pregnancy are thought to play a role in disease activity – often necessitating changes in immunosuppression therapy. SLE is common in Cape Town, however, the effect of pregnancy on SLE and vice versa have not been well characterised. The aim of this study is to report on the pregnancy outcomes of patients with SLE presenting to the maternity department of Groote Schuur Hospital, Cape Town.

Methods:

This study was designed as a retrospective review of records of pregnant women known with SLE and followed-up at the maternity section of Groote Schuur Hospital. The duration of survey was from the 1st January 2003 to 31st December 2013. Records were identified using the attendance registers in the relevant departments.

Results:

There were 61 pregnancies reviewed in 49 patients; 80.3% of the pregnancies were in patients of mixed ancestry and the rest (19.7%) in black African patients. The mean age at presentation of the current pregnancy was 27.2±5.0 years. Mean gestational age at presentation and delivery was 13.0 ± 6.0 weeks and 28.9 ± 9.8 weeks respectively and 47.5% of the pregnancies were in patients with lupus nephritis (LN). Thirty nine (63.9%) pregnancies reached the third trimester and 11.5% of all pregnancies ended in the first trimester. There was a lower number of live births to mothers of African ancestry than to those of mixed ancestry (p=0.001). In 55.7% of the pregnancies, no flare was reported while a renal flare was reported in 23%. Pregnancies in patients with LN had higher frequencies of flares (58.6% vs 31.3%; p=0.032), pre-eclampsia (34.5% vs 12.5%; p=0.041), longer stay in hospital (12.0 ± 9.1 days vs 6.1 ± 5.1 days; p=0.004) and low birth weight babies (1.94 ± 1.02 kg vs 2.55±0.95 kg; p=0.046) than in patients without LN. Only 36 (59%) of the neonates were discharged home alive and of these 2 (5.6%) were to mothers of black African ancestry (p=0.001). The frequency of neonates discharged home alive was not different between for mothers with lupus nephritis and those without lupus nephritis (p=0.270).

Conclusion:

Increased lupus activity in pregnant SLE patients may account for the increased deaths of neonates born to SLE mothers. Patients of black African descent and those with LN tend to have a poorer outcome. A multi-disciplinary approach to the management of SLE patients (of child-bearing age or pregnant) needs to be further assessed for better outcomes

Introduction:

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown aetiology and is characterized by multi-system involvement associated with variable clinical manifestations and disease course that is characterised by pathogenic autoantibody formation, immune complex deposition, and end organ damage.[1] SLE is a manifestation of complex interplay between genetic factors, hormones, autoantibodies and environmental factors.[1] Like most autoimmune diseases it affects mostly women of childbearing age; up to 90% at diagnosis; all genders, ages and ethnic groups are susceptible. [2, 3]

The evolution of SLE is known to be changed by natural hormonal events that could occur in a woman's life (e.g. menstrual period, menopause and pregnancy). The care of pregnant women with SLE as well as pregnancy outcomes in women with SLE has been reported to have significantly improved even though these reports are often from developed countries.[4] Pregnancy in SLE is, however still considered "high-risk" especially in developing countries where all the facilities or options of therapy may not be available. Adverse short term and long term maternal outcomes that have been reported in SLE includes maternal death, stroke, hypertension, pre-eclampsia or eclampsia and LN with accelerated end organ damage requiring dialysis.[5] In one study, SLE patients were twice more likely to have a caesarean section and their neonates were more likely to be of low birth weight, preterm delivery and had higher frequencies of congenital malformations than reference patients.[6]

Data is limited from countries in Africa, although one study from South Africa reported no loss to maternal life, 13% occurrence of mild flares, 33.3% pre-eclampsia, 77% live births and 14% intra-uterine growth retardation; the study, however, did not look for factors associated with the pregnancy outcomes.[7]

We therefore sought to retrospectively assess the impact of pregnancy on SLE and vice versa at Groote Schuur Hospital, Cape Town and to identify, where possible, factors associated with the outcome.

Methods:

This study was approved by the University of Cape Town Human Research Ethics Committee (HREC REF 038/2013). Records of patients known with SLE meeting the American College of Rheumatology criteria for SLE 1982 (revised in 1997) who presented to the GSH gynaecology emergency unit, ante-natal clinic or maternity wards in gestation from 1 January 2003 to 31 December 2013 were accessed for retrospective analysis. The patients' records were identified using the attendance registers in the relevant departments (Rheumatology and Nephrology) involved in the care of patients with SLE. Patients were excluded if they didn't meet the American College of Rheumatology criteria for SLE, if they had mixed connective tissue disease of those who presented to the Obstetrics department outside the period of the study. Records obtained included ethnicity, age of the patient at presentation, gestational age at presentation, history of chronic diseases (hypertension, diabetes) and current and past gynaecological and obstetric history.

Complications that occurred during pregnancy such as pre-eclampsia, flare of SLE (defined as a change in clinical and/or serological parameters requiring adjustment of doses of immunosuppression were categorised as renal, skin, joint, or any

combination of these)[8], pre-term delivery, and method of delivery were documented. Pre-eclampsia was as diagnosed by the attending obstetrician. Duration of maternal hospitalisation and gestational age at delivery were also recorded. Foetal outcomes were documented as birth weight (normal or low birth weight), duration of hospitalisation after delivery and status of the neonate at discharge (alive or died). Patients were treated in line with the rheumatology and nephrology divisions protocols for the management of SLE.

Definition of terms: [9]

Birth weight and gestational age:

Low birth weight: neonatal weight 1000 – 2499g

Pre-term baby: birth at gestational age of 28 – 37 weeks

Term baby: birth at gestational age of > 37 weeks

Pregnancy outcomes:

Miscarriage: pregnancy loss from time of conception until 24 weeks and 28 weeks of gestation or delivery of foetus below 500g in weight or

Pre-term labour: the onset of labour before 37 completed gestational weeks.

Term labour: the onset of labour after 37 completed gestational weeks.

Foetal outcomes

A stillbirth: is a baby born dead. The legal definition used in South Africa is baby born after 28 weeks of gestation or weight of 1000g or more.

Neonate: an alive new born baby

Statistical Analysis:

The data were analysed using IBM SPSS Statistics 21 software (SPSS, Chicago, IL). Categorical variables were presented as percentages and continuous variables as means ± SD. Comparison was made between pregnancies in patients with LN and those without LN using the Student's t-test, chi-square test or Fisher's exact test. Significant P-value was taken as $P<0.05$.

Results:

1. Baseline demographics features of patients

Initially, we reviewed the data of 62 pregnancies in 50 women. One patient was excluded as there was inadequate evidence to show that she fulfilled the ACR criteria for the diagnosis of SLE. Hence, the baseline features of 61 singleton pregnancies (49 women) that fulfilled the ACR classification criteria for a diagnosis of SLE are shown in Table 1, and 12 women had more than one pregnancy during the course of the study. Of the 49 women 12 had an index diagnosis of SLE. The mean age at presentation (for the assessed pregnancy) was 27.2 ± 5.0 years, most of the patients (80.3%) were of mixed ancestry and 47.5% of the pregnancies occurred in patients known with biopsy proven LN (Figure 1).

Treatment records at presentation included use of glucocorticoids (67.2%), cyclosporine A (9.8%), Azathioprine (23.0%), chloroquine (50.8%) and various anti-hypertensive agents (none – 50.8%, 1 anti-hypertensive agent – 23.0%, 2 or more anti-hypertensive agents – 26.2%) (not shown in Table).

2. Maternal and foetal features and outcomes

Table 2 and 3 summarises the recorded maternal and foetal features and outcomes from pregnancy to time of delivery. The mean gestational age at delivery was 28.9 ± 9.8 weeks, most of the deliveries (63.9%) occurred in the third trimester of pregnancy and over half of deliveries (52.5%) were either by evacuation of retained products of conception or Caesarean section. Pre-eclampsia occurred in 23% of all the pregnancies. A lupus flare was documented in 44.3% of pregnancies; most flares predominantly affected the kidneys (23.0%) (Figure 2).

At birth, 64% of neonates were born alive, 9.8% were stillbirths (Table 3). However, only 59% of the neonates were discharged home alive as three infants died shortly after birth. The average birth weight of infants was 2.24 ± 1.02 kg and 54.5% were low birth weights. The average duration of hospitalisation post-delivery for neonates was 9.2 days (min – 0; max – 70 days). Neonates born to black African mothers significantly had lower survival rates than those born to mothers of mixed ancestry (5.6% vs 94.4%; p=0.001) (Figure 3)

3. Differences in features and outcomes in pregnancies of patients with lupus nephritis and those without kidney involvement

Table 4 shows the differences in pregnancy features and outcomes between patients with LN and those without LN. Importantly, pregnant women with LN had a higher frequency of flares (58.6% vs 31.3%; P=0.032), higher rate of pre-eclampsia (34.5% vs 12.5%, P=0.041), longer duration of hospitalisation (12.0 ± 9.1 vs 6.1 ± 5.1 days; P=0.004) and lower mean birth weight of the neonate (1.94 ± 1.02 vs 2.55 ± 0.95 kg; P=0.046) than those without kidney involvement. Patients with LN had a lower

neonatal survival (51.7%) at discharge compared to those without LN (65.6%), however, this was not significantly different (p=0.270) (Table 3).

Discussion:

Systemic lupus erythematosus is predominantly a disease of women of child-bearing age; it is therefore not uncommon or unexpected that these patients may present with pregnancy and this can be associated with hormonal changes likely to increase activity of lupus and affect the outcome of pregnancy. The key findings in the current study relates to our observation of overall increased neonatal morbidity and mortality especially if born to patients known with LN or patients of black African ancestry. We also noted a relatively high neonatal mortality in comparison with the results of studies published elsewhere (Table 5).[7,10-15] We consider the high neonatal mortality in our study as a reflection of the severity of lupus activity and not of the state of healthcare in South Africa as all our patients were treated in a large tertiary health care facility. Increased lupus activity,[13] previous obstetric history (i.e. previous pregnancy loss)[16], renal involvement in lupus[17] and secondary anti-phospholipid syndrome[18] have been identified as predictors of pregnancy loss in patients with lupus and some of these factors might explain the poor outcome in our study.

In one study, Yang et al assessing lupus activity with the SLEDAI score reported the incidence of preeclampsia/eclampsia, foetal loss, and preterm birth to be significantly higher in patients with active pregnancy related lupus compared to those with stable pregnancy related lupus ($p<0.05$).[19] They also reported that despite receiving a more

vigorous glucocorticoid treatment, mothers with active pregnancy related lupus had a poorer prognosis compared to those with stable lupus in pregnancy ($p<0.001$).[19] Although lupus activity scores were not directly assessed in our study, activity was indirectly measured through the occurrence of lupus flares which we found to be more common in those with LN (Table 4). Also, we observed that in 36.1% of mothers, there was a history of pregnancy loss in previous pregnancies and mothers with such history had a higher chance or recurrent loss of current pregnancy (results not shown). Ramsey-Goldman et al have shown in their study of SLE patients with either positive or negative anticardiolipin antibodies that in both groups, if there was an adverse outcome in their first pregnancy had at least a 50% chance of another adverse outcome in their second pregnancy.[16] Hence, SLE patients with previous pregnancy loss may be at greater risk of loss of conception in subsequent pregnancies. Although we did not find any significant correlation between previous pregnancy loss and outcome in current pregnancy, this may be an important factor to consider in patients with SLE who become pregnant.

We also found that LN was associated with increased flare in pregnancy ($p=0.032$), increased frequency of pre-eclampsia ($p=0.041$), low neonatal birth weight ($p=0.046$) and increased maternal duration of hospitalization all of which are surrogates of poor maternal and foetal outcomes (Table 4). One meta-analysis of pregnancy outcomes in patients with SLE and LN comprising of 1842 patients with 2751 pregnancies reported the rates of lupus flare, pre-eclampsia, spontaneous abortion, stillbirth, and neonatal deaths to be 25.6%, 7.6%, 16%, 3.6%, and 2.5% respectively.[11] However, in a multicentre study of 81 women (113 pregnancies) with pre-existing biopsy-proven LN that assessed the risk factors for complicated pregnancy (foetal loss and renal flares), Imbasciati et al reported nine spontaneous abortions, one stillbirth and

five neonatal deaths.[20] They also reported that renal flares during and after pregnancy are not uncommon and can be predicted by renal status assessed before pregnancy. Taken together, these findings show that in patients with SLE and LN there is an increased risk of maternal and foetal complications and further supports the need for timing of pregnancy relative to SLE activity and multispecialty care of these patients.

Finally, we report from our study lower neonatal survival for those of black African ancestry compared to those of mixed ancestry (p=0.001) (Figure 3). As all the mothers and newly born would have received the same level of care from our hospital, this outcome is thought to be related to an increased severity of lupus in those of African ethnicity or may be due to differences in other socio-demographic factors such as level of education, nutritional status and attitude relating to the use of medical facilities (the later factors were not assessed in this study). In this study, among patients of African ancestry, 58.3% had a flare during pregnancy compared to 40.8% in those of mixed ancestry. SLE has been reported to be more severe in those of African descent often with less favourable outcomes than in Caucasians and in those of poor socio-economic status.[21-24] In the LUMINA study, 34 of 288 SLE patients had died within 5 years of study onset; most were African Americans and some factors that were associated with mortality included poverty, less than full-time employment, difficulty in accessing health care and cardiovascular and renal involvement.[23] Ward et al also reports on univariate analyses of their study that mortality rates increased with age and were higher among males, blacks, those without private medical insurance, and those living in census tracts with lower household incomes in the US.[24] Other factors relevant to the ethnic varience in the outcome may be genes related to pregression of renal disease, such as ACE

polymorphisms. These findings support the role of race and socio-demographic factors in the outcome of patients with SLE and this can be extended to the outcomes observed in pregnancy as in our study. The higher severity of lupus with increased activity during pregnancy in black African patients may suggest that such patients will require closer monitoring of lupus flares and perhaps a more intensive follow-up at the ante-natal clinics in order to improve outcome of pregnancy.

Our results are limited in some ways including the retrospective design of this study which meant that not all patients' records could have been obtained. For example the results of serological assays for SLE (anti-double stranded DNA antibodies, anti-SSA/Ro and anti-SSB/La antibodies, antiphospholipid antibodies, C3 and C4 compliment level) were not always available and hence not presented in our data. Also, the retrospective design means that the interpretation of flares (disease activity) was sometimes done retrospectively as the attending physicians made the diagnosis of flares differently and the small sample size of this study may be a limitation of how the results are interpreted; although other published studies have reported on similar sample sizes.

Conclusion:

Our results suggest that pregnancy in patients with SLE is associated with a relatively poor maternal and foetal outcome, particularly in those with LN and those of African descent. There is need for intensive monitoring of these patients during pregnancy and perhaps a multi-disciplinary approach to the management of SLE patients, including an obstetrician (optimally a maternal foetal medicine specialist), a rheumatologist, and a nephrologist. Preconception counselling in non-pregnant SLE patients to increase awareness of the disease should be routinely carried where the

goal is to optimise her health before becoming pregnant. Such an approach could help in reducing the relatively high maternal and foetal morbidity and mortality often reported in developing countries like South Africa.

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Graphs and Tables

Table 1: Baseline demographics features of SLE pregnancies

Variable	Frequency (n=61)*
Age at SLE diagnosis (Years)	23.3 ± 6.3
Age at presentation – current pregnancy (years)	27.2 ± 5.0
Race:	
• Blacks	12 (19.7%)
• Mixed ancestry	49 (80.3%)
GA at presentation (weeks)	13.0 ± 6.0
Trimester at presentation	
• First	41 (67.2%)
• Second	17 (27.9%)
• Third	3 (4.9%)
Kidney involvement in SLE :	
• Lupus nephritis	29 (47.5%)
o Proliferative LN	25 (86.2%)
o Others	4 (13.8%)
• No-lupus nephritis	32 (52.5%)
History previous pregnancies (%):	
Primigravida	20 (32.8%)
Others	41 (67.2%)

* This number represents the total number of pregnancies assessed in this study.

Table 2: Maternal features and outcomes (n=61)*

Variable	Value
Mean gestational age at delivery (weeks)	28.9 ± 9.8
Trimester at time of delivery (%)	
• First Trimester	11.5
• Second Trimester	24.6
• Third Trimester	63.9
Method of delivery (%)	
• Normal vaginal delivery	47.5
• Evacuation**	24.6
• Caesarean section	27.9
Pre-eclampsia (%)	23.0
Previous pregnancy loss #	36.1

* -This number represents the total number of pregnancies assessed in this study

** - This refers to evacuation of the retained products of conception

- Represents all previous termination of pregnancy, stillbirths and miscarriages

Table 3: Foetal features and outcomes (n=61)*

Variable	Value
Average birth weight (kg)	2.24 ± 1.2
Birth weight (%)	
• Low birth weight	54.5%
• Normal birth weight	45.5%
Mean duration of Hospitatlization (days)	9.2 (0-70) [min –max]
Status at birth (%)	
• Alive	64.0
• Medical termination	3.3
• Miscarriage	23.0
• Stillbirth	9.8
Outcome at discharge (%)	
• Alive	59.0
• Died	41.0

* The number represents the total number of deliveries assessed in this study

Table 4: Differences in pregnancy outcomes between patients with lupus nephritis and patients with SLE without nephritis

Variable	Lupus Nephritis (n=29)	SLE without nephritis (n=32)	P-value
Mean gestational age at delivery (weeks)	28.0 ± 9.0	29.6 ± 10.6	0.532
Flare (%)	58.6	31.3	**0.032**
Pre-eclampsia (%)	34.5	12.5	**0.041**
Mean Maternal Hospital stay (days)	12.0 ± 9.1	6.1 ± 5.1	**0.004**
Pregnancy outcomes (%)			0.218
• Miscarriage	20.7	25.0	
• Medical termination	6.9	0	
• Still birth	10.3	9.4	
• Preterm live birth	44.8	28.1	
• Term live birth	17.2	37.5	
Mode of delivery (%)			0.427
• Evacuation**	24.1	25.0	
• Normal vaginal delivery	55.2	40.6	
• Caesarean section	20.7	34.4	
Neonatal outcomes			
• Alive on discharge (%)	51.7	65.6	0.270
• Mean birth weight (kg)	1.94 ± 1.02	2.55 ± 0.95	**0.046**
• Mean neonatal hospitalisation (days) [Min-Max]	9.13 [1 – 70]	9.24 [0 – 52]	0.984

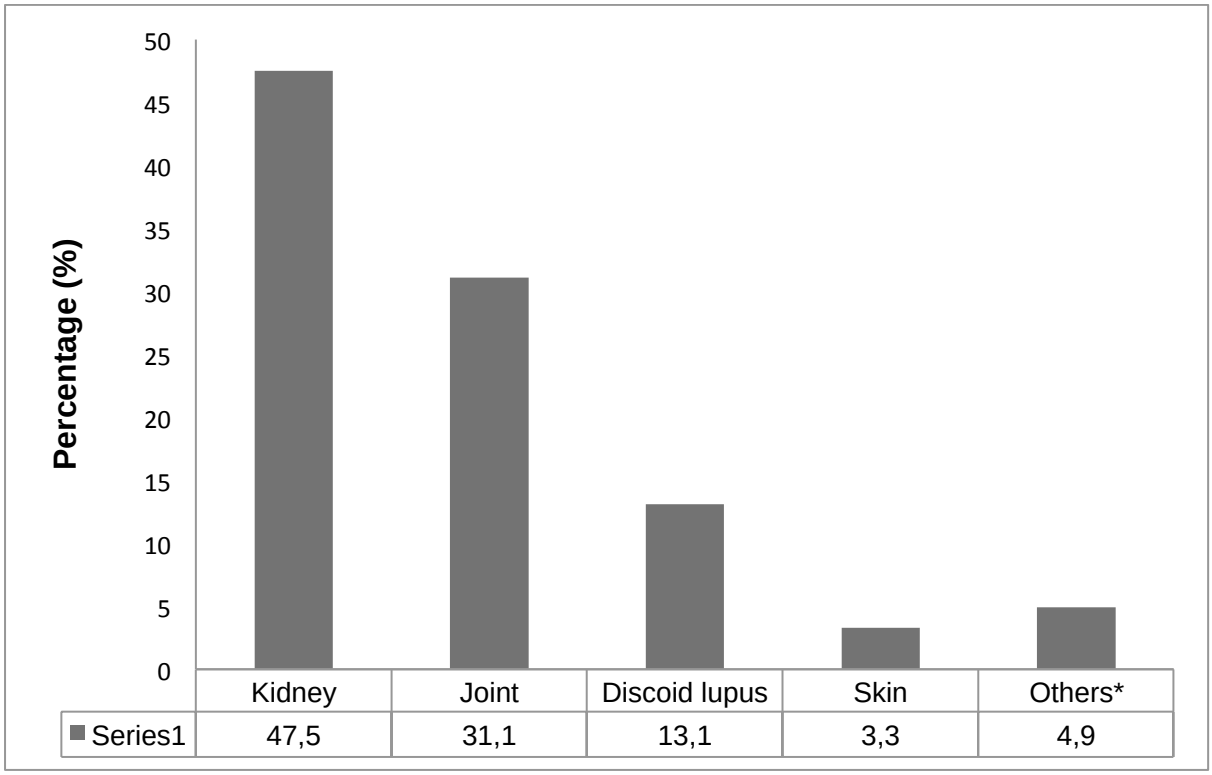
** - This refers to evacuation of retained products of conception

Table 5: Pregnancy outcomes reported from various studies worldwide

Country	Author (Year) [Ref]	Number of pregnancies	Pregnancy outcomes		
			Miscarriage (%)	Premature deliveries (%)	Live Birth (%)
China	Liu et al. (2012) [10]	111	22.5	25.2	74.8
Systemic review & meta-analysis	Smyth et al. (2010) [11]	2751	16 *	39.4	74.5
Portugal	Carvalheiras et al. (2010)[12]	51	6	16	74
USA	Clowse et al.(2005)[13]	267	7	40	85.8
South Africa	Whitelaw et al. (2008) [7]	47	21	39	77
India	Chandran et al. (2004)[14]	52	28.6	1.9	46.1
Taiwan	Wong et al (2006) [15]	24	8.3	33.3	91.6
This study	Mbuli et al (2015)	61	23	36.1	64.0

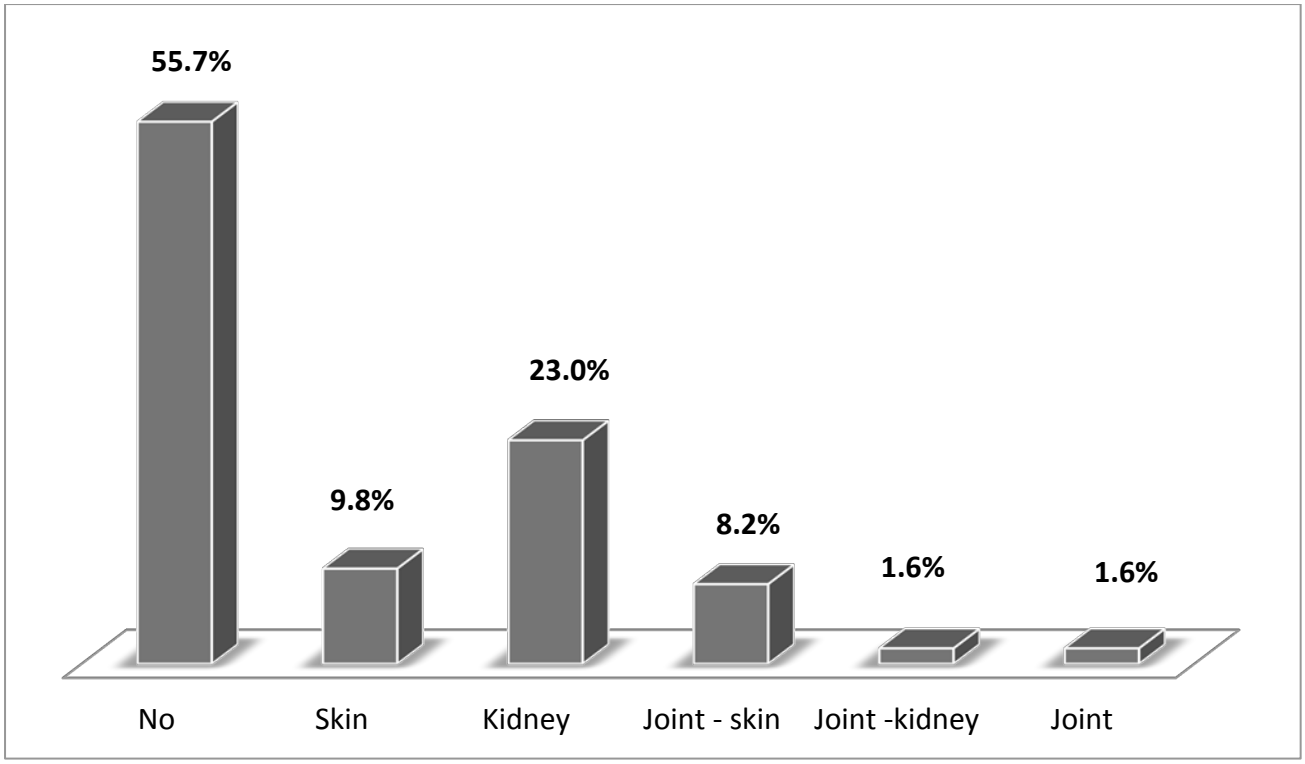
*** Excluded 5.9% induced abortions**

Graph 1: Main clinical manifestation of SLE in all the pregnancies assessed

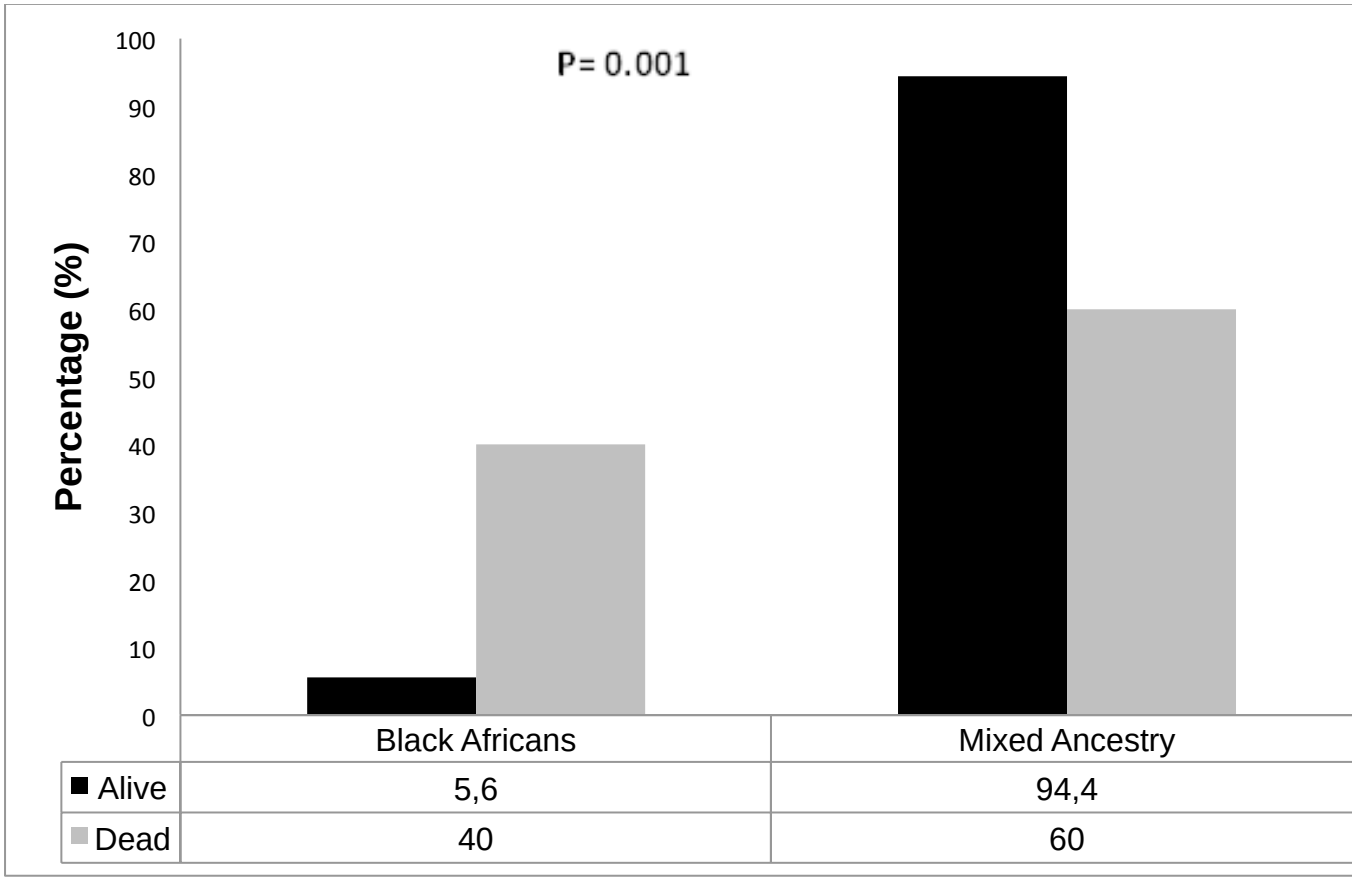


* Others features of SLE and immune thrombocytopenic purpura

Graph 2: Organ involvement during flares in SLE pregnant patients

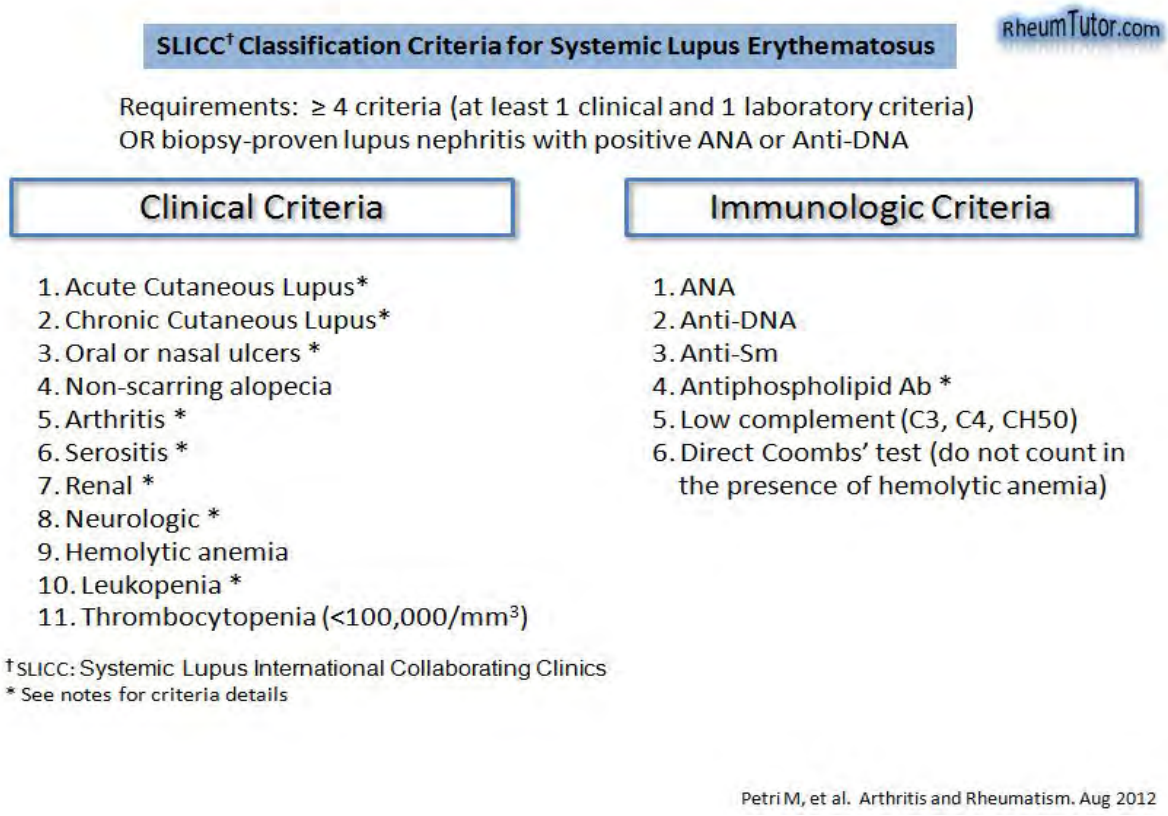


Graph 3: Neonatal discharge outcomes by maternal race



Appendices

Appendix 1: 2012 SLICC criteria:



Appendix 2: Faculty of Health Sciences (UCT) ethics approval

HREC Ref 038/2013 – 25Jan2013

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za
www.health.uct.ac.za/research/humanethics/forms

25 January 2013

HREC REF: 038/2013

Dr L Mbuli
c/o Dr I Okpechi & Dr L Schoeman
Department of Nephrology

Dear Dr Mbuli

PROJECT TITLE: AN EVALUATION OF PREGNANCY OUTCOMES IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS IN GROOTE SCHUUR HOSPITAL

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year till the 15th February 2014

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

s.thomas

Appendix 3: University Of Cape Town Candidature Approval for MMed in Medicine

Dear Dr Mbuli

Candidature Approval (MBLLIN002)

Degree	MMed in Medicine
Title	An evaluation of pregnancy outcomes in patients with systematic Lupus Erythematosus in Groote Schuur Hospital
Department	Medicine
Supervisor	Dr I Okpechi
Ethics Approval	038/2013

I am pleased to advise that the Chair of the Dissertations/Doctoral & Masters Committee has approved your candidature for the above degree on behalf of the Committee. Formal approval was obtained by publication in the Dean's Circular, PG-MedJuly-Sept2014.

Yours sincerely

Vuyi Mgoqi

Vuyiseka Mgoqi |Receptionist: PG Academic Administration |Faculty of Health Sciences | University of Cape Town | Room N2.19, Wernher & Beit North, Health Sciences Campus, Anzio Rd, Observatory, 7925 | ☎ + 27 21 406 6751 🖷 + 27 21 406 6584 | Office Hours: 08h30 - 16h30 Unavailable Hours: 13h00 - 13h30