The Long term outcomes of children born to mothers with Systemic Lupus Erythematous (SLE)

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Abstract

Introduction: Immunosuppressive agents are commonly used in Systemic Lupus Erythematous (SLE) during pregnancy, to ensure optimum outcome for both mother and child. However there is little literature regarding long term outcomes (LTO) of these children.

Aims: This pilot study aims to test the hypothesis that the mother's medications taken during pregnancy and/or antibodies are associated with an increased risk of adverse outcomes in children born to mothers with lupus.

Methods: Women regularly attending specialist UK lupus clinics were identified and consented to take part in this study if they had children up to the age of 17 years born after the diagnosis of SLE. A standard questionnaire developed for this multi-centre study was used to collect the data.

Results: In total data were collected for 285 children born to 199 mothers. Neonatal rash, complete heart block or congenital anomalies were each reported in 2% of children, and developmental problems in 17/284(6%). Hospital management was required for infection in 25% (69/274) of children, the only significant risk factors identified were birth weight and maternal aspirin use which are likely to be surrogate markers for more severe maternal disease.

Conclusion: This study demonstrated reassuring LTO of children born to mothers with SLE.

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Table 1 - List of abbreviations

ACR	American College of Rheumatology
ADHD	Attention Deficit Hyperactivity Disorder
Anti-dsDNA	Anti-Double Stranded DNA
APS	Antiphospholipid Syndrome
ASD	Autistic Spectrum Disorder
AZA	Azathioprine
BILAG	British Isles Lupus Assessment Group
CHB	Congenital Heart Block
eGFR	Estimated Glomerular Filtration Rate
EUROCAT	European surveillance of congenital anomalies
FVC	Forced Vital Capacity
HCQ	Hydroxychloroquine
IBD	Inflammatory Bowel Disease
IUGR	Intrauterine Growth Restriction
LFTs	Liver Function Tests
NSAIDs	Non-steroidal Anti-inflammatory Drugs
OR	Odds Ratio
SLE	Systemic Lupus Erythematous
SD	Standard Deviation
USA	United States of America

Introduction

a. What is SLE?

Systemic lupus erythematous (SLE) is a multisystem, autoimmune disease, which can cause constitutional or organ-specific symptoms. Any part of the body can be affected, including the skin, mucous membranes, joints, kidney, peripheral and central nervous system, serous membranes, lung, heart, lymph nodes, genital tract and occasionally the gastrointestinal tract may all be involved(1;2). SLE is an autoantibody-mediated disease with immune complex formation and complement activation which results in organ inflammation.

b. Who gets SLE?

SLE has a prevalence of around 73 cases per 100,000, which is higher in those of African American or Indian descent, predominantly affecting women of childbearing age (15–55 years) the female: male ratio peak is 12:1 (3-6).

SLE is more common in non-Caucasians, black patients are younger at diagnosis, in addition to having a greater than 2 fold increase in incidence and prevalence (1-3;5). Lupus disease is also more severe in non-Caucasians, studies have identified that there is a higher proportion of renal disease and progression to end stage renal disease (ESRD) (1-3;7).

c. What are the manifestations?

The incidence of significant features of SLE are summarised in Table 2. Arthritis in SLE can be divided into a deforming and non-deforming arthropathy. Constitutional symptoms

consist of fever, malaise, fatigue, weight loss, lymphadenopathy, and anorexia (1;2). There are multiple cutaneous manifestations of lupus: commonly these include photosensitivity (>50% of patients), butterfly/malar rash, painful/painless oral ulcers, diffuse alopecia, and livedo reticularis (1;2). The effects of SLE on the reproductive system, including fertility and pregnancy will be covered later in the pregnancy considerations section.

Renal disease is one of the most serious SLE manifestations and presents with proteinuria, red cells and casts in the urine. Neuropsychiatric SLE (NPSLE) is a major diagnostic and treatment problem. The (American College of Rheumatology) ACR has provided NPSLE classification criteria, describing central and peripheral types of neurological involvement that may be found in lupus patients(2).

Pulmonary features of SLE include pleurisy, pneumonitis, pulmonary hemorrhage, pulmonary embolism, pulmonary hypertension, and diaphragmatic weakness causing shrinking lungs. Pericarditis is the most common cardiological manifestation; others include myocarditis, endocarditis, accelerated atherosclerosis, and, rarely, pericardial tamponade(2). Abdominal pain, nausea, vomiting, and diarrhea occur in up to 50% of SLE patients. Gastrointestinal involvement includes mesenteric vasculitis (high risk of death), aseptic peritonitis (with or without ascites), subacute bowel obstruction, hepatitis, sclerosing cholangitis, protein-losing enteropathy, pancreatitis, and ascites(2).

Cytopenias, including anemia, leucopoenia or thrombocytopenia, are commonly associated with SLE; they may be immune-mediated or due to other factors, e.g. menstrual losses. Antiphospholipid antibodies and lupus anticoagulant are found in about 30–40% of patients, associated with venous and arterial thrombosis, recurrent fetal loss, pre-eclampsia, headache, and epilepsy(2).

A firm diagnosis of lupus is made based on appropriate clinical findings and the measurement of at least one antibody. Antibodies are the hallmark of SLE, and (anti-double-strandedDNA (anti-dsDNA) levels fluctuate with disease activity and are measured in clinical practice to assess disease activity. There are a number of antibodies associated with SLE, the most common being ANA (antinuclear antibody), which is found in over 95% of patients. Other associated autoantibodies include anti-dsDNA antibodies in approximately 60% of patients, the highly specific anti-Sm antibody (Smith proteins) in 10–30% of patients, and anti-RNP (ribonucleoprotein) also in 10–30% of patients (2;8). Anti-Ro and anti-La antibodies can be seen in approximately 40% of patients (2;9). They are associated with Sjogrens syndrome, cutaneous and neonatal lupus and congenital heart block(2;9).

d. How is it treated

The treatment of SLE is tailored to the severity of disease. General lifestyle advice includes avoidance of sunlight and use of sun block. Patients should have regular disease assessments, and be screened for SLE complications, such as infection, diabetes, hyperlipidaemia, and hypertension.

Mild cases with intermittent rashes, arthritis, and other mucocutaneous features can usually be treated with corticosteroid creams, short courses of NSAIDs, and hydroxychloroquine (<6.5mg/kg/day). More severe cases of SLE usually require oral corticosteroids. Patients who need 10mg/day of prednisone or more despite hydroxychloroquine, or those who present with more severe manifestations (such as nephritis, gastrointestinal vasculitis or

central nervous system disease) that need higher initial doses of prednisone (0.5-1mg/kg/day) are likely to need azathioprine(AZA), methotrexate, mycophenolate mofetil or cyclophosphamide as steroid-sparing immunosuppressive agents. If conservative treatment and traditional immunosuppressives fail then biologics should be considered.

Rituximab is a monoclonal antibody against the B-lymphocyte marker CD20 expressed on B cells, it has been used in SLE patients since 2002, and observational studies have suggested that rituximab is effective in treating active SLE refractory to standard immunosuppressant(10). Recent data have demonstrated that repeated treatment with rituximab is effective in treating refractory SLE and has a favourable safety profile (11;12). Lightstone and co-workers are currently investigating the possibility of corticosteroid avoidance regimes using rituximab at initiation of therapy for lupus nephritis (11;12).

Table 2- Cumulative Incidence of SLE Manifestations

Adapted from Pons-Estel et al (9)

Manifestations		Cumulative Incidence (%)
Systemic	Fever	57
	Weight loss	27
Musculoskeletal	Arthritis & Arthralgia	93
	Myalgia	18
Cardiorespiratory	Pericarditis	17
	Pleural Effusion	22
Cutaneous	Alopecia	58
	Oral/nasal ulcers	42
	Photosensitivity	56
	Raynaud	28
	Discoid Lesions	12
Neurologic	All types Central Nervous System damage	26
	Psychosis	4
Renal	Proteinuria/Abnormal sediment	46
	Nephrotic Syndrome	7
Gastrointestinal	Ascites	1
Haematological	Lymphadenopathy	15
	Haemolytic anaemia	12
	Leucopenia (< 4500 leucocytes/mL)	42
	Thrombocytopenia (< 100, 000	19

	platelets/mL)	
Serological	ANA	98
	Anti-dsDNA	71
	Anti-Smith	48
	Anti-Ro	49
	Anti-RNP	51
	Anticardiolipin IgG/IgM	51/41

Pregnancy considerations

Introduction

In the past women with SLE were advised against pregnancy due to maternal and fetal morbidity and mortality and the complex influence of sex hormones on immunity(13). Studies have found that women with SLE have fewer children than they might desire, and a reduction in family size has been demonstrated (14-17). There are many potential factors that may influence family size including, physical and psychosocial, which may vary depending on current and/or past disease activity, damage, and/or treatment (14-17). There are several potential complications women need to be counselled about which include miscarriages, stillbirth, preterm birth, intrauterine growth restriction (IUGR), pre-eclampsia, neonatal lupus and congenital heart block (CHB). These complications are discussed in the relevant sections below.

Effect of pregnancy on the mother

Possible maternal complications include disease flare, hypertension and pre-eclampsia. However in recent years, it has been found that with good disease control and rigorous monitoring, there is no reason why the majority of these women should not have the opportunity to bear children (13;18). It is recommended that women should have stable

disease for a minimum of six months, as active disease is associated with a 3-fold increase in pregnancy loss (miscarriages and perinatal mortality)(19).

a) Lupus Flare

Generally the risk of flare is least if disease is well controlled for six months prior to pregnancy (19-21). There is no consensus on whether lupus flares increase in pregnancy, but historically patients used to stop all their drug therapy when a pregnancy was confirmed, which may have led to an increased risk of flare in pregnancy. Other possible explanations for this include the differences in lupus flare definitions, assessment of disease activity, and differentiation between lupus flare and pregnancy associated complications or physiological changes of pregnancy(22).

b) Pre-eclampsia

Pre-eclampsia is defined as new hypertension after 20 weeks of pregnancy with significant proteinuria (urinary protein: creatinine ratio greater than 30 mg/mmol or 24‑hour urine collection result greater than 300 mg protein(23). Advanced maternal age, previous personal or family history of pre-eclampsia, pre-existing hypertension or diabetes mellitus and obesity, are all pre-disposing factors for pre-eclampsia(24)

Pre-eclampsia effects 16-30% of SLE pregnancies, the lupus specific associated risk factors are; (past or current) hypertension, lupus nephritis, high SLEDAI score and antiphospholipid antibodies (25-27).

Although pre-eclampsia and lupus nephritis can co-exist in pregnancy, it is essential to distinguish the two conditions see Table 3, as steroids are necessary to treat lupus nephritis but will aggravate pre-eclampsia. In contrast delivery of the fetus will be the ultimate treatment for pre-eclampsia, although anti-hypertensives may be tried initially.

Table 3 - Summary of key clinical and serological differences between lupus flare and pre-eclampsia

	Lupus Flare	**Pre-eclampsia**
Hypertension	Anytime in pregnancy	After 20 weeks gestation
Urine analysis	Proteinuria Red Cell Casts	Proteinuria
Platelet Count	Low	Low
Abnormal LFTs	Unusual	Common
Creatinine	Raised	Raised
dsDNA*	Raised	Normal
Complement**	Low	Normal
Uric Acid	Can be raised in the presence of CKD 2-5	High
Response to steroids	Yes	No

*Rising anti-DNA antibodies are the best marker of flare, but only 60% of lupus patients make them

**C3 and C4 usually rise 10-50% in pregnancy, a fall of 25% suggests active disease(28).

Effects of maternal Antibodies on pregnancy

a) **Neonatal lupus/congenital heart block**

Neonatal lupus syndrome occurs due to the transmission of maternal anti-Ro and/or La antibodies across the placenta from week 16. It may present as transient cutaneous lupus lesions, complete heart block, cytopenia, hepatic and other manifestations, occurring in infants born to mothers with positive anti-Ro or anti-La antibodies (29;30).

IgG antibodies can cross the placenta from approximately 16 week gestation, neonatal lupus syndrome occurs in about 5% of mothers (30-33). With the exception of the cardiac manifestations of neonatal lupus, the manifestations resolve with the clearance of maternal antibodies by the age of 6-8 months (30-33).

Anti-Ro and La antibodies are reported to be present in 40 and 20% of SLE patients respectively (34). The presence of anti-Ro/La antibodies is associated with a 5% risk of neonatal lupus rash and CHB in about 1-2% of babies, with an increased risk of up to 20% of a subsequent child having CHB if a previous child had CHB (33;35-39) .

If complete CHB is identified, mortality in utero or in the first three months has been reported to be up to thirty percent, despite intensive care (33). Permanent pacemakers are required by 67% of survivors with complete CHB(29).

Pregnant women with anti-Ro/SSA or anti-La/SSB autoantibodies are closely monitored during pregnancy as early identification and prompt treatment with dexamethasone may

dampen down myocarditis or cardiac failure, but there is no evidence that it prevents development of CHB (38;40;41;41). There is no evidence that plasma exchange or IV immunoglobulin will prevent the reoccurrence CHB (42-44).

b) What are the factors that increase the risk of Antiphospholipid Antibodies?

Antiphospholipid antibodies (Lupus Anticoagulant and/or anti-cardiolipin IgG and or IgM) antibodies (aPL) are commoner in patients with SLE (30–40%) than the background population (1–5%), and are associated with an increased risk of thrombosis(45). Studies have found that certain antibodies and/or combinations are associated with a greater risk of thrombosis (46). High risk antibody profiles include: Lupus anticoagulant, triple positivity (Lupus anticoagulant and anti-cardiolipin and B2 glycoprotein antibodies) and persistently positive anticardiolipin antibodies at medium–high titres (46), whereas an isolated, intermittently positive anti-cardiolipin or B2 glycoprotein antibodies at low-medium titres has been demonstrated to carry a lower risk of thrombosis (46)

The presence of antiphospholipid antibodies is significant in pregnancy as the following adverse pregnancy outcomes have been observed in pregnant SLE women with antiphospholipid antibodies: miscarriages, IUGR, pregnancy associated hypertension, preterm birth, still birth and small for dates babies(45;47-53). The Euro-phospholipid international study, studied a 1000 patients with antiphospholipid syndrome, and identified early fetal losses, <10 weeks, (35.4%), late fetal losses, ≥ 10 weeks (16.9% of the pregnancies) and preterm birth (10.6% of live births) and pre-eclampsia (9.5%)(45). Recent data from the European neonatal registry of babies born to mothers with

antiphospholipid syndrome found that despite recommended treatment there is still a greater risk of the following complications: preterm delivery and IUGR than in general population, about which mothers will need to be counselled (52).

Pregnancy outcomes can be optimised in pregnancy by testing for antiphospholipid antibodies prior to pregnancy, so an accurate risk assessment can be made and appropriate treatment initiated with low dose aspirin and, if appropriate, low molecular weight heparin(51;54). These pregnancies will need to be closely managed by an obstetrician and medical team (haematologist and/or Rheumatologist), to monitor and treat any pregnancy complications, which will increase the chance of a good pregnancy outcome to up to 75-80% (51;54).

Effects of SLE on the baby

There is a wealth of clinical experience and expert opinion, on the management of SLE in pregnancy, and what drug treatment is considered suitable. The multiple studies which have looked at the short term outcomes, normally only address the first few months of life. Studies performed on the obstetric (short term) outcomes have identified several risk factors for adverse events, and these form the basis of pre-pregnancy counselling and current practice

a) Miscarriages/still birth?

The risk of fetal loss has significantly decreased in pregnancies in patients with SLE, from 43% before 1975 to 17% in 2000–2003(55).

Antiphospholipid antibodies (Lupus Anticoagulant and/or anti-cardiolipin IgG and or IgM) are common in SLE patients, and are associated with an increased risk of miscarriages and still birth (13;47;53;56). A higher rate of adverse obstetric outcomes, including miscarriages and still birth have also been demonstrated in women with SLE and hypertension(13). Disease activity as indicated by hypocomplementaemia, lupus nephritis and high disease activity in the six months prior to conception is associated with an increase in miscarriages and still birth (20;48;53;57-62). Other predictors include the presence of thrombocytopenia, proteinuria and hypertension (20;63).

b) Small for dates/IUGR

IUGR is defined as a foetus that has failed to achieve their growth potential, and their estimated fetal growth below the 10 the percentile for gestational age.(64) There is a three-fold higher rate of IUGR, in pregnancies complicated by both SLE and hypertension (13;65). Nearly 25% of pregnancies in women with SLE are complicated by hypertensive disorders (65). The risk of IUGR is increased in those with active disease at conception and in those with anti-phospholipid antibodies (53;60;63;66;67). Low birth weight (<2.5kg), is either due to IUGR, prematurity or both, and is associated with increased neonatal morbidity and mortality(68).

Small for dates is defined as a foetal birth weight below the tenth percentile of that population for sex and gestational age at delivery(69). Small for dates babies are significantly more frequent among SLE patients with renal disease compared to non-renal patients (25;53;63;67).

c) Preterm birth

Preterm delivery, which is defined as occurring before 37 weeks of gestation, is commoner in lupus, than in the general population (52). Varying rates of preterm delivery have been reported in the literature, a meta-analysis reported a 39.4% rate in lupus patients (53). Preterm delivery can be spontaneous, but is more often due to induction or emergency caesarean section due to another complication e.g. IUGR and/or fetal distress.

Several risk factors have been identified to be associated with preterm delivery in the literature, these include the presence of lupus nephritis and active disease during pregnancy [19, 28, 57, 53]. The presence of antiphospholipid antibodies has been linked with preterm delivery in several studies [19, 54]. Hypertension during pregnancy is also associated with IUGR and preterm delivery, and should be appropriately treated prior to and during pregnancy [18].

Effect of medications on pregnancy?

It is essential to ensure good disease control throughout pregnancy, as active disease during pregnancy can result in adverse outcomes for both mother and child as described above: including reduced live births, earlier deliveries, pregnancy loss and small for gestational age babies(19;20;55;60) This often necessitates the use of disease modifying therapy to allow the disease process to be brought under control, and so pregnancy can be achieved and maintained to term.

Drugs to be stopped

Certain medications, including mycophenolate mofetil, cyclophosphamide and methotrexate used in the treatment of lupus are known to be teratogenic, and as a consequence are not recommended. There are several case reports in the literature that have attributed congenital anomalies to these drugs (70-84).

Mycophenolate Mofetil

Mycophenolate is not advised during pregnancy due to the multiple congenital anomalies reported with its use (70;72-75;78;80;81;83;84). Multiple case reports and series, including the transplant data, support the teratogenicity of Mycophenolate exposure in utero (70;72-75;78;80;81;83;84). A specific phenotype including microtia, auditory canal atresia, cleft

lip and palate, micrognathia, hypertelorism, short fingers and hypoplastic nails has been identified (74).

A recent prospective study of the European Network of Teratology Information Services investigated 57 pregnancies exposed to mycophenolate in the first trimester (74). In total 45% of the pregnancies ended in spontaneous abortion (74). Congenital malformations were identified in 6 out of 29 live born children; four of these infants had a clinical phenotype consistent with mycophenolate embryopathy (74). There was a 26% malformation rate after mycophenolate exposure, which means that patients should be informed of the need for effective contraception whilst taking the drug (74).

Women are recommended to switch to an alternative drug compatible with pregnancy such as azathioprine. A recent study found that in women with quiescent lupus nephritis who switched to azathioprine had a low risk of renal flares(85).

Methotrexate

Methotrexate is a folate antagonist, which is also used to induce medical abortions. Data from animals and humans exposed to methotrexate in utero have reported congenital anomalies, which usually involved the central nervous system, cranial ossification, the limbs and the palate and growth restriction (79;82). In view of this it is recommended that methotrexate is stopped three months prior to conception(86) .

Cyclophosphamide

Cyclophosphamide is a human tetragon, and effective contraception must be used. Cyclophosphamide embryopathy, including anomalies of craniofacial structures, ears and limbs, visceral organs, growth restriction and developmental delay during have been reported in the literature(79). Recent case reports have confirmed the teratogenicity of cyclophosphamide (76;77).

Medications and DMARDS considered compatible with pregnancy and lactation

Disease modifying anti-rheumatic drugs that are considered safe in pregnancy and breastfeeding are: hydroxychloroquine, azathioprine, sulphaslazine, ciclosporin and tacrolimus(79).

NSAIDS (Non Steroidal Anti-Inflammatory Drugs)

Patients who are struggling to conceive are advised to stop taking NSAIDS as there is possible increased risk of luteinized unruptured follicle syndrome (87;88). This condition is characterized by clinical signs of ovulation with the absence of follicular rupture and ovum release, which is caused by the inhibition of the cyclooxygenase- 2 (COX-2) needed during follicular development.

NSAIDS can be used in pregnancy in short limited courses, care must be taken with their use as they can be linked with maternal renal and cardiac failure, hypertension, and fluid overload, and oligohydramnios and renal impairment in the fetus if used for long periods of time(79;89). However NSAIDS must be stopped at the end of pregnancy, after week 32, as they are associated with an increased risk of preterm closure of the patent ductus arteriosus in the fetus(79;89;90).

Aspirin and Heparin

Pre-eclampsia is increased in SLE patients, compared to the general population, as discussed earlier. Low dose aspirin has been demonstrated to reduce the risk of pre-eclampsia in all pregnant patients considered to be at risk of pre-eclampsia, relative risk of 0.81, 95% CI 0.75-0.88, there is a modest reduction in preterm delivery, neonatal death and IUGR(91).

In pregnant SLE patients with Antiphospholipid Syndrome (APS), a Cochrane Review concluded that combined unfractionated heparin and aspirin, compared to aspirin alone, may reduce the risk for pregnancy loss (RR 0.46, 95% CI 0.29 to 0.71)(92). The combination of low-molecular-weight heparin and aspirin compared to aspirin alone, was not so effective (RR 0.78, 95% CI: 0.39 to 1.57)(92). More recent meta-analyses have demonstrated the benefits of combined treatment with aspirin and heparin during pregnancy, but further evidence is needed to confirm that low weight molecular heparin is equivalent to unfractionated heparin (93;94).

Steroids

Non fluorinated steroids (prednisolone, methylprednisolone and hydrocortisone) are metabolised by placental 11 β-hydroxysteroid dehydrogenase, and less than ten percent is found in the fetal circulation(95). Oral steroids are considered compatible with pregnancy, potential side effects for mothers are as for non-pregnant women. Those of relevance to pregnancy include increased blood pressure, osteopenia, osteonecrosis and susceptibility to infection are of special relevance in pregnancy. The risk of gestational diabetes will be increased, as pregnancy induces insulin resistance and glucose intolerance.

Fluorinated steroids (dexamethasone and betamethasone) can cross the placenta and are recommended in pregnant women to improve surfactant levels before preterm birth(96). Fluorinated steroids are also used for myocarditis and hydrops in babies with CHB (40;97).

Hydroxychloroquine

Hydroxychloroquine has been demonstrated to be safe in pregnancy and lactation, with most studies on infants demonstrating normal visual function and neurodevelopmental outcome (98-104). There were no statistically significantly increase in congenital anomalies in a recent prospective observational study(105). The safety and benefits of using hydroxychloroquine therapy in pregnancy was also demonstrated in systemic reviews (103;104).

A randomised controlled study found that women with SLE who continued hydroxychloroquine throughout pregnancy, had lower disease activity and lower prednisolone doses at the end of pregnancy(100). This was corroborated in a further study, in which women with SLE who discontinued or had never taken hydroxychloroquine, had higher disease activity scores and were on higher doses of prednisolone, compared to those who had continued hydroxychloroquine (99).

It is important to note that hydroxychloroquine has a half-life in the blood of approximately 50 days, so even if stopped in pregnancy or prior to lactation, it will still be present in the maternal blood and breast milk and many more babies have been exposed to it than is generally recognised.

Azathioprine

Azathioprine is an antimetabolite immunosuppressant used to treat SLE, IBD (inflammatory bowel disease), haematological malignancies and transplant patients. Azathioprine has been used in solid organ transplantation for more than 50 years and is used frequently for therapy of organ-threatening autoimmune diseases. Previously published reports investigating mothers who take azathioprine during pregnancy and lactation, found that the concentration of azathioprine's active metabolite, 6-mercaptopurine, in breast milk was negligible(106). The fetus is thought to be protected from the potential teratogenic effects of the drug as they lack the enzyme inosinatopyrophophorylase that is required to convert azathioprine to the active metabolite 6-MP. The teratogenic effects of azathioprine have been reported in animal studies, where higher doses were administrated (79). However there was no increase in the rate of congenital anomalies in humans in previous studies (79).

Sulphasalazine

A meta-analysis of women with IBD showed that sulfasalazine is not related to teratogenic effects (107). Sulphasalzine inhibits the gastrointestinal and cellular uptake of folate, women should be advised to take high-dose folic acid (5 mg/day) from 3 months prior to conception until at least the end of the first trimester, in order to reduce the risk of neural tube defects.

Ciclosporin

Ciclosporin is considered compatible with pregnancy and breast feeding, greater than 800 human pregnancies have been published in the literature (108) . However care must be taken when using ciclosporin, as an increased rate of hypertension, pre-eclampsia and gestational diabetes have been reported with its use (108). Ciclosporin should be prescribed at the lowest effective dose with monitoring of blood pressure and renal function (79;108). No concerns have been identified with breast feeding(109).

Tacrolimus

Tacrolimus is considered to be compatible with pregnancy and breast feeding, the majority of data on tacrolimus use is from the transplant literature (110-113), There have been case reports of its successful use in refractory disease in the rheumatology population(110;111;114). A recent publication reported that tacrolimus has been successfully used in pregnancy both to treat women with stable disease and lupus nephritis flares, whilst preventing the commencement and/or escalation of steroids in the majority of cases(115). Minimal levels of tacrolimus have been identified in breast milk, and blood levels were not found to be higher when breast fed and bottle fed infants were studied (116;117).

Pre pregnancy counselling

Women of childbearing age should be advised regarding the importance of good disease control before conception, the need for close monitoring during pregnancy, and the risk of postpartum disease flare.

It is essential that a full clinical history, including current and past SLE disease manifestations and antibody profile is obtained, specifically including antiphospholipid antibodies, anti-Ro/SSA or anti-La/SSB. Contraindications to pregnancy should be identified, including pulmonary hypertension, active disease and contraindicated drugs (118).

As in the general population, all women should be encouraged to stop smoking, to reduce/cease their alcohol and take folic acid (0.4 mg/day) 12 weeks before and after conception in order to prevent fetal neural tube defects.

Contraindicated drugs should be replaced with drugs compatible with pregnancy, as discussed in the medications in pregnancy section. Women taking steroids and those with risk factors for diabetes including maternal ethnicity, polycystic ovary syndrome, should have a glucose tolerance test around 24–28 weeks' gestation in order to exclude gestational diabetes and avoid further obstetric risk(119). Patients who take steroids, heparin or have other risk factors for osteoporosis should take prophylactic calcium and Vitamin D supplements(119).

Women with anti-Ro/SSA or anti-La/SSB autoantibodies will require regular fetal heart monitoring from week 16 by the midwife or obstetric unit (13;120). Thus heart block can be identified as early as possible and treatment can be initiated if necessary. As early identification and prompt treatment with dexamethasone may dampen down myocarditis or cardiac failure, but there is no evidence that it prevents development of CHB (40;41). There is no evidence that IV immunoglobulin will prevent the occurrence CHB (42-44).

Women with antiphospholipid antibodies will require treatment with low dose aspirin, combined with low molecular weight heparin in certain circumstances including recurrent early miscarriages (<10 weeks of gestation), women with previous fetal death (>10 weeks of gestation) and/or preterm delivery (<34 weeks gestation) (93;118;119).

Data in the literature on the long-term outcomes of children

This section will review what is known in the general population, lupus and transplant groups, on the relevant long-term outcomes. The transplant population has been chosen, as many of the mothers will be taking similar drugs throughout pregnancy. In addition renal disease itself will predispose mothers to an increased risk of similar confounders including; hypertension, IUGR and pre-eclampsia.

CHB

CHB is associated with anti-Ro/SSA or anti-La/SSB autoantibodies, it is estimated to occur in 2% of pregnancies, the risk of reoccurrence in a subsequent child is increased to 20% (33;40;121;122). There is a 10–20% risk of perinatal death amongst affected children and most of surviving children need a permanent pacemaker (123;124). Incomplete forms such as first or second-degree heart block, can progress to complete forms during childhood(120).

Retrospective data were reviewed comparing children with complete CHB, born to mothers with anti-Ro/SSA antibodies with their unaffected siblings, Impaired neurodevelopment was reported in 16% of the children (18/114) during a median follow-up time of 13 years(125). Reported problems included speech (9%), motor (8%) and learning (8%) impairment, attention deficit (5%) and behavioural impairment (4%)(125). Learning impairment was significantly influenced by maternal SLE ($p < 0.005$), while

attention deficit was influenced by both maternal SLE ($p < 0.05$) and CHB in the child ($p < 0.05$)(125). This study indicates that both maternal SLE and CHB may influence neurodevelopment in those children (125).

Long term outcomes of children born with CHB, have been reported in 91 infants from Finnish tertiary referral centres(124). In total 82% of the cohort were alive at 10 years, mortality was associated with congestive dilated cardiomyopathy(124). Cardiac pacing was required in 53% of neonates and 40% required pacing after the neonatal period(124).

Congenital anomalies

The EUROCAT (European surveillance of congenital anomalies) data, derived the overall prevalence of major congenital anomalies in the general population diagnosed during pregnancy, at birth, or in early infancy at 26 per 1000 births in 2010(126).

SLE literature

There has been a small study on the risk of congenital physical abnormalities in 30 children born to mothers with lupus in the United States of America (USA) , which demonstrated a similar incidence to that of the general population (98). A population registry study in Western Australia, linked dispensed prescriptions with a birth defects registry for a 3 year period (2002-5), to calculate an OR (odds ratio) when comparing the number of birth defects if a minimum of one prescription was dispensed during pregnancy, with that of all offspring not exposed to that medication(72). This study identified an increased risk of congenital anomalies, following pregnancies where at least one prescription was dispensed for hydroxychloroquine (72). This study did not take account of several confounders including: maternal age, diagnosis and other medications (72). In addition the results are not statistically significant as the 95% confidence interval for the OR crosses one (72).

An abstract from a recent Canadian, case control study, analysing medical databases of 507 women with SLE who had 721 children and 5862 matched healthy controls who had 8561 children, reported slightly more major congenital anomalies, [13.6% (95% CI 11.3, 16.3)

compared with 10.4% (95% CI 9.7, 11.1)], in controls(127). The congenital anomalies associated with certain drugs have been discussed in the medication in pregnancy section.

Transplant literature

A large study, which assessed the outcome of 362 children, born to mothers after kidney transplant, found a birth defect rate of 5% (110). No predominant pattern of malformations was identified in this study(110). It has been reported by the NTPR (National Transplantation Pregnancy Register), that although the rate of congenital anomalies in the transplant population is comparable with that of the general United States population, there is a substantially increased anomaly rate of 23%, in those pregnancies where there has been in-utero mycophenolate mofetil exposure (128). The observed pattern of malformation associated with Mycophenolate in both animal models and human data have resulted in the recommendation in the renal literature that mycophenolate should be stopped and an alternative agent should be started before conception (74).

Immune function and risk of infection

Prematurity and low birth weight in the general population are associated with an increased risk of infections, the risks have been estimated to be three to tenfold compared to full term normal birth weight infants(68). It has also been demonstrated that the risk for adverse fetal outcomes including; mechanical ventilation, new born sepsis, hypoglycaemia, admission to the neonatal intensive care, and hospitalization for 5 days or more; are significantly reduced for every week that elective caesareans are performed after 37 weeks gestation(129). Low birth weight is associated with a significant increase in adolescent (aged 12-20) hospital admissions for respiratory complaints, including infections(130). The relationship was stronger in adolescents who had a very low birth weight (<1.5kg) compared to those with a moderately-low-birth weight (1.5-2.499kg)(130). This relationship was maintained when adults with a history of very low birth weight or moderately low birth weight were compared to age matched controls (131). Studies have also demonstrated a relationship between low birth weight and reduced lung function in adult life (132;133).

The long term outcomes of children who are breast fed by women with IBD was compared in those who did or did not take azathioprine (134). The mean age of children was 3.3 years in the azathioprine exposed group and 4.7 years in the control group, there was no statistical difference in rates of hospitalisation for infection between the two groups (134).

SLE literature

There have been several small studies investigating both the humoral and cellular components of immunity in children born to mothers with connective tissue diseases exposed to immunosuppression in utero (102;135-137).

A number of small studies have demonstrated that children born to mothers with connective tissue disease, exposed to immunosuppression in utero have normal levels of serum IgG subclasses and lymphocyte subpopulations (102;135).

The immune response to the C.Tetani toxoid was assessed, by evaluating the titre of circulating antibodies, in twenty-two babies born to mothers with a connective tissue disease taking hydroxychloroquine or dexamethasone during pregnancy (137). There was no clear relationship between specific drug exposure and antibody response in the five children who did not achieve a protective titre of anti C. Tetani (137). In contrast, another study, which assessed the response to hepatitis B vaccination, in nine children, found that all the children had a satisfactory response to hepatitis B vaccination, in addition to normal Lymphocyte subpopulations, serum immunoglobulin levels, and IgG subclasses serum levels (136).

An abstract from a recent Canadian, case control study, analysing medical databases of 507 women with SLE who had 721 children, and 5862 matched healthy controls who had 8561 children, reported slightly more serious infections, 31.5% (95% CI 28.2, 35.0) compared with 26.0% (95% CI 25.1, 26.9) of controls(127). Serious infections in this study were

identified as greater than one hospital admission with a primary diagnosis of infection These serious infections were also reported at a younger age in the children born to mothers with SLE, 1.8 (95% CI 1.6, 2.0) years of age for children born to women with SLE and 2.1 (95% CI 2.0, 2.2) in the control group(127). The increased rate of serious infection in children born to mothers with SLE, remained after multivariate analysis, (adjusted HR 1.76, 95% CI 1.21, 2.56)(127).

What is known about infection risk in children exposed to immunosuppression from the Transplant data

There is little long term data of child outcomes in the renal literature, some very small studies, which reviewed six patients in the renal literature concerning children exposed to immunosuppression, the studies found that B and T cells were low at birth and when repeated in one of the studies had normalised within a few months (138-140). These infants did not develop opportunistic or chronic infections, and had a normal growth during their first year of life. However, the authors suggested that conventional vaccinations should be delayed in these infants(141).

Larger studies of renal transplant registry data, have used telephone interviews and/or questionnaires, to collect long term information on children born to renal transplant recipients, and have not found any reported immune dysfunction in the children (110;128).

Developmental problems

Several studies have been carried out in the general population that have identified possible associations with developmental problems as outlined below. Developmental problems was used as a collective term to describe developmental delay, Attention Deficit disorder, special needs and special schooling, identified by a relevant health care professional in this study.

Very low birth weight (<1.5kg) and very preterm (27-33 week) infants, have an increased risk of long term educational and behavioural difficulties (142-146)

Delays in several neurodevelopmental domains, including attention and social interaction were reported to be significantly reduced in small for gestational age term infants with normal placental function when compared to the general population (147)

There are a number of factors that can have an adverse effect on perinatal and early childhood brain development in the general population. An increase in the risk of ADHD (Attention Deficit Hyperactivity Disorder) or attention deficit disorder without hyperactivity is associated with maternal smoking, alcohol consumption, very low birth weight and fetal hypoxia(148). There are papers in the literature on Attention Deficit Hyperactivity Disorder and autism and autoimmunity that are described in the discussion.

SLE literature

1.2.1.1 The role of autoantibodies and developmental problems

Maternal autoantibodies, which are known to cross the placenta, have been implicated as a contributor to developmental problems. The fetal blood-brain barrier is not fully formed, so the developing brain is exposed to maternal autoantibodies.

a. Anti-phospholipid Antibodies

A previous case control study, found increased evidence of developmental problems, particularly in male children (149). A previous study which studied forty-seven offspring of SLE patients, found that maternal SLE does not impair intelligence levels, but may increase the occurrence of learning difficulties, the three children with impaired learning difficulty tests were all born to mothers with anti-phospholipid antibodies (150).

Recent data from the European neonatal registry of babies born to mothers with antiphospholipid syndrome, which observed forty-two children up to twenty four months, identified four children with developmental problems(52). The identified developmental problems were: one case of autism, two cases of learning disabilities and one case of psychomotor delay associated with axial hypertonia(52). All four children were born at term, to mothers with primary purely obstetric anti-phospholipid syndrome, treated with both aspirin and heparin during pregnancy(52). There is a passive acquirement of maternal antiphospholipid antibodies in a sub-group of 30 children compared to age matched

controls, when fetal blood was examined, there was an absence of clinically evident thrombotic events (52).

b. Anti-Ro/SSA and/or anti-La/SSB antibodies

Anti-Ro and/or anti-La antibodies have known effects on the fetal heart, skin, blood and liver. It has been postulated that since the blood-brain barrier is not fully formed in utero, that antibodies may be able to cause neurological damage as part of the neonatal lupus syndrome (151;152).

A large multicentre cohort study recruited, hundred and four anti-Ro exposed offspring with a mean age of 14.5 years (range 5-39) and twenty-two friend control children, mean age 11.2, good matching was demonstrated for gender, ethnicity, race and socioeconomic status(151). In total forty-two (40%) of the 104 anti-Ro exposed children were reported by their parent to have a neuro-psychiatric disorder, compared with 6 (27%) of the friend controls ($p = 0.34$). Neuro-psychiatric disorders included depression, anxiety, developmental delays, learning, hearing, and speech problems, which individually were not significantly different between groups (151).

A case control study comparing 58 children born to mothers with SLE with58 healthy controls, found that sons of women with SLE were more likely to have a learning difficulty than the daughters of women with SLE and children of either sex in the control group(153), Children in both groups were age, sex, and socially class matched

children(153) The significant risk factors associated with learning difficulties were flare of maternal SLE in pregnancy and the presence of anti-Ro/SSA and/or anti-La/SSB antibodies(153). Children were assessed using a standardised intelligence test (Wechsler Intelligence Scale for Children-III), standardised tests for reading, arithmetic, and writing achievement.(153).

A retrospective study, which tested 49 pairs of SLE offspring and matched controls, revealed impairment in the SLE offspring group in two of the nine domains: learning and memory and behaviour(154). The pairs were matched for ethnicity, age, sex and socioeconomic status(154). However it is difficult to draw conclusions from such small numbers(154).

A study that evaluated 47 children (23 male and 24 female) born to women with SLE, included age appropriate testing (150). In total 3 children were identified to have learning difficulties, all three children's mothers were antiphospholipid antibodies (aPL) were positive, other maternal autoantibodies or drugs administered during pregnancy were not associated with learning difficulties(150).

There have been small studies which observed and tested the offspring of SLE patients for neurocognitive/psychiatric impairment, which suggested that there may be an increased risk of neuropsychological and learning difficulties (150;154).

1.2.1.2 Drugs and developmental problems

a. Dexamethasone

A study assessed neuropsychological development in a total of sixteen children; eleven children with CHB born to mothers with anti-Ro/SSA antibodies, who were exposed to high dose dexamethasone in utero, two children not exposed to in-utero dexamethasone and three healthy siblings, all of anti-Ro/SSA-positive women, were evaluated health controls (155). The mean age of the children was five (range 2–12) years, eleven were preschool age mean age 3.01, (range 14–65 months) and five of school age (7–11 years) (155). Age appropriate tools were used to assess IQ(155). The mean total dose of dexamethasone in exposed children was 186.6 mg (155). Children had normal IQ (mean IQ 105.1, standard deviation (SD) 9.5) (155). Only one child had a learning disability, of borderline clinical significance, but this child had never been exposed to dexamethasone (155). Data in the literature have suggested an increased risk of development problems in the offspring of non SLE women exposed to fluorinated steroids (dexamethasone/betamethasone) during pregnancy (79;156).

What is known about the risk of developmental delay from the Transplant Data?

Data available from the NTPR (National Transplantation Pregnancy Register) based in the United States identified 304 female kidney recipients on ciclosporin-based immunosuppression, with 456 pregnancies delivered between March 1983 and November

1999. Initially, 133 female recipients were contacted for information on their 175 children(128). In this group, 71 of the children were older than 5 years, and 8 (11%) of these were diagnosed with ADHD (110;128). Two years subsequent to this initial survey, 114 of 133 recipients were again contacted, and detailed information was gathered on 147 children(110). At follow-up, the mean age of the children was 6.5 ± 2.8 years(110). The rate of ADHD was similar to that found in the general population(110).

Summary

There is a gap in the literature when counselling women with SLE, regarding the risks of her child needing hospital attention or special schooling during childhood. In addition there is a paucity of data regarding how the mother's disease type or activity, antibody profile and drug use in pregnancy, may affect the child's outcome.

Providing women with SLE with up to date and evidence-based information on the potential risks of pregnancy for both themselves and their offspring will help to address both patient's expectations and knowledge when deciding to plan a family. There are few published studies in the literature on the long term effects on children born to mothers with SLE. Further research into this area will provide evidence for pre-pregnancy counselling, an essential component of holistic care, enabling mothers to make an informed decision.

Studies in the literature have looked at certain outcomes for children born to mothers with SLE including, neonatal lupus, CHB, physical anomalies and neuropsychological development, but there is nothing in the literature that considers all these factors together. This study aimed to assess a large cohort of UK children born to mothers with SLE seen at BILAG (British Isles Lupus Assessment Group) centres in the UK.

Aims and Objectives

The primary aim is to determine the frequency of adverse events, which occur in the children born to mothers with SLE, at a national level. These data from a large national cohort will also help us to identify and understand the predictors for adverse outcomes in children born to mothers with lupus.

The key questions that will be addressed are:

1. Does exposure specifically to hydroxychloroquine during pregnancy and/or breast feeding alter the risk of:
    1. Maternal Complications
        - Pre-eclampsia
        - IUGR
    2. Neonatal Outcomes
        - Congenital anomalies
        - Complete heart block
    3. Long term Outcomes of child
        - Hospital management of infection
        - Developmental problems

2. Does exposure to azathioprine specifically during pregnancy and/or breast feeding alter the risk of:
    1. Maternal Complications
        Pre-eclampsia
        IUGR
    2. Neonatal Outcomes
        Congenital anomalies
    3. Long term Outcomes of Child
        Hospital management for infection
        Developmental problems

3. Are there any non-drug risks and/or protective factors related to lupus disease in mother (particularly autoantibodies), pregnancy complications or fetal drug exposures when looking at infection requiring hospital management?

4. Are there any non-drug risk and/or protective factors when analysing congenital anomalies?

5. Are there any non-drug risk and/or protective factors when analysing child development?
    i. Developmental delay
        i. Delay in achieving milestones
    ii. Special Needs and/or Special schooling

i. Defined as a child that was deemed to require specialist schooling by an appropriate professional

iii. Attention Deficit Disorder

i. Diagnosed by an appropriate health professional and sufficient to require a defined intervention

Following initial univariate analysis, multivariate analyses will be carried out to determine if adjusted maternal risk factors are associated with adverse outcomes.

Methods

2.1 Data Collection

The study was approved and conducted in compliance with regulations of relevant ethics committees (South Birmingham National Research Ethics Service and hospital research and development departments) and all participants provided written consent in accordance with the Declaration of Helsinki.

Retrospective data were collected using an approved questionnaire designed to address the questions, developed to address aims and objectives. See appendix for further details. The inclusion criteria were: women who had a pregnancy after fulfilling a minimum of four ACR criteria for SLE, had a child below the age of seventeen and who regularly attended a rheumatology outpatient department. Any patients that did not fulfil the inclusion criteria were excluded. If a child was over the age of twelve at recruitment, then assent was taken via the mother, as approved by the ethic committee.

There were a total of 10 centres, Birmingham (Birmingham Women's Hospital, Queen Elizabeth/University Hospital, and City Hospital), London (St Thomas's and University College London), Bath, Manchester, Blackburn, Sheffield and Southampton. The data collected were from a non-selected sample. All eligible patients should have been approached to take part and we are unaware of any bias in recruitment. Data about patients that refused were not routinely collected. Data were excluded if the mothers had not developed a minimum of four ACR criteria, by the time the child was born, and if a child was over the age of seventeen.

In total data were collected for 287 children, born to 200 women after the fulfilment of a minimum of four ACR criteria for SLE, making this one of the largest studies to date.

The data were collected using the standardised questionnaire by a physician or research co-ordinator (nurse or research assistant) at the specialist centre. The first part of the questionnaire collected data on number and dates of pregnancies, drug exposure, smoking and alcohol intake during pregnancy, and the outcome in terms of miscarriages, stillbirths, live births, preterm delivery, birth weight and gestational age and data on maternal disease including antibodies, ACR criteria and renal biopsy results.

A second part of the questionnaire was completed by the mother to collect data on outcomes of children up to the age of 17 including; neonatal lupus syndrome (including CHB), any other congenital malformations, any outpatient visits or admissions to hospital, including the diagnosis of developmental delay and the need for special schooling, recurrent or serious infections and any chronic illnesses. Information was also collected about immunisations and prescribed drugs (other than antibiotics, cough mixtures and calpol) that the children have received, but the data were not analysed.
The relevant general practitioners or hospital doctors were contacted and notes reviewed as necessary to confirm details.
Children were defined as having an infection requiring hospital assessment if they had an in or outpatient visit due to infection, to account for different admission policies in different units. Children were defined as having a congenital anomaly based on the EUROCAT definitions(157)

2.2 Data Analysis

The data were analysed to produce mean and SD for continuous variables, median and range for non-continuous data. Categorical data were presented as frequencies and percentages. Preliminary analysis of categorical variables and normally distributed continuous variables utilised chi squared, or fisher's exact test for low frequency characteristics. Continuous variables that are non-parametric were analysed using Mann-Whitney U test. Multivariable logistic regression was used to adjust for variables considered to be clinically relevant (potential confounders) based on previous literature regardless of statistical significance on univariate analysis.

This enabled the calculation of ORs, p values and 95% CIs to assess the association between maternal/fetal factors and the outcomes of interest. All statistical analyses were performed using SPSS version 22. Detailed data analysis plan for each long term outcome studied are included in the appendix.

Results

Overall data Summary

In total data were analysed for 199 women, and 285 live born children. Overall the median age of mothers at delivery was 32 as shown in table 4. The overall ethnic mix was; 67% Caucasian, 16% South Asian, 11% Afro-Caribbean, 1% Chinese, 1% Hispanic and 4% other (Table 15). The ethnic mix of patients in this study is representative of a typical UK lupus cohort.

The median age of children at assessment in this study was 3 years, with a range of 0.1-17.3 years, as shown in Table 8. The age distribution of children at entry into the study is summarised in Table 19. The median gestational age at delivery was 38 weeks, with a range of 25-42 weeks and median birth weight of 2.94kg (Table 8). There was no statistically significant difference in the number of male or female children recruited, as shown in Table 8. The data are presented for the whole cohort and then subdivided by exposure to hydroxychloroquine, and then exposure to azathioprine.

Additional maternal items that were not analysed by drug exposure are in the appendix; supplementary tables section, (Tables 15-21). The following additional maternal demographical data are available (Table 15) in the appendix: maternal ethnicity, maternal years in education, pregnancy number, smoking (current, ex-smoker or nonsmoker) and alcohol intake during pregnancy. Additional tables available in the appendix are: maternal drugs in pregnancy (Table 16), maternal drug combinations (Table 17) and maternal antibody status (Table 18).

Child demographic data on age at entry and mode of delivery (Table 19) are included in the appendix. Additional data on infection (Table 20) and developmental delay by age (Table 21) are also in the appendix.

Maternal Demographics

The maternal demographics are summarised in table 4. The median age at delivery was 32 in all women, regardless of drug exposure Table 4. In total 34% (92/275) of the population were Caucasian and 66% (183/275) were all other ethnicities/racial groups combined. There were significantly more Caucasians, 72%, (107/148) in the hydroxychloroquine group (versus 60% (76/127) in the non hydroxychloroquine group (p=0.029). There was no ethnic differences identified comparing azathioprine exposed (Caucasian, 63%, 52/83) and unexposed (Caucasian 68%, 131/192), p=0.368. The median disease duration was 6 years in the whole cohort, Table 4. The disease duration range was very wide (0-27 years), reflecting the small number of women who had lupus diagnosed around puberty, and had children in their late thirties, Table 4. Disease duration prior to pregnancy was significantly longer in those who took azathioprine during pregnancy and/or breast-feeding (7 versus 6 years, p=0.0078) Table 4. No significant difference was identified in the disease duration between hydroxychloroquine and no hydroxychloroquine groups.

Maternal Drugs

Maternal medications ever taken throughout conception, pregnancy and breast feeding (if applicable) are summarised in tables 7, 16 and 17. When the data were reviewed, it was identified that the vast majority of children were exposed during both pregnancy and

breastfeeding, so there was an insufficient difference to justify a separate analysis for each of these.

The majority of women (71%) took aspirin and over half took prednisolone and hydroxychloroquine (53%) during pregnancy and/or breast feeding, as shown inTable 16 - Maternal Medication. There was a statistically significant increase in steroid use during pregnancy and/or breastfeeding, in the azathioprine group (87%) compared to the no azathioprine group (47%) ($p<0.0001$) (Table 7). The increased use of steroids in the hydroxychloroquine group (65% Vs 53%, in the no hydroxychloroquine group, $p=0.052$) Table 7 was not significant. There was a significantly increased use of aspirin in the azathioprine group (81%) versus the no azathioprine group (66%), $p=0.013$, which may reflect that these patients had more severe disease (Table 7).

Maternal Antibodies

The presence of maternal anti-double stranded DNA antibodies and lupus anticoagulant and/or anticardiolipin antibodies was statistically higher in the azathioprine exposed group (table 6). However the presence of the antibodies individually or in a diagnosis of maternal anti-phospholipid syndrome was not found to be significantly different between any of the treatment groups. Anti-Ro and/or anti-La antibodies were present in 43% of patients overall and there were no statistically significant differences associated with different drug exposures table 6.

Maternal disease Characteristics

In this study we used a history of renal biopsy as a surrogate marker for renal disease. This was felt to be something that mothers would be able to accurately recall. In the 243 pregnancies for which this data was obtained, a renal biopsy had been performed in 27% (65 pregnancies)table 4.

There were significantly more women in the azathioprine group who had had a previous renal biopsy, which is likely to signify more severe disease in this group. In total 16% (44/275) of the cohort had a history of hypertension prior to pregnancy, and the proportions were significantly increased in the group who did not have hydroxychloroquine during pregnancy and/or breast feeding and the group who took azathioprine during pregnancy and/or breast feeding (table 4).

Pregnancy Complications

There were no statistically significant differences in the rate of hypertension during pregnancy, pre-eclampsia or IUGR between the groups, and these were reported in the overall cohort at 17%, 10% and 12% respectively Table 5. This was despite the statistically significant increase in maternal steroid and renal disease in the azathioprine group

Table 4 - Maternal Characteristic's

Median, range, IQR Or n (%)	All n=285 children	HCQ n=150 Children	NO HCQ n=135 Children	p Value	AZA n=87	No AZA n=198	p value
Age at delivery	32 (19-44) 7	32 (19-44) 7	32 (19-42) 7	0.279*	**32.5, (22-42) 6**	**32.0, (19-44) 7**	**0.508***
Disease Duration yrs.	6 (0-27) 7	6 (0-21) 7	7 (0-27) 8	0.107*	**7.0 (1-21) 7**	**6.0 (0-27) 8**	**0.0078***
Previous Renal biopsy	65/241 (27)	32/132 (24)	32/109 (29)	0.371	**37/66(56)**	**27/175(15)**	**<0.0001**
Hypertension prior to pregnancy	44/275(16)	**16/144(11)**	**28/131(21)**	**0.020**	**31/82(38)**	**13/193(7)**	**<0.0001**

HCQ= Hydroxychloroquine, AZA = Azathioprine

All p values were calculated using Pearson's Chi2, except where indicated by *symbol. The *p values were calculated using a Mann–Whitney U test for continuous variable

Table 5 Pregnancy complications

Median, range, IQR Or n (%)	All n=285 children	HCQ n=150 Children	NO HCQ n=135 Children	p Value	AZA n=87	No AZA n=198	p value
Hypertension during pregnancy	48/278(17)	27/149 (18)	21/129(21)	0.685	12/84(14)	36/194(19)	0.387
Pre-eclampsia	28/268 (10)	15/143(11)	13/125(10)	0.981	11/82(13)	17/186(9)	0.831
IUGR	31/268 (12)	16/141(11)	15/127(12)	0.906	10/82(12)	21/186(11)	0.376

HCQ= Hydroxychloroquine, AZA = Azathioprine

All p values were calculated using Pearson's Chi2

Table 6 - Maternal antibodies

N (%)	All n=285 children	HCQ n=150 Children	NO HCQ n=135 Children	p Value	AZA n=87	No AZA n=198	p value
Anti-double stranded DNA ever present	177/268 (66)	91/137(66)	86/131(66)	0.894	**58/80(73)**	**119/198(60)**	**0.002**
Ro ± La antibodies	112/263 (43)	55/141(39)	57/122 (47)	0.207	37/78(47)	75/185 (41)	0.302
Lupus anticoagulant and/or Anticardiolipin IgG and/or IgM	122/250 (49)	68/131(52)	54/119 (45)	0.302	**42/72 (58)**	**80/178(45)**	**0.055**
Lupus anticoagulant	93/259 (36)	53/137 (39)	40/122(33)	0.323	30/74 (41)	63/185(34)	0.326
Anticardiolipin IgG and/or IgM	67/251(27) (23)	34/132 (23)	33/119 (28)	0.523	25/73(34)	42/178(24)	0.083
Diagnosis Antiphospholipid Syndrome	30/254(12)	15/134 (11)	15/120 (13)	0.747	7/77(9)	23/177(13)	0.376

HCQ= Hydroxychloroquine

AZA = Azathioprine

All p values were calculated using Pearson's Chi2, except where indicated by *symbol.

The *p values were calculated using a Mann–Whitney U test for continuous variable

Table 7 - Maternal drug treatment

N (%)	All n=285 children	HCQ n=150 Children	NO HCQ n=135 Children	p Value	AZA n=87	No AZA n=198	p value
Steroids	169/285(59)	**97/150 (65)**	**72/135(53)**	**0.052 borderline**	**76/87 (87)**	**93/198(47)**	**<0.0001**
HCQ	150/285 (53)	n/a	n/a	n/a	44/87 (51)	106/198 (54)	0.740
Azathioprine	87/285 (31)	44/150 (29)	43/135 (32)	0.740	n/a	n/a	n/a
Aspirin	200/282(71)	112/150 (75)	88/150(59)	0.140	**69/85(81)**	**131/197(66)**	**0.013**
Heparin	69/281(25)	42/149 (28)	27/132 (20)	0.133	**27/85 (32)**	**42/196(21)**	**0.064**

HCQ= Hydroxychloroquine
AZA = Azathioprine

All p values were calculated using Pearson's Chi2, except where indicated by *symbol.
The *p values were calculated using a Mann–Whitney U test for continuous variable

Neonatal/Long term child Outcomes (Table 8)

Although the median gestational age at delivery was 38 in all groups (table 8), there was a statistically significant difference between the azathioprine and no azathioprine group, due to the different distribution of ages between the different groups.

The median birth weight was significantly reduced in the babies who were exposed to azathioprine in utero, compared to the unexposed groups, there was no difference associated with HCQ exposure. There were no statistically significant differences in child gender between the groups.

The presence of neonatal rash, complete heart block or congenital anomaly using the EUROCAT definitions were each reported in 2% of the children in this study. The two cardiac congenital anomalies reported were AVSD (Atrioventricular Septal Defect) (n=1) and a double aortic arch (n=1). The four other congenital anomalies were Hirschsprung's (n=1), Hypomelanosis of ito (n=1), syndactyly (n=1) and spina bifida (n=1).

Children were significantly younger in the hydroxychloroquine versus non hydroxychloroquine exposed group. This is likely to reflect a change in practice, which has resulted in more women receiving hydroxychloroquine during pregnancy and/or breastfeeding in recent years, due to increasingly reassuring data in the literature.

There was a statistically increased risk of infections requiring hospital management, in children exposed to azathioprine during pregnancy and/or breast feeding (37% compared with 20%, p= 0.002) table 8. Overall there were a very low number of developmental

problems individually or combined in our cohort, and there was no statistically significant difference in those children who were exposed or unexposed to hydroxychloroquine or azathioprine during pregnancy and/or lactation (if applicable), as shown in**Table 8.**

Table 8 - Neonatal and long term outcomes

Neonatal Outcomes N(%) or median, range, IQR	All Women n=285	HCQ n=150	No HCQ n=135	P Value	AZA n=87	No AZA n=198	p value
Gestational age at delivery	38, 25-42 2	38, 25-42 2	38, 25-41 3	0.378*	**38, 28-42, 3**	**38, 25-42, 3**	**<0.0001***
Birth weight	2.94 0.59-4.70 0.82	2.89 0.59-4.35 0.835	3.0 0.65-4.64 0.873	0.987*	**2.66, 0.59-4.40 0.957**	**3.0, 0.65-4.64 0.820**	**0.022***
Child Gender Male Female	128/285(44.9) 157/285 (55.1)	72/150(48) 78/150(52)	56/135(41) 79/135(59)	0.269	36/87 (41) 51/87(59)	92/198(46) 106/198(54)	0.427
**EUROCAT Congenital anomalies	6/285 (2.1)	4/150 (2.6)	2/1345(1.5)	0.468	2/87 (2)	4/198 (2)	0.880
Neonatal lupus rash	6/285 (2)	4/150(2.6)	2/135 (1.5)	0.486	2/87(2)	4/198 (2)	0.880
CHB	7/285 (2)	4/150 (2.6)	3/135 (2.2)	0.809	2/87(2)	5/198 (2.5)	0.909
Age of child at entry into study	3.00, 0.1-17.3 5.4	**2.29, 0.07-17.09 4.23**	**3.93, 0.13-17.03, 5.82**	**<0.0001***	3.09 0.07-17. 5.87	2.88, 0.08-16.20, 5.02	0.709*
All infections requiring hospital management	69/274(25)	35/143(24)	34/131 (26)	0.778	**32/86(37)**	**37/188(20)**	**0.002**
Developmental delay or Attention deficit disorder or special schooling or special needs	17/284 (6)	6/149 (4)	11/135(8)	0.144	6/87(7)	11/197(6)	0.667
Developmental delay	14/285 (4.9)	6/150(4)	8/135 (6)	0.485	5/87 (6)	9/198(5)	0.733
Attention Deficit Disorder	7/285 (2.5)	1/150(0.67)	6/135 (4.44)	0.078	3/87 (3.4)	4/198 (2%)	0.623
Special Schooling	3/285 (1.1)	0/135 (0)	3/135 (2.2)	0.119	0	3/198 (2)	0.410
Special Needs	6/285 (2.1)	1/150 (0.7)	5/135 (3.7)	0.132	2/87 (2)	4/198 (2)	0.794

All p values were calculated using Pearson's Chi2, except where indicated by *symbol.
The *p values were calculated using a Mann–Whitney U test for continuous variable

**Defined using EUROCAT definitions

Long term outcome Analyses

Further analyses were undertaken to address the three main long term outcomes of interest; congenital anomalies (including CHB), infection and developmental delays.

Congenital anomalies

Univariate analysis did not demonstrate any significant associations with congenital anomalies, using the 95% confidence interval and two tailed p value for increased accuracy.

Table 9 - Congenital anomalies univariate analysis

Suspected risk factors for congenital anomalies	P value	OR	95% CI min	95% CI max
Maternal Risk Factors/Characteristics				
Maternal Ethnicity (Caucasian Vs all others)	0.995	1.006	0.181	5.594
Maternal Disease characteristics				
Previous Renal biopsy	0.115	4.303	0.702	26.368
Anti-phospholipid syndrome	0.711	1.510	0.170	13.384
Maternal Antibodies				
Anti-dsDNA ever	0.974	1.029	0.185	5.726
Anticardiolipin ±Lupus anticoagulant	0.953	1.050	0.208	5.307
Maternal medications ever taken during pregnancy				
Steroids	0.212	0.335	0.06	1.862
Hydroxychloroquine	0.493	1.822	0.328	10.109

Azathioprine	0.880	1.141	0.205	6.350
Aspirin	0.269	0.401	0.079	2.029
Heparin	0.653	0.609	0.070	5.303
Obstetric/Perinatal				
Hypertension during pregnancy	0.308	2.457	0.437	13.811
Pre-eclampsia	0.089	4.538	0.793	25.987
IUGR	0.117	4.017	0.705	22.904
Pregnancy duration	0.507	1.133	0.783	1.640
Birth weight	0.884	1.092	0.336	3.547
Log of child age at entry	0.894	0.960	0.526	1.751

Congenital anomalies multivariate analysis

An initial larger model, investigated the following variables: birth weight, log of child age at entry, maternal drugs (azathioprine, steroids, hydroxychloroquine, aspirin and heparin), maternal ethnicity, IUGR, anticardiolipin +/- lupus anticoagulant, pre-eclampsia, hypertension prior pregnancy, anti-double stranded DNA, hypertension during pregnancy, antiphospholipid syndrome and previous renal biopsy. The only significant risk factors identified at the final stage of the analysis (step 14) were previous renal biopsy (OR 11.4,

p=0.025, 95% CI 1.35-96.5) and pre-eclampsia (OR =20.895, p=0.017, 95%CI 1.71-256). It is of note that although the p values were significant, the 95%CI were very wide.

A multivariate analysis using stepwise logistic regression, used the following variables: pregnancy duration, birth weight, maternal drugs (azathioprine, steroids, aspirin or heparin ever), IUGR, anti-double stranded DNA ever, maternal ethnicity (Caucasian versus all) and previous renal biopsy. The final step (eight) of the analysis is shown below. The models p value is 0.49, which is the limit of significance, which is likely due to the low event frequency (6 using EUROCAT definitions). The only statistically significant variable was IUGR, but the confidence interval is very wide, this link is likely to be due to a baby with a congenital anomaly not growing as well in utero. Reassuringly when counselling lupus patients these results did not identify any SLE specific risk factors.

Table 10 - Congenital anomalies multivariate analysis

Suspected risk factor	P value	OR	95% CI min	95% CI max
Pregnancy duration	0.144	1.450	0.880	2.386
IUGR	**0.020**	**15.024**	**1.525**	**148.002**
Previous renal biopsy	0.077	5.697	0.827	39.221

CHB

The univariate analysis assessing possible associations with CHB and/or neonatal lupus are outlined in Table 8. The only positive association was the presence of maternal anti-Ro and/or La antibodies, as expected.

A logistic regression stepwise analysis model was used to analyse the effects of hydroxychloroquine, steroids, azathioprine, anti-Ro, anti-La and anti-Ro and/or anti-La antibodies. Anti-La antibodies had the strongest relationship with CHB, as this was the last remaining factor. Steroids were weakly protective against CHB, but this was far from significant.

Table 11 - CHB univariate analysis

Suspected risk factors for CHB	P value	OR	95%CI min	95% CI max
Maternal Risk Factors/Characteristics				
Maternal Ethnicity (Caucasian Vs all others)	0.395	2.556	0.294	22.206
Maternal Disease characteristics				
Previous Renal biopsy	0.705	1.395	0.249	7.807
Maternal Antibodies				
Anti-Ro	0.042	9.118	1.082	76.854
Anti-La	0.006	10.250	1.932	54.379
Anti-Ro and/or La	0.049	8.491	1.007	71.559
Anti-dsDNA ever	0.206	0.375	0.082	1.713
Anticardiolipin ±Lupus anticoagulant	0.359	0.344	0.035	3.356

Maternal medications ever taken during pregnancy				
Steroids	0.379	0.506	0.111	2.304
Hydroxychloroquine	0.809	1.205	0.265	5.486
Azathioprine	0.909	0.908	0.173	4.775
Aspirin	0.117	0.297	0.065	1.357
Heparin	0.803	1.236	0.234	6.518
Obstetric/Perinatal				
IUGR	0.559	1.942	0.210	17.950
Pregnancy duration	0.896	0.983	0.757	1.276
Birth weight	0.610	0.765	0.273	2.140
Log of child age at entry	0.410	1.319	0.682	2.552

Infection

Univariate analysis demonstrated significant associations between infection and azathioprine, and aspirin, as demonstrated in Table 12.

Table 12 - Infection univariate analysis

Suspected Risk factor for Infection	P value	OR	95% CI min	95% CI max
Maternal Risk Factors/Characteristics				
Maternal Ethnicity (Caucasian Vs all others)	0.226	1.933	0.665	5.620
Maternal Disease characteristics				
Previous Renal biopsy	0.386	1.342	0.690	2.612
Hypertension out of pregnancy	0.897	0.950	0.440	2.054
Anti-phospholipid syndrome	0.238	0.514	0.170	1.554
Maternal Antibodies				
Anti-dsDNA ever	0.432	1.278	0.692	2.360
Anticardiolipin ±Lupus anticoagulant	0.784	0.920	0.509	1.665
Maternal medications ever taken during pregnancy				
Steroids	0.294	1.355	0.768	2.391
Hydroxychloroquine	0.778	0.925	0.536	1.596
Azathioprine ever	0.002	2.402	1.364	4.232
Aspirin	0.038	2.038	1.041	3.991
Heparin	0.110	1.652	0.893	3.056
Obstetric/Perinatal				
Hypertension during pregnancy	0.721	0.874	0.417	1.831
Pre-eclampsia	0.540	0.727	0.262	2.016
IUGR	0.166	1.800	0.784	4.133
Pregnancy duration	0.132	0.929	0.843	1.023
Birth weight	0.894	1.028	0.686	1.539

A stepwise backward regression model was used to assess infection, using the following variables: pregnancy duration, birth weight, azathioprine ever, steroids ever, IUGR, anti-dsDNA ever, anti-cardiolipin IgG/IgM or lupus anticoagulant, pre-eclampsia, hypertension out of pregnancy, antiphospholipid syndrome, maternal ethnicity (Caucasian versus all other), log of child's age at entry, heparin ever, aspirin ever and previous renal biopsy. It was proposed that there will be greater than one factor contributing to infections in children, so both statistically significant and insignificant variables of clinical importance were included in the model to assess their potential effects.

In a smaller more specific and robust model we adjusted for fewer variables; pregnancy duration, azathioprine ever, steroids ever, IUGR, anti-dsDNA ever, maternal ethnicity (Caucasian vs all others), aspirin or heparin ever and previous renal biopsy. Although on univariate analysis aspirin and azathioprine use during pregnancy and/or breastfeeding was significant, they are likely to be a surrogate marker for more severe disease. The only significant predictors of infection on stepwise backward regression were birth weight ($p=0.027$) and aspirin ($p=0.037$). Aspirin is likely to be a predictor of low birth weight, as is likely to be associated with more serious maternal disease. Gestational age and azathioprine were the last factors to fall out of the model.

Developmental problems

A composite outcome of development delays and /or Attention Deficit Disorder and/or special schooling and/or special needs was used, as the frequency rate of individual outcomes were low. The only statistically significant variable identified on univariate analysis was the age of the child at entry into the study as shown in Table 13. The log of the child's age was used, as data was not normally distributed.

Table 13- Developmental problem Univariate analysis

Suspected risk factors for Developmental problems as a composite outcome	P value	OR	95% CI min	95%CI max
Maternal Risk Factors/Characteristics				
Maternal Ethnicity (Caucasian Vs all others)	0.724	0.829	0.291	2.355
Maternal educational needs	0.521	0.951	0.815	1.109
Maternal ever smoking	0.305	0.511	0.142	1.844
Maternal Disease characteristics				
Previous Renal biopsy	0.115	4.303	0.702	26.368
Hypertension out of pregnancy	0.387	1.677	0.520	5.404
Anti-phospholipid syndrome	0.445	0.448	0.057	3.508
Maternal Antibodies				
Anti-dsDNA ever	0.612	0.759	0.262	2.202
Anticardiolipin ±Lupus anticoagulant	0.614	0.739	0.228	2.393
Maternal anti-Ro	0.514	1.471	0.461	4.687
Maternal anti-La	0.290	1.951	0.565	6.735
Maternal anti-Ro and/or anti-La	0.596	1.368	0.429	4.359
Maternal medications ever taken during pregnancy				
Steroids	0.967	0.979	0.362	2.652
Hydroxychloroquine	0.148	0.470	0.169	1.307
Azathioprine	0.660	1.259	0.450	3.521
Aspirin	0.263	0.564	0.207	1.536
Heparin	0.498	0.643	0.179	2.307
Obstetric/Perinatal				
Hypertension during pregnancy	0.606	0.671	0.147	3.053
Pre-eclampsia	0.577	0.556	0.071	4.373

IUGR	0.904	1.099	0.238	5.080
Pregnancy duration	0.981	1.022	0.835	1.203
Birth weight	0.683	0.866	0.435	1.725
Log of child age at entry	0.008	2.227	1.238	4.007
Child Gender	0.750	0.850	0.314	2.301

A multivariate analysis using stepwise logistic regression used the following variables: hydroxychloroquine, steroid, azathioprine aspirin and log of age at entry. The only variable that remained significant was the age at entry into study, OR 2.212, $p<0.0001$ (95%CI 1.231-3.973). There is no evidence in this study that any of the drugs studied had any detrimental effect, in fact hydroxychloroquine was the last to drop out in this model, and looked as if it might have protective properties, OR 0.699, $p=0.508$ (95%CI 0.242-2.020).

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Discussion

This study is one of the largest studies of long term outcomes of children born to mothers with SLE up to the age of 17. In total data were analysed for 285 children, born to 199 women. The long term outcomes assessed were congenital anomalies, CHB, infection requiring hospital management and developmental problems. The rates of congenital anomalies as defined by EUROCAT and of complete CHB were both 2%. Infection requiring hospital management was reported in 69/274 (25%). There were very few developmental problems reported; development delay (5%), special needs (2%), attention deficit disorder (1%) and special educational needs (2%). Prior to discussing the long term outcomes in more detail, the characteristics of the population will be reviewed.

Maternal Characteristics

There were several differences between the data in this study and the general population data which will be discussed. The average age of mothers at delivery in this study was 32, which was slightly older than the combined English and Welsh national average age of 29.5 years in 2010 (158). Lupus mothers were also found in a US study to be significantly older at 30, compared to those in the general population 27.5, $p<0.001$ and a Norwegian study 29.4 compared with 27.7, $p<0.001$ (25;25;159). The patient ethnicity proportions in the lupus groups differed in our study compared to a US study, this study had a lower proportion of African patients 11% compared to 20%, and an increased proportion of white patients 67% compared to 55% (25).

This study found that 4% of women smoked during pregnancy, in contrast 13% women who gave birth in England in 2011/12 reported smoking during their pregnancy(158). This is very reassuring in view of the link between smoking and poor pregnancy outcomes. A US and Norwegian study found no differences between women with lupus and those in the general population who smoked (25;159).

In total 17% of mothers in this study drank alcohol, normally between 1-3 units per week, with only one mother drinking 5 units per week. Our results demonstrated 100% of women consumed no to moderate amounts (3–7 glasses/week) of alcohol during pregnancy compared to 95.5%, in a recent UK study (160).No differences in excess alcohol consumption were demonstrated in lupus patients compared to the general population in the literature(25).

Our data identified that mothers who were taking azathioprine during pregnancy, were significantly older at delivery. It is likely that this group of patients had to wait for the disease to be stable, on drugs compatible with pregnancy. This is consistent with previous studies reporting that mothers with SLE have smaller families, later in life (14-17).

Outcomes of Pregnancy

Caesarean section

The English average for emergency and elective caesarean sections was 24% over 2010-11 in comparison 37% of the women in our study required a caesarean section(158) . This may in part attributable to a difference in policy in many specialist obstetric clinics that treat women with lupus, inducing SLE pregnancies at thirty-eight weeks, due to the increased risk of stillbirth, which is not standard practice in the national population.

Data was not routinely collected on any pregnancies prior to the fulfilment of a minimum of four ACR criteria, so it was not possible to assess if the higher rate of caesarean sections compared to the normal population was due to previous caesarean section and/or induction. However a previous caesarean does not preclude a vaginal delivery in a subsequent pregnancy, guidelines from the royal college of obstetricians and gynaecologists advises that vaginal birth after caesarean section can be safely considered on a case by case basis for both spontaneous and induced deliveries(161)

The higher risk of caesarean sections in lupus patients, OR of 1.7, compared to the general population was also identified in a US Nationwide Inpatient Sample (NIS) study reviewing four years of data(25). A Norwegian study also identified a twofold increased risk of caesarean in first and subsequent deliveries when compared to the general population(159). A Canadian study which also compared SLE patients to the general population, found that the increased OR (3.47) for caesarean was maintained after adjustment for dysfunctional labour, instrumentation and previous caesarean section(162).

IUGR and Pre-eclampsia

The rate of IUGR in our study at 4% (12/270) for the not severe enough to be induced group and 7% (19/270) in the severe enough to be induced group. The overall rate of IUGR reported was 12%, with no significant differences between pregnancies with hydroxychloroquine or azathioprine exposure. IUGR is commoner in SLE patients compared to the general US population, 5.6% versus 1.5%, $p<0.001$(25;159). IUGR was present in a higher proportion of patients in this study, which may be due SLE patients being recruited from specialist centres, who tend to have patients with more severe disease.

Pre-eclampsia was reported at 4% (12/270) for the not severe enough to be induced group and 7% (19/270) in the severe enough to be induced group in this study. Pre-eclampsia was found to be commoner in SLE pregnancies than the general population in several studies (25;159;162). The overall rate of pre-eclampsia in this study was 11% which is comparable to rates reported in Canadian study (9.5%) and a Norwegian study reported a rate of 14.7% in first births and 10.3% in subsequent births(159;162). However a US study reported an increased rate of 22.5%(25).The pre-eclampsia rate in our study was lower than expected, possibly due to aspirin being given to over 70% of patients. These data are very interesting and would be worthy of testing in a prospective study.

Child Demographic Data

Gestational age and Birth weight

The median gestational age in this study was 38 weeks with a range of 25-42 weeks, 73% of deliveries in this study were delivered between 37 and 41 weeks in comparison to 88.6% in the general UK population(163). There were no significant differences in mothers who were exposed or not exposed to hydroxychloroquine or azathioprine. A Canadian study also identified higher rate of preterm births compared to the general population, with 34% of deliveries in the SLE group occurring before 37 weeks gestation, compared with 24% in our study(162).

The average birth weight in our study was 2.67kg, which is lower than the UK national data average of 3.3kg; this may be partially explained by the younger gestational age in our cohort (164;165). This discrepancy may also be due to the underlying SLE diagnosis and the different distribution of ethnicities in our cohort, which has a higher proportion of Afro-Caribbean and Asian patients due to the nature of SLE (164;165). Studies have demonstrated increased low birth weight infants born to mothers from Asian and Afro-Caribbean groups compared to Caucasian (164;165).

Our data are consistent with Canadian and US studies, which have also identified significantly more small for gestational age babies born to women with lupus than the general population. Interestingly the average birth weight of children born to mothers with SLE was significantly lower for both the first and subsequent pregnancies, 2.996kg and 3.249kg respectively then the general population in a Norwegian study(159). However this was not specifically addressed in our study.

Congenital Anomalies

The British Isles Network of Congenital Anomaly Registers (BINOCAR) is a group of regional and disease-specific registers collecting information about congenital anomalies occurring in England, Ireland, Scotland and Wales(166). They published data which looked at several UK registries which also used EUROCAT definitions in 2011(166). In 2011, there were 5,718 cases with one or more congenital anomalies notified to six BINOCAR registers (East Midlands & South Yorkshire; Northern England; Oxfordshire, Berkshire & Buckinghamshire; South West England; Wessex; and Wales)(166). The birth prevalence was 2.19%, 1 in 46 total births(166).

This is comparable to the congenital anomaly rate identified, 6/285 (2%), from our UK based cross sectional survey which will provide reassuring data with which to counsel women with SLE planning future pregnancies. The results from this study are also consistent with a smaller prospective and two recent large Canadian and Norwegian studies, that did not identify an increased rate of congenital anomalies in children born to mothers with SLE in comparison with the normal population (98;162;167).

A weak association between IUGR and congenital anomalies was identified, on multivariate logistical analysis, which has also been confirmed in the general population (168).

Hydroxychloroquine

Hydroxychloroquine has been demonstrated to be compatible with pregnancy in two systematic reviews (103;104). Many previous studies showed no increased risk of congenital anomalies as outlined in the section congenital anomalies and discussed in the introduction. This has increased hydroxychloroquine use in pregnancy and/or breast feeding, as demonstrated by the shorter disease duration in women who took hydroxychloroquine in our study. A recently published observational comparative cohort study, collected prospective data on 114 pregnancies with hydroxychloroquine and identified a non significant increase in congenital anomalies when compared to 455 controls, but this was not corrected for confounders (169).

Azathioprine

Several large recent studies have published data demonstrating no increase in congenital anomalies in the offspring born to women and/or men who took azathioprine during pregnancy to treat underlying IBD (170-174). A large UK primary care record database that identified 1703 children born to mothers with IBD identified no increase in congenital anomalies when compared to controls or when specifically observing azathioprine/6-mercaptopurine exposed children (171). Of interest recent studies have also demonstrated no increased risk of congenital anomalies following exposure to azathioprine in either parent, prior to or during pregnancies (170;173;175). Our study, combined with these

recent studies and previously published studies discussed in the relevant sections of the introduction have not demonstrated an increased risk of congenital anomalies in children where there was maternal or paternal exposure to azathioprine

Neonatal Lupus Rash

Cutaneous Neonatal lupus is reported to occur in 2-10% of children, born to mothers with anti Ro/SSA and anti La/SSB antibodies (32;119;176). The lesions often resolve within the first 3-6 months of life as maternal antibodies are cleared from the circulation. In total 42% of mothers had anti Ro/SSA and anti La/SSB antibodies and a neonatal rash was reported in 2% of cases. The rate of neonatal lupus rash in this study is lower than that reported in the literature, which is likely due to the condition being under recognised and reported by mothers.

CHB

Complete heart block was reported in 2% of cases in this study, which is comparable to the 1-2% reported in the literature (31-33;120;122;177). Several studies have recently looked into the possibility that hydroxychloroquine may prevent CHB. The possible relationship has been investigated based on the potential involvement of Toll-like receptor (TLR) signalling in the pathogenesis of neonatal lupus (NL). It was hypothesised that fetal exposure to hydroxychloroquine (HCQ), a TLR inhibitor, might reduce the risk of anti-SSA/Ro/SSB/La antibody-associated cardiac manifestations of NL (178;179)

There has been one case-control study which has found that the use of hydroxychloroquine in anti-Ro/SSA or anti-La/SSB autoantibody positive SLE women with a previous child with CHB did not result in a statistically significant reduced risk of CHB in subsequent pregnancies as shown in Table 11 (180). However hydroxychloroquine was found to be significantly associated with a reduction in recurrent CHB when all mothers were anti-Ro/SSA or anti-La/SSB autoantibody positive, but did not necessarily have a diagnosis of SLE (181). A retrospective review of women with anti-Ro antibodies, who did not necessarily have a diagnosis of SLE found that maternal treatment with either hydroxychloroquine or daily low-dose prednisone throughout pregnancy may provide a protective effect against CHB(182). The key findings of the studies recently published in the literature are outlined below in Table 11.

Our study did not identify a protective effect of hydroxychloroquine against complete heart block, but our study did not look at reoccurrence, due to the low frequency rate. Furthermore in our study approximately 40% of our cohort had anti-Ro and/or LA antibodies, in contrast to these previous studies, which exclusively recruited antibody positive women.

The logistic multivariate analysis performed in our study identified that anti-La antibodies had the strongest association with CHB. There have been conflicting studies in the literature regarding the pathogenic role of anti-Ro and anti La antibodies individually in fetal heart block (183-185). This study and another recent study, suggested a potential role of anti-La antibodies, which were identified to bind to myocytes in fetal heart tissue in a smaller study (184;185). However a larger more recent study identified that cardiac complications of neonatal lupus were associated with the concentration of anti-Ro antibodies, irrespective of the presence of anti-La antibodies(182). This is an area of research that requires further study to confirm the potential associations.

Table 14 - Key findings of recently published CHB literature

Study	Study Type	Antibodies	Disease	OR CHB in HCQ group	95% CI	p Value
1. Izmirly. ARD. 2010	Case Control N=201	Anti-Ro/SSA &/or anti-La/SSB	SLE only	OR = 0.46 Any CHB	0.18-1.18	p=0.10
2. Izmir. Circulation. 2012	Retrospective N=257	Anti-Ro/SSA ±anti-La/SSB	Any	OR = 0.23 Recurrence	0.06–0.92	p=0.037
3. Tunks. AJOG. 2013	Retrospective N=33	Anti-Ro/SSA	Any	OR=0.14 Any CHB	0.002–1.35	p= 0 .09

A recent Abstract from a Canadian single centre retrospective study confirmed the protective effect of maternal antimalarials in women with a diagnosis of SLE, cutaneous lupus, Sjogren's dermatomyositis or rheumatoid arthritis during pregnancy against CHB(185). A prospective study to address the potential beneficial effects of hydroxychloroquine against CHB is currently being undertaken(185).

Gender ratio

Our study demonstrated no significant gender difference, the male to female ratio was 128/157 (0.8), (p=0.75, 95%CI 0.31-2.3). Recent Canadian data, using physician billing and hospital databases suggested an increase in the male-to-female ratio in children born to women with SLE, which was also found in murine studies (186;187). The gender discrepancy may be due to the presence of anti-NMDAR (N-methyl D-aspartate) receptor antibodies, a subset of anti-dsDNA antibodies. An increased male-to-female ratio was noted in pregnant mice exposed to anti-NMDAR antibodies, as there was a marked loss of female fetuses compared to unexposed pregnant mice (186).

However results combined from PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Syndrome and Systemic Lupus Erythematous) a multi-centre, prospective study, and RRNL (Research Registry for Neonatal Lupus), a registry of families in which the mother has anti-SSA/Ro and/or anti-SSB/La antibodies and at least 1 child with neonatal lupus did not identify a gender discrepancy, as did this UK data (188).

Infection

This study identified that 69/274(25%) of children for whom data was available required hospital management for infection. A statistically significant increased infection rate was identified in children born to women who took azathioprine during pregnancy and/or breastfeeding. However following multivariate analysis, this rate was accounted for by duration of pregnancy and birth weight, which are also predictors of infection in the general population. In addition the increased frequency of infections seen in children who took aspirin during pregnancy remained significant after multivariate logistic regression. This is likely to be due to aspirin being a confounder for severity of maternal disease, rather than as a direct action of the aspirin itself.

In contrast to our study findings, an abstract from a recent Canadian case control study, analysing medical databases of 507 women with SLE who had 721 children, and 5862 matched healthy controls who had 8561 children, reported slightly more serious infections at a younger age, the risk remained higher in the offspring of SLE patients after multivariate analysis (adjusted HR 1.76, 95% CI 1.21, 2.56) (189). This may be because of differing study methodologies, but as the Canadian study has only been published in abstract format, it is difficult to make any detailed comparisons.

A recent study which compared 15 women with IBD who took azathioprine (median dosage 150 mg/day) during pregnancy and/or lactation with 15 who did not, found no statistically significant difference in hospital admissions for infection(134). In contrast to this study the number of children who were hospitalised for infection in the IBD study, were higher in the group not exposed to azathioprine (6/15, 40%) compared with (3/15,

20%) in azathioprine exposed group, but this was not statistically significant (134). The discrepancy between this study and our study may be explained by the increased percentage of preterm or the longer follow up period, combined or individually, reported in the non azathioprine exposed group in the IBD study. Prematurity as previously discussed is a risk factor for childhood infections, and the older a child is the more chance they have had to acquire an infection requiring hospital management.

Information Services Division Scotland, published discharge diagnosis for emergency admission for certain infections including intestinal infections, tuberculosis, viral meningitis, chicken pox and measles was 1, 103 per 100, 000 population(190). This was lower than the rates reported in this study, but this may be as only certain infections were included, whereas this study included all infections(190).

Several recent large population studies have looked into the outcome of late preterm birth with regard to infections. A study which assessed hospitalisations for nonspecific and bacterial infections in the general population during the first year of life by gestation found an increase in infection in infants with lower gestational age at birth (191). This finding was also corroborated in a study, which found that emergency respiratory admissions, up to the age of five years reduced with every successive gestational week up to 40 to 42 weeks (192). The discharge diagnoses studied were acute upper respiratory tract, influenza, pneumonia, acute lower respiratory tract infections, acute bronchiolitis and asthma (192). A Canadian population study established that late preterm infants had significantly increased risk of infectious disease, respiratory disease and hearing loss (193). A preliminary Italian cohort study suggested that hospitalizations for lower respiratory tract infections were more frequent in lower gestation groups; 4.4% in 33-34 gestational week

group, 4.6% in 35-37 gestational week groups and 3.5% in infants born ≥38 weeks (194). Our study looked at any infections requiring hospital management; the numbers in our study were much smaller which may be why no association with gestational age was identified.

Low birth weight in the general population has been linked to an increased risk of hospitalisation for respiratory including infections, during both adolescence and adulthood (130-132).

Developmental Problems

Overall there was a low rate of all developmental problems whether analysed individually or combined. In total 6% (17/284) had developmental delay and/or attention deficit disorder and/or special schooling and/or special needs. Developmental delay was reported in 14/285 (4.9%), special needs in 7/285(2.5%), attention deficit disorder 3/285(1.1%) and the requirement for special schooling 6/285(2.1%). There was no statistical significant association identified with any maternal or child variables. Although autism was not specifically enquired about, it will be captured in the composite endpoint used. However an adequately powered prospective study would be needed to study any possible relationship.

There is a potential association between developmental problems and autoimmune disease, specific antibodies and drugs which will be discussed in separate sections.

Our results identified ADD in 3/285(1.5%) of the children, which is lower than the prevalence rates identified in a UK study using medication treated ADHD in children over six, adolescents and adults in primary care(195). The prevalence per 100, 000 in 6-12year was 9.2 (95% CI: 8.8–9.6) and 7.4 (95% CI: 7.0–7.8) in the 13–17 year age group (195).

There was no significant difference in the frequency of developmental problems in children who were exposed or not to azathioprine during pregnancy and/or breastfeeding as shown in Table 8.

The number of events identified in our study was very low, as the median age of children at enrollment was 3.0 years, so developmental problems may not yet have been identified. Developmental problems will normally be identified in school aged children, in our study 97/285 (34%) were five or over. Several studies in the literature have looked into the possible underlying mechanisms behind neurodevelopmental problems in the offspring of SLE patients, as outlined below. Further follow up of this cohort should help to define this.

The protective effects of hydroxychloroquine during pregnancy may be due to its beneficial effects on the placenta in vitro studies of APS patient placentas(196). In this study hydroxychloroquine reversed the anti-phospholipid inhibition of trophoblast interleukin-6 secretion in addition to partially limiting anti-phospholipid inhibition of cell migration(196). However further research will need to be undertaken to assess the effect of hydroxychloroquine in vivo

Parental Autoimmune disease

A recent large population based cohort study found that the presence of any maternal autoimmune condition, including lupus, were more likely in children with autism spectrum disorder (ASD) and developmental delay without autism (DD) than in controls(197). The largest study to date included 3,325 cases from a Danish registry, investigating autism and autoimmune conditions (198). The study observed an increased risk of ASDs in children with a maternal history of rheumatoid arthritis, coeliac disease and a family history of type 1 diabetes (198). This relationship is felt to be attributable to a combination of genetic background, prenatal antibody exposure or alteration in fetal environment during pregnancy (198).

A smaller Swedish registry study, that were linked to both biological parents, identified 1237 cases and 30,925 controls(199). Autism spectrum disorders were associated with parental autoimmune disease; maternal OR = 1.6 [95% confidence interval = 1.1–2.2] and paternal OR = 1.4 [1.0 –2.0](199). Several maternal autoimmune diseases were significantly associated with autism, including type-1 diabetes, idiopathic thrombocytopenic purpura, myasthenia gravis, and rheumatic fever(199). SLE was not found to be significantly associated with autism in this study, but there were only 20 women with SLE in this study, 2 of whom had a child with an ASD(199).

Autoantibodies

At present the precise mechanism underlying the relationship between children born to mothers with SLE and neurodevelopmental and learning disabilities is unknown. Animal studies have identified that maternal antibodies may contribute to abnormal neurodevelopment and congenital cortical impairment (200).

A recent study which tested the serum of 2431 mothers of autistic spectrum children and 653 controls for anti-brain antibodies via immunohistology on mouse brains(201). It identified mothers of autistic spectrum children were four times more likely to have brain-reactive antibodies and of those with antibodies a higher prevalence of autoimmune disease especially SLE(201). This study provides evidence that there are increased brain reactive antibodies in the serum of mothers of autistic spectrum children, which may be associated with maternal autoimmunity(201). This suggests that a further avenue for research will be

to look into characterising these antibodies further to identify the potential pathogenicity of these antibodies on the developing brain(201).

Anti-Ro/SSA and Anti-LA/SSB antibodies

A study identified 26 children born to mothers with SLE, with an average age of 6.6 (range 0.7-12.8) and suggested a possible link between Ro/SSA antibodies and neurodevelopment(202), Although IQ was normal in all children, Sequential Processing scores were significantly lower in the nine children with Ro/SS-A-positive mothers, compared with the 17 negative mothers. However it is of note that there was also an increased incidence of other potential confounders; IUGR, low birth weight and prematurity (202).

In a study which looked at the outcome of 114 children born to mothers with Ro/La antibodies, 63 of the children had CHB and the remaining 62 children were siblings without CHB(203). Children were born between 1980 and 2009, with a median follow up time of 13 years (25th–75th percentile: 8.2–17.5 years)(203). This study identified the following significant relationships; increased impaired motor skill development in boys ($p < 0.001$) and preterm children ($p < 0.001$), increased learning impairment in maternal SLE ($p < 0.005$), increased attention deficits with both maternal SLE ($p < 0.05$) and CHB ($p < 0.05$)(203).

Antiphospholipid Antibodies

Data presented at the American College of Rheumatology analysed two hundred and nine pregnancies in one hundred and twelve women, using this UK questionnaire in the Baltimore lupus centre in the USA, (204). No autoantibody was statistically significantly associated with attention deficit disorder or with dyslexia, but the frequency of anticardiolipin was increased in both conditions(204).

Studies of children with no known autoimmune diagnosis have found that children with a known diagnosis of autism have elevated levels of anti-phospholipid antibodies (anti-cardiolipin, β 2-glycoprotein 1, and anti-phosphoserine antibodies) compared with age matched healthy controls and children with non autistic developmental delays(205).

The largest study to date looking at the long term outcomes of children born to women with antiphospholipid antibodies is the European registry of babies born to mothers with antiphospholipid syndrome (52;206;207). Intermediatory results demonstrated transfer of autoantibodies to the neonate, which were confirmed in subsequent analysis of the data (52;206;207). Antiphospholipid antibody placental transfer was identified in the preliminary analysis on the follow-up of 141 babies, in 20, 25 and 43% of cases for lupus anticoagulant, anticardiolipin and anti-β2-glycoprotein I antibodies, respectively(52).

Recently the European registry group published 5 year follow up data on 134 children, born to 133 women with antiphospholipid syndrome and of these 18 also had a diagnosis

of SLE (207). The four neurocognitive problems identified were (autism, hyperactive behaviour, feeding disorder with language delay and axial hypotony with psychomotor delay (207).

A subsequent study which looked at the offspring of women with primary Antiphospholipid syndrome (n=36) and SLE without antiphospholipid syndrome (n=12), identified 3 case of autism, which were all from the primary Antiphospholipid syndrome group(208). All these pregnancies were treated and no adverse obstetric events including IUGR were present, APS antibodies were implicated as during follow up all these children had persistent anti-β2 GPI antibodies, but with no antiphospholipid features of APS or thrombus(208).

A study which looked at the neurodevelopment in 17 children born to mothers with primary antiphospholipid syndrome, identified 4 children with learning difficulties on formal testing(209). However they also alluded to the presence of other potential risk factors including prematurity, that could interact with maternal antiphospholipid antibodies(209).

In contrast a study, which reviewed the outcomes of 26 children, aged between 6 months and 12 years, born to women with SLE, found no relationship between the presence of maternal antiphospholipid serology (n=10) and intelligence test scores(202). Our study also did not demonstrate an association between developmental problems and antiphospholipid syndrome.

Azathioprine

Our study did not identify an increase in developmental delays in contrast to a study using the same standardised questionnaire in the United states (US) (210). The US study suggested that there may be an association between in utero azathioprine exposure and an increased requirement for special education requirements, assessed by an appropriately qualified professional(210). However there were only 13/60 (22%) children exposed to azathioprine at a single centre in the US in contrast to 85/287 (30%) children in this study from multiple UK centres, but the children in the US study had a higher median age of 5.7 years in comparison to 3.2 years in our study(210). In addition there was a higher proportion of renal disease in the US group 45%, comparison to 23% in this study cohort(210). The authors do state that the study does not establish sufficient risk, and warn that untreated disease in pregnancy is a risk in itself for adverse maternal and fetal outcomes(210).

A recent study from the IBD literature compared 15 exposed and 15 nonexposed children with a median and range ages of 3.3 (0.6–6) and 4.7 (1.1–8.6) respectively, all the children had appropriate mental and physical development (134;134). Although the numbers in the IBD study were smaller than this study, it is of interest that the median age of children in our study was 3.0, (range of 0-17), but the range was wider in our study (134).

Other relevant risk factors linked to developmental delay in the general population include autism and childhood infection(198;211) as well as late preterm birth (34-37 weeks gestation) and cerebral palsy(212). A recently recognised subgroup of preterm babies, are those born between 34 and 36 weeks (late preterm), which account for approximately 70% of all preterm deliveries (213;214). Several recent studies have looked at the educational and neurodevelopmental outcomes of children born late preterm and have identified increased problems when compared to children who were born at term (215-224). In this study the mean gestational age was 36.3 week (sd 4.13), a substantial proportion were late preterm, and it may have been that because a lot of children in our study were under 5 and did not undergo formal neurodevelopmental assessment, as in the majority of these studies in the general population that no increase in developmental problems were identified.

Limitations

This study had several methodical considerations. Data were collected retrospectively, which increases the possibility of bias due to recall or loss to follow up. However patients were not aware of the specific hypothesis being examined in this study. The data was self-reported and confirmed with the medical records when possible, but many were not confirmed by GPs. Unfortunately it was difficult to ensure that GPs respond to letters requesting information about children, probably as no payment for their contribution to this research study was available.

Data was not collected on disease activity or on prednisolone dose throughout pregnancy, so the effect of longitudinal patterns of disease activity and medication dose on maternal and fetal complications could not be assessed.

Another limitation was that relatively few developmental problems were reported in this cohort, which may have confined the identification of potential risk factors in this cohort. This questionnaire has been used internationally and international analyses of these data have been planned in the future to overcome the limitations of analysing relatively few events in this cohort. However validated instruments were not used across the whole cohort, which would have helped to account for geographical differences in identification and referral of childhood outcomes such as infection and developmental problems. The median age of children in our cohort was relatively young, 3.3 years, which may have led to an underestimation of developmental problems, as they have not yet reached school age. This bias may have been introduced, as pregnancy data were more readily available for younger children.

In retrospect it would have been ideal to collect data on maternal pregnancy and post-partum disease activity, as maternal health can effect childhood development and how readily parents seek healthcare advice. More detailed maternal socioeconomic data, including maternal and paternal occupation, would have allowed its inclusion in multivariate analysis, as a potential confounder for child health. These considerations would be important in a future prospective study.

Pregnancy losses (miscarriages or still birth) were not addressed in this study as the main aim of this study was to investigate the long term outcomes of live born children. There were also methodological limitations in collecting pregnancy data, as they were collected retrospectively and inconsistently across the centres as women had pregnancies in other hospitals.

Data were not collected on maternal use of fluorinated steroids, which cross the placenta, for prematurity and/or myocarditis due to CHB prior to delivery, as this will be difficult to accurately recall retrospectively. A prospective study would be better able to address this potential confounder for developmental delay

Analyses not carried out:

There were a wide range of children recruited, and medical practice has changed over the years, so carrying out an analysis taking this into consideration would have allowed correction for this. Furthermore we did not control for the number of children born to each mother. In addition developmental problems will usually become evident when children

start formal education at the age of 4-5, so an analysis looking at children over five would have helped to correct for this.

However this study reviewed a well characterised group of SLE patients recruited from specialist UK centres. All the centres form part of the BILAG Group. It is believed that the data provided covers a broad spectrum of disease, as demonstrated by the drug data, 20% of women took no DMARD, including prednisolone, during pregnancy and/or breastfeeding (table 17).

Further development

A meta-analysis of the international data is planned, which may be able to provide more information on the incidence and possible risk factors for maternal and fetal complications.

However based on the results of this UK analysis, this project could be further developed by setting up a prospective registry, which would overcome the issues of recall bias and the likely too few events for a case control study.

A future prospective study would allow the associations identified in this study, to be studied further. However the study would need to be set up to regularly review children for a minimum of five to ten years after enrolment to enable the identification of neurocognitive disorders. A further study with increased numbers would also be able to address any potential protective effects of hydroxychloroquine on developmental delays

Summary

Data was presented on 285 children born to 199 mothers after a diagnosis of SLE that met all the inclusion and exclusion criteria. Overall the data from this study provided reassuring evidence when looking at the three key long term outcomes of interest congenital anomalies infection and developmental problems. Once controlled for confounders there was no evidence that any of the drugs had a detrimental effect. The risk factors for an infection requiring hospital management are those of the general population, specifically birth weight. Aspirin appeared to be a risk factor, but this is likely to be due to the underlying maternal disease being an indication for aspirin use.

Overall the results from this study are very encouraging, and can provide reassurance, when counselling mothers with SLE regarding long term outcomes of children. In addition our study will provide data to support physicians, using drugs and treating these diseases in pregnancy.

Appendix

Congenital Anomaly Analysis Plan

Univariate analysis will be performed to use the following variables which are suspected risk factors,

Maternal Risk Factors/Characteristics
Maternal Ethnicity
(Caucasian Versus all others)

Maternal Disease characteristics
Previous Renal biopsy
Hypertension out of pregnancy
Anti-phospholipid syndrome
Maternal Antibodies
Anti-dsDNA ever
Anticardiolipin ±Lupus anticoagulant

Maternal medications ever taken during pregnancy
Steroids
Hydroxychloroquine
Azathioprine
Aspirin
Heparin

Obstetric/Perinatal
Pre-eclampsia
IUGR
Pregnancy duration
Birth weight
Log of child age at entry

CHB Analysis plan

The following variables will be assessed using univariate analysis:

Maternal Risk Factors/Characteristics

Maternal Ethnicity
(Caucasian Versus all others)

Maternal Disease characteristics

Previous Renal biopsy
Maternal Antibodies
Anti-Ro
Anti-La
Anti-Ro and/or La
Anti-dsDNA ever
Anticardiolipin ±Lupus anticoagulant

Maternal medications ever taken during pregnancy

Steroids
Hydroxychloroquine (possibly protective)
Azathioprine
Aspirin
Heparin

Obstetric/Perinatal factors

IUGR
Pregnancy duration
Birth weight
Log of child age at entry

Infection Analysis Plan

Infection requiring hospital management, in Accident & Emergency departments or as an in or outpatient will be studied to account for the differences in individual hospital admission policies and differing ages of children within the study.

The suspected risk factors assessed for infection were:

Maternal Risk Factors/Characteristics
Maternal Ethnicity
(Caucasian Versus s all others)

Maternal Disease characteristics
Previous Renal biopsy
Hypertension out of pregnancy
Anti-phospholipid syndrome
Maternal Antibodies
Anti-dsDNA ever
Anticardiolipin ±Lupus anticoagulant

Maternal medications ever taken during pregnancy
Steroids
Hydroxychloroquine
Azathioprine ever
Aspirin
Heparin

Obstetric/Perinatal variables
Hypertension during pregnancy
Pre-eclampsia
IUGR
Pregnancy duration
Birth weight
Log of child age at entry

Developmental Problems Analysis Plan

Univariate analysis will use a combination of any one of the 4 variables below, as a composite outcome:

Development Delay
Special Needs
Special schooling
Attention Deficit Disorder

The following suspected risk factors for developmental problems as a composite outcome will be assessed:

Maternal Risk Factors/Characteristics
Maternal Ethnicity
(Caucasian Vs all others)
Maternal educational needs
Maternal ever smoking

Maternal Disease characteristics
Previous Renal biopsy
Hypertension out of pregnancy
Anti-phospholipid syndrome
Maternal Antibodies
Anti-dsDNA ever
Anticardiolipin ±Lupus anticoagulant
Maternal anti-Ro
Maternal anti-La
Maternal anti-Ro and/or anti-La

Maternal medications ever taken during pregnancy
Steroids
Hydroxychloroquine
Azathioprine
Aspirin
Heparin

Obstetric/Perinatal factors
Hypertension during pregnancy
Pre-eclampsia
IUGR
Pregnancy duration
Birth weight
Log of child age at entry
Child Gender

Supplementary Tables

Additional Maternal Demographics

The ethnic mix of patients in this study is representative of a typical lupus cohort. The maternal education, smoking and alcohol consumption during pregnancy in those that took alcohol are outlined in Table 15. No mothers reported using illicit drugs during pregnancy.

Table 15 - Additional maternal demographics

Characteristic	Mean/median or Number (%)	SD/Other Information
Ethnicity n=275	**Afro-Caribbean = 30/275 (11%)** **Asian= 44/275 (16%)** **Caucasian = 183/275 (67%)** **Oriental = 4/275 (1%)** **Other=12/275 (4%)** **Hispanic = 2/275 (1%)**	
Maternal Education (Years)	**Median=16** **Available in 250**	**Range 5-30** **IQR 13-18**
Pregnancy number	**1st= 52%** **2nd =26%** **3rd = 15%** **4th = 49%** **5th = 1%** **6th= 1%** **9th = <1%** **NK = 1%**	**Average = 2** **Range = 1-9**
Smoking – Current, Ex-smoker or Non smoker	**Smoking Status NK = 16** **Never Smoked = 188** **Ex-Smoker = 64** **Current Smoker = 18**	**Smoking during pregnancy=11**
Alcohol (During pregnancy)	**Alcohol during pregnancy=48** **No alcohol during pregnancy=237** **Not known =2**	**Average no of units=2**

Medications

Maternal medications ever taken throughout conception, pregnancy and breast feeding (if applicable) are summarised in table 16. When the data were reviewed, it was identified that in those who chose to breast feed, most women continued drugs taken during pregnancy. This meant that the numbers between only pregnancy exposed and breast exposures were not sufficiently different for this analysis to be relevant. The majority of women took aspirin and over half took prednisolone and hydroxychloroquine during pregnancy and/or breast feeding, as shown in Table 16 - Maternal Medication. Only one baby was exposed to mycophenolate throughout pregnancy and three were exposed to ciclosporin, as demonstrated in Table 16 - Maternal Medication.

Table 16 - Maternal Medications

SLE medications	Ever during pregnancy and/or breastfeeding Number (%)	Never during pregnancy Number (%)
Aspirin	200/282 (71)	82/282 (29)
Heparin	69/281 (25)	212/281 (75)
Prednisolone	169/285 (59)	116/285(41)
Hydroxychloroquine	150/285 (53)	135/285 (47)
Azathioprine	88/287 (31)	198/287 (69)
Mycophenolate	Conception only= 2 Throughout pregnancy=1	
Ciclosporin	3 conception & throughout pregnancy	
Tacrolimus	Nil	
Methotrexate	Nil	

Table 17 summarises the drug combinations mothers took during conception, pregnancy and breast feeding (if applicable). Mothers were again classified as taking a drug if they had ever taken the drug, to accurately capture the possible effects of drugs on maternal, fetal and long term child outcomes. It is of note that a fifth of women took no DMARD during pregnancy. The commonest drug combination was azathioprine and prednisolone with or without hydroxychloroquine as shown in Table 17. Azathioprine was almost always co-prescribed with prednisolone.

Table 17 - Maternal drug combinations

Drug Combination	Yes %	No %
AZA alone	2	98
AZA & HCQ & no pred	2	98
AZA & no pred	4	96
AZA & Pred & HCQ	14	86
AZA & Pred ±HCQ	26	74
No DMARD	20	80
HCQ alone	16	84
Pred alone	12	88
Pred & HCQ only	20	80
Pred & AZA only	13	87

Aza=Azathioprine, Pred=Prednisolone, HCQ=Hydroxychloroquine, DMARD=Disease Modifying Anti-Rheumatic Drug

Maternal Antibody Status

The presence of maternal lupus and anti-phospholipid antibodies individually and combined are summarised in table 15. The majority of women were not positive for antiphospholipid antibodies, either individually or combined as shown in Table 18. In total 66% of mothers had ever had dsDNA and under half (42%) had anti Ro and/or anti-La antibodies as demonstrated in Table 18.

Table 18 - Maternal Antibody Status

Antibody	Present Number (%)	Not present
Presence Antiphospholipid antibodies I.e. LAC±ACL IgG±IgM	123/251 (49)	128/251 (51)
Lupus anticoagulant	93/260 (36)	166/260 (64)
Anti-cardiolipin IgG	62/251 (25)	189/251(75)
Anti-Cardiolipin IgM	38/251 (15)	213/252 (85)
Anti-Cardiolipin IgG and/or IgM	67/251 (27)	184/251 (73)
dsDNA	178/269 (66)	91/269 (34)
RNP and/or Sm	72/266 (27)	197/266 (73)
Anti-Sm	40//263 (15)	223/263 (85)
Anti-Ro	106/262 (40)	156/262 (60)
Anti-La	53/260 (20)	207/260 (80)
Maternal Ro and/or La antibodies	110/261 (42)	151/261 (58)

Additional child Demographic Data

The median and range age of child at entry into the study were 3.26(0-17), as shown in Table 19, the majority (67%) of children were under five when data was collected. In total 61% of children were born vaginally, of these 11% required instrumentation with forceps or ventouse, as shown in Table 19.

Table 19 – Additional child demographics

Characteristic	**N(%)**	**Range**
Child age at entry to study (n=285)	0-<12 months = 69/285 (24) 12 months-<24months = 34/285 (12) 24 months to <5yrs = 85/285 (30) 5 yrs - <10 yrs = 53/285 (19) 10yrs to <15yrs = 40/285 (14) 15yrs to 17years = 4/285 (1)	Range 0-17 IQR 1.3-6.9 Median 3
Mode of delivery (n=283)	Vaginal=141/283 (50) Forceps/Ventouse=31/283 (11) C section= 111/283 (39)	

Infections sub divided

In total 69 out of 274 children for whom data was available required a hospital management for infection, the number and percentage of children in each age group are illustrated Table 20. The highest percentage and number of infections was seen in the under 5 group. Hospital management was used rather than in and/or outpatient admissions to account for the different geographical and age admission criteria.

Table 20 - Infection by age

Age	Total number analysed N=274	No of pts with variable No (%)	No of pts without variable No (%)
0-1	63	11(17)	52(83)
1-2	33	9 (27)	24 (73)
2-5	83	29 (35)	54 (65)
5-10	53	12 (23)	41 (77)
10-15	37	7 (19)	30 (81)
15-17	4	1(25)	3(75)

Developmental problems subdivided by age

Table 21 - Developmental problems overall and subdivided by age

The frequency of developmental problems is demonstrated for the group overall and subdivided by age. There were very few if any children who had a problem identified below the age of two.

	Age	Present No(%)	Not Present No(%)
Developmental delay	All	14/285 (5)	271/285 (95)
	0-<12 months	0/69	69
	12 months-<24months	2/34(6)	32/34(94)
	24 months to <5yrs	5/85(6)	80/85(94)
	5 yrs - <10 yrs	3/53(6)	50/53(94)
	10yrs to <15yrs	3/40(8)	37/40(92)
	15yrs to 17years	1/4(25)	3/4(75)
Special Needs	All	6/285(2)	279/285(98)
	0-<12 months	n/a	n/a
	12 months-<24months	1/69(1)	68/69(99)
	24 months to <5yrs	1/85(1)	84/85(99)
	5 yrs - <10 yrs	0	53
	10yrs to <15yrs	2/40(5)	38/40(95)
	15yrs to 17years	2/4(50)	2/4(50)
Attention Deficit Disorder	All	3/285(1)	282/285(99)
	0-<12 months	0	69
	12 months-<24months	0	34
	24 months to <5yrs	0	85
	5 yrs - <10 yrs	0	53
	10yrs to <15yrs	2/40(5)	38/40(95)
	15yrs to 17years	1/4(25)	3/4(75)
Special Educational Needs	All	6/285(2)	279/285(98)
	0-<12 months	n/a	n/a
	12 months-<24months	1/34(3)	33/34(97)
	24 months to <5yrs	1/85(1)	84/85(99)
	5 yrs - <10 yrs	0	53
	10yrs to <15yrs	2/40(5)	38/40(95)
	15yrs to 17years	2/4(50)	2/4(50)

LONG-TERM OUTCOMES IN SLE

PART A: MOTHER

CENTRE No: _____ PATIENT ID: _____ DATE: _____

DEMOGRAPHIC DATA

(**Hospital/research staff to complete from medical notes)**

*** not to be entered on database. For all items including race put NK if NOT KNOWN.**

First Name*		**Home Telephone***
Surname*		**Work Telephone***
Postcode		**Country of Birth**
Unit No.		**Occupation**
DOB		**Years of Education**

RACE:1=Afro-Caribbean, 2=Asian, 3=Caucasian, 4=Oriental, 5= Other/mixed, NK=Not known
RACE/ Mother:1=Afro-Caribbean, 2=Asian, 3=Caucasian, 4=Oriental, 5= Other/mixed or NK
RACE/ Father:1=Afro-Caribbean, 2=Asian, 3=Caucasian, 4=Oriental, 5= Other/mixed or NK
YEAR of ONSET (SLE 1st ARA): YEAR of DIAGNOSIS (SLE 4th ARA):
Marital Status: Married / Single / Widowed / Divorced / Separated / Partner/Not known

LUPUS FEATURES

ARA Criteria	Year of Onset
Malar rash	
Discoid rash	
Photosensitivity	
Oral ulcers	
Arthritis	
Serositis	
Renal disorder	
Neurological disorder	
Haematological disorder	
Immunological disorder	
Antinuclear factor	

Renal Biopsy
Yes/No/Not known
WHO grade _____
Date : _____
Comments on reverse of form

HYPERTENSION – requiring treatment out of pregnancy?
Yes/No/Not known
HYPERLIPIDAEMIA– requiring treatment out of pregnancy?
Yes/No/Not known

Does the patient have ***Anti-Phospholipid Syndrome**?
Yes/No/Not known
If Yes Date diagnosed: _____
* Wilson WA et al (1999)

Ever Present	Yes	No	Not measured	Ever Present	Yes	No	Not measured
ACLG				Anti-Ro			
ACLM				Anti-La			
Anti-ds DNA				Anti-Rnp			
Lupus Anticoagulant				Anti-Sm			

CENTRE No: _____ PATIENT ID: _____

Past Medical History (Discuss this page with patient in clinic if necessary)

Thyroid Disease	Yes/No/Not known	If Yes, give year of diagnosis
Type I - Diabetes Mellitus	Yes/No/Not known	If Yes, gives year of diagnosis
Pernicious Anaemia	Yes/No/Not known	If Yes, give year of diagnosis
Rheumatoid Arthritis	Yes/No/Not known	If Yes, give year of diagnosis
Other Yes/No/Not known	If Yes, give year of diagnosis	
Thrombosis	Yes/No/Not known	If Yes, give year of diagnosis

Number of pregnancies: [ ] Number of children born: [ ] Any twins or multiple births: Yes / No

Ever had a termination?	Yes/No/Not known	If Yes, year(s): _____
Ever had a miscarriage?	Yes/No/Not known	If Yes, year(s): _____
Ever had a stillbirth?	Yes/No/Not known	If Yes, year(s): _____

Family History

If yes, please state which of these relatives: mother, father, sister or brother

Other family member(s) with SLE	Yes/No/Not known - _____
Thyroid Disease	Yes/No/Not known - _____
Diabetes Mellitus	Yes/No/Not known - _____
Angina or Heart Attack	Yes/No/Not known - _____
High Blood Pressure	Yes/No/Not known - _____
High Cholesterol levels	Yes/No/Not known - _____
Anti-phospholipid Syndrome (Sticky Blood or Hughe's Syndrome)	Yes/No/Not known - _____

Alcohol Intake

Did you drink alcohol during any pregnancy? Yes/No/Not known
If Yes, how many units per week in which pregnancies (approximately)?

Pregnancy 1 _____Pregnancy 2 ___ Pregnancy 3 _____Pregnancy 4 _____
Pregnancy 5 _____Pregnancy 6 _____
*Unit of alcohol is equivalent to the amount of alcohol in a half-pint (250ml) of beer, or a small glass of wine, or a single measure of spirits

Smoking History

Ever smoked cigarettes?Yes / No
Date Started: _____ Date Finished: _____
Smoking during any pregnancy: Yes/No/Not known
Pregnancy 1 _____
Pregnancy 2_____
Pregnancy 3 _____
Pregnancy 4_____
Pregnancy 5_____
Pregnancy 6_____
Others _____

Did you use in any recreational drugs in pregnancy?
Yes/No/Not known
If yes: which pregnancies?
Pregnancy 1 _____
Pregnancy 2 _____
Pregnancy 3 _____
Pregnancy 4 _____
Pregnancy 5_____
Pregnancy 6_____
Others _____

1

First Pregnancy

Name of child:_____

DOB of child_____ Gender: F / M

Miscarriage: Yes / No/ Not known

Stillbirth: Yes / No/ Not known

Slow Heart Rate:Yes / No/ Not known

Weight @ birth: _____ or Not known

Duration of Pregnancy: _____weeks

Delivery: 1. Normal vaginal delivery [ ]
2. Forceps / Ventouse [ ]
3. Caesarean Section [ ]
4. Not known [ ]

During First Pregnancy

- High Blood Pressure only in pregnancy? Yes / No / Not known
- Pre-eclampsia (High Blood pressure + ankle swelling + protein in urine) Yes / No / Not known
  Severe enough to have baby induced? Yes / No / Not known
- Growth restriction Yes / No / Not known
  Severe enough to have baby induced? Yes / No / Not known
- Protein in Urine Yes / No / Not known
- Blood Clots/Thrombosis Yes / No / Not known
- Other medical problems in mother:_____

Drug exposure during First Pregnancy

Please mark: **Y** = Yes or **N** = No or **NK** for Not known.

If possible, please clarify if started by putting **1** and if stopped put **2** in relevant column

Therapy	At Conception	First 13 weeks	Weeks 14 to 26	More than 26 weeks	Breast-feeding
Hydroxychloroquine (Plaquenil)					
Steroids (Prednisolone)					
Azathioprine (Imuran)					
Cyclophosphamide					
Methotrexate					
Ciclosporin A (Neoral)					
Mycophenolate (CellCept)					
Aspirin					
Heparin (Clexane)					
Warfarin					
Antiepileptics (specify if possible)					
ACE Inhibitors (e.g. Lisinopril)					
Nifedipine / Amlodipine					
Labetalol					
Methyldopa					
Other or not known antihypertensives					
Folic Acid					
NSAIDs (eg Ibuprofen)					
Other Drugs (specify if possible)					

1

LONG-TERM OUTCOMES IN SLE

PART B: CHILD

(Centre number: deleted)
Study ID: Mother ID ____Child ID _____ Gender: F [ ] M[ ]

First 6 months:

Neonatal Lupus Syndrome Yes / No
Congenital Heart Block Yes / No
Was the baby born with any abnormality Yes / No
Please specify _____

First 2 years:

Developmental delay Yes / No
Special Needs Yes / No
Attention Deficit Disorder Yes / No

Immunisations received ***(Please circle as appropriate)***

BCG at birth (Asian babies) Yes / No/Not known

DTP

2, 3 and 4 months old

Diphtheria *Yes / No/Not known*

Tetanus *Yes / No/Not known*

Pertussis *Yes / No/Not known*

(Whooping cough)

Polio and Hib Yes / No/Not known

MenC – Meningitis C Yes / No/Not known

Outpatient Appointments - First 2 Years

Has your child ever attended an outpatient clinic? Yes / No
If yes, please tell us about the appointments at the outpatient clinics:

Hospital	**Speciality and Consultant if known**	**Disease or symptom**	**Period of follow-up (months/years)**

Hospital admissions

Has your child ever been admitted to hospital? Yes / No
If Yes, How many times? _____

Hospital	**Speciality and Consultant if known**	**Disease or symptom**	**Length of stay (days/weeks)**

Education

Does your child have any special needs? (e.g. dyslexia) Yes / No

If yes, please state the special need: _____

Drug exposure **Child ID: _____**

We would like you to document as precisely as possible all prescribed medicines (excluding: calpol (paracetamol), antibiotics, and cough mixtures) received by your child in the following age groups: first two years, 2 to 5, 6 to 11, 12 to 16. With your permission, we would complete this information from your GP records but your feedback with this would be greatly appreciated. Put NK if Not Known.

Age of child	**Name or type of drug** (e.g. Carbamazepine, anti-epileptic)	**Duration of therapy (estimate)**		
		Up to 7 days	**7 to 0 days**	**More than 1 month**
First 2 years				
2 to 5 years				
6 to 11 years				
12 to 16 years				

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