Pregnancy and Lupus Nephritis: A Review

by

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DISSERTATION

Presented to the Faculty of the Medical School

The University of Texas Southwestern Medical Center

In Partial Fulfilment of the Requirements

For the Degree of

DOCTOR OF MEDICINE WITH DISTINCTION IN GLOBAL HEALTH

The University of Texas Southwestern Medical Center

Dallas, TX

ABSTRACT

Pregnancy and Lupus Nephritis in the Developing World: A Review

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Background: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder often affecting women of reproductive age, whose fertility is typically unaltered by their disease. SLE – and lupus nephritis (LN) in particular – has a significant impact on the course of pregnancy, as well as the outcomes for mother and fetus. Ideally patients have been in remission for a minimum of 6 months prior to conception. LN in pregnancy increases the patient's risk of SLE flare, as well poor outcomes including fetal loss, pre-eclampsia, and maternal death. Good outcomes are achievable for these patients, and have been well documented in the developed world, but less is known about patients in developing nations.

Methods: A literature review was performed of the available literature in regards to lupus nephritis and pregnancy in developing nations. Few studies were available, primarily retrospective case series. A review of these studies was performed, and analyzed for trends in regards to the impact of active disease at conception or lupus nephritis on flare rates, live birth rates, and fetal loss rates. The studies were also examined for any notable geographic trends.

Results: Based on the studies reviewed, there is a trend observed between active disease at conception and a lower rate of live birth. A trend was observed between high rates of LN and higher rates of flare, which many studies reported as being statistically significant. A relationship between high rates of LN and higher rates of fetal loss was also observed. With regards to geographic trends, lower overall live birth rates and higher rates of active disease at conception were noted in Indian studies. Interestingly, lower rates of pre-eclampsia were also noted in the Indian studies. Higher rates of flare were observed in the Asian studies.

Conclusion: Good outcomes are possible for patients with lupus nephritis seeking pregnancy, even in low resource settings. More research is necessary to fully understand the relationships between active disease at conception or lupus nephritis on flare rates, live birth rates, and fetal loss rates.

Table of Contents

Chapter 1: Introduction

In my study of global health, I aim to increase my understanding of how the intersection of culture, health care systems, environment, and social conditions come together to affect medical practice. When I began my global health track, I did not know what specialty I wanted to pursue. I only knew that no matter the specialty, a deeper understanding of the social and environmental contributors to health would enhance my future practice. As is often said by those active in global health, medicine is the same around the world. What is different is how social and environmental factors impact the practice of medicine. The road to my final project is a complex one; one that has involved first hand interaction with several common challenges faced by those who pursue a career in global health.

My interest in global health began prior to entering medical school, when throughout my four years of college, I worked with the organization, Timmy Global Health, as a student leader in my college's chapter. During my four years with Timmy I had the opportunity to meet and learn from numerous people involved in global health work. All of them stressed the role of social and environmental determinants of health, and the importance of a global approach to treating disease. Often a patient's health issues have little to do with medicine and far more to do with their socioeconomic status and living conditions. As part of my work with Timmy I got to personally witness this effect in Guatemala in Timmy's partner clinics with Pop Wuj. In these primarily rural clinics, many of the patients suffered from back pain and osteoarthritis caused by their daily labor. The ideal solution of rest and physical therapy was not a possibility for our patients – if they did not work not only did they not eat, they lost their land, their income, and the inheritance they intended to give to their children. As a solution, Timmy and Pop Wuj worked with the communities on strategies of pain relief, safer living conditions, and scholarships for training in other livelihoods. For me this was an interesting look at how communities and health systems can work together to improve the health of community, particularly in a low resource setting. I also was able to see how vital partnerships, communication, mutual respect and a willingness to learn are to effective global health work.

My experiences in Guatemala made me curious to see how other countries dealt with similar problems, so I embarked on a study abroad program in Copenhagen, Denmark – a country famous for its 'socialist' approach to medicine. Denmark turned out to be an excellent case study in the wide-reaching impact of culture on the practice of medicine and health care. Denmark, although a highly individualistic culture, has a populace that is heavily invested in idea of social contract – where all members of society contribute to a single pot and thus take care of other members of their society. In terms of health care this manifests in many ways. The most obvious being their state-run, universal health care program. Subtler expressions of this general mindset can be seen in the grocery store – foods that are highly processed, high in sugar, saturated fat, or otherwise would be generally considered 'unhealthy' are heavily taxed, leading to lower consumption. Cars are highly taxed for environmental reasons, making bicycling the main form of transportation for Danes, followed by public transportation. Many, many more such examples in Danish life come together and add up to form social and environmental determinants of the Dane's general good health.

Coming to medical school I hoped to delve further into study of how social, cultural, and environmental factors impacted the practice of medicine in other parts of the world. My goal was to be able to find a way to quantify the effects culture have on the treatment and experience of patients. I quickly discovered that was a far more complicated project than I had envisioned, and struggled to find a more digestible project. With the help of my mentors, I was able to devise a project that interested me, even though it did not appear at first glance to be related to my initial interests. My project was a comparison of living donor renal transplants at a single center in Gurgaon, India and in the US.

My experiences in Gurgaon were eye opening. I found that renal transplants were an excellent way to [unwittingly] learn more about the effects a health care system has on the practice of medicine. Transplants are complicated, extensive therapies, that [surprisingly] can be the better treatment option in otherwise low resource settings. It can be far more difficult for a patient with end stage renal disease to receive dialysis three times a week than it is to get a transplant and remain on immunosuppression. In

addition, the stringent medical requirements for becoming an organ donor or an organ recipient mean that the main differences in the treatment are a result of health care systems, rather than due to discrepancies in resources or training. India's self-pay, fee for service system, with its extensive doctor and hospital shopping manifests in a different care model than seen in the US. We found that patient outcomes were quite similar, despite these differences in practice.

However, as can happen in global health, there was a change in the leadership of our partnered department in India, with a request to end the research project. Respecting the desires of the new head of the department, we also agreed not to publish further using the data we had collected there. I found myself starting my final year of medical school needing to find a new project if I wanted to be able to complete my distinction.

At this point in my training, I had determined which specialty I wanted to pursue. Going through our required clerkships, I felt that obstetrics and gynecology was the best fit for my interests. I enjoyed the wide scope of practice, and the massive need for women's health care providers in the global setting was a major appeal. As such, my global health mentor and I strove to develop this current project, as it combines some of my prior experiences with my current interests.

In an effort to gain more firsthand experience with lupus nephritis and pregnancy, I did a rotation in high risk obstetrics at Parkland, as well as a general obstetrics rotation at Bangalore Baptist Hospital – a private missionary hospital located in Bangalore, India. While at Parkland, our team cared for several patients with lupus nephritis. I was able to witness and participate in the complex care required for patients with lupus nephritis. Although my time at Bangalore Baptist did not involve complex pregnancies, I was able to gain some insight into some of the challenges involved in women's health care in a very diverse culture with a wide variety of attitudes regarding women's health.

Chapter 2: Global Burden of LN and its effects in Pregnancy

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that manifests in a wide variety of patterns, thus its alternate name 'the disease of a thousand faces'. Common manifestations include dermatologic rashes, arthritis, nephritis, hemolysis, and thrombosis. Currently the standard of diagnosis is to use the 2012 Systemic Lupus International Collaborating Clinics guidelines, which require patients meet 4 of 17 criteria, including one clinical and one immunologic criterion.[1] Previously the standard of diagnosis was the 1997 American College of Rheumatology guidelines, which required patients meet 4 of 11 criteria.[2] Reports on the prevalence of lupus worldwide vary significantly, in part due to its variable presentation and the changes in diagnostic criteria, but also likely due to differences in economics, geographic location, health care systems, environmental factors, and population genetics.[3] In general, SLE affects women considerably more often than men, particularly women of reproductive age.[3,4] While SLE has many systemic effects, the fertility of these patients is typically unaltered from the general population.[5,6]

Pregnancy in SLE

Historically pregnancy for patients with SLE has been contraindicated. However, in the last several decades, therapy and disease management for patients with SLE has improved to the point that good outcomes are achievable for many of these patients.[7] Such patients are still considered to have high risk pregnancies, ideally managed under the coordinated care of a maternal fetal medicine specialist, a rheumatologist, and other specialists as needed.[5,8]

While the exact results of studies vary, the general trend shows that pregnancy in patients with SLE tend to have higher maternal mortality, effects on disease activity, fewer live births, and more complications during pregnancy, including a higher risk of pre-eclampsia/eclampsia, C-section, prematurity, and post-partum infection.[5,7,9,10] SLE also has unique congenital disorders associated with it, notably neonatal lupus

and congenital heart block.[5,11,12] Other fetal conditions associated with SLE pregnancy include prematurity, intrauterine growth restriction (IUGR), neonatal death (NND), and hematologic or hepatic lab abnormalities.[5,8] In addition, the unique immune tolerance that is typically achieved in pregnancy has been shown to be disordered in patients with SLE.[6,12] This effect appears to be related to the higher risk of SLE flare during pregnancy and the post-partum period, as the hormonal and cytokine changes of pregnancy, which stimulate the T-helper 2 cell (Th2) response and reduce the T-helper 1 (Th1) cell response.[6,8,12-14] These same immunological changes are thought to be related to many of the maternal and fetal complications seen in pregnancy with SLE.[10,12] Further complicating factors in the treatment of SLE with pregnancy are the appropriate use of immunosuppressants – many of which are teratogenic.[4,5,15] This limits the treatment options for patients requiring immunosuppression to maintain quiescence or treat flares who are also seeking pregnancy. Available treatment options are steroids, cyclophosphamide (contraindicated in the first trimester), azathioprine, calcineurin inhibitors, and hydroxychloroquine.[4-6,8] The use of biologics in treating immunosuppression is largely still unstudied in pregnancy.[7] The management of immunosuppression thus becomes particularly difficult not only for SLE patients seeking pregnancy, but even more so for those SLE patients who have received a transplant.[16]

As such, the current recommendations for pregnancy in patients with SLE are for planned conception after at least 6 months of disease quiescence, with appropriate transition to non-teratogenic immunosuppression as needed to maintain quiescence.[5,7] More recent studies have suggested that the necessary quiescence period may only be 4 months rather than 6 months[7], but this is controversial. Quiescent disease is the only well-established predictive factor for reducing risk of flare or other pregnancy complications.[11] The risk factors associated with poor outcomes likely also affect the ideal length of remission prior, but these risk factors still remain to be fully elucidated.[13] Several implicated risk factors for poor outcomes include lupus nephritis, anti-phospholipid syndrome (APS), active disease during the course of pregnancy or prior to conception, arterial hypertension (HTN), and anti-dsDNA

antibodies (particularly anti-Ro/La which are associated with congenital heart block in the fetus).[5,8,11] New onset of disease appears to have the strongest impact on risk of poor outcomes.[11]

Lupus Nephritis and Pregnancy

Lupus nephritis (LN) is a common, more severe manifestation of SLE. While SLE can impact the kidney in multiple ways resulting in renal insufficiency, LN refers specifically to glomerulonephritis caused by immunoglobulin complex deposition.[17] Patients with LN compromise a unique population within patients with SLE, particularly when it comes to pregnancy. Unlike most other manifestations of lupus, LN can have an impact on fertility, as chronic kidney disease (CKD) of any cause can reduce fertility, particularly for women with baseline elevated Cr levels.[8,14] Of the causes of CKD, LN seems to have a greater impact on fertility than others.[14] Immunosuppressants used to treat LN also impact fertility, specifically cyclophosphamide, which has dose dependent effects on fertility that can be more pronounced in older patients.[5,8,11,14] There have been studies showing that a longer period of quiescence will benefit patients with LN seeking pregnancy, extending it to 12-18 months, rather than the more common guideline of 6 months to reduce risks.[8] Complicating factors that impact risks seen with pregnancy in LN include concurrent HTN, proteinuria, APS, anti-Ro/La antibodies, and renal insufficiency. HTN, proteinuria, and renal insufficiency all increase the risk of developing pre-eclampsia/eclampsia, pre-term delivery, placental abruption, IUGR, and pregnancy loss. Concurrent APS is highly associated with miscarriage (SAB), intrauterine fetal demise (IUFD), as well as stroke, thrombosis, and pre-eclampsia/eclampsia.[5,6,8,10,11] APS can also effect renal function, worsening the effects of renal insufficiency on pregnancy.[17] Anti-Ro/La antibodies, besides being associated with congenital heart block and neonatal lupus, can also increase the risk of IUFD and NND.[4,18]

Beyond the effects of LN on pregnancy outcomes, pregnancy also appears to have effects on LN and SLE disease activity and progression.[4,10,18] These effects are less well established than those of SLE on pregnancy outcome.[8] Some studies have noted that pregnancy increases risk of SLE flare, particularly for patients who have LN.[8,11,14,18] The increased risk of SLE flare in pregnancy is believed to be related to the

hormonal and cytokine changes that alter the immune system during pregnancy. In particular, the increased Th2 response and decreased Th1 response – SLE is primarily modulated by Th2 cells.[8,10,11] Patients with LN have a 2-3 fold higher risk compared with SLE patients without LN, although the etiology of this is not well understood.[10] The risk of flare during pregnancy also appears to be higher in patients with active disease or quiescence <6 months.[18] For patients with LN, renal flares are of particular concern, as patients are subsequently at higher risk of renal insufficiency or even progressing into end stage renal disease (ERSD).[14,18] As such, proper planning for patients with LN who desire pregnancy is essential to reduce the risk of poor pregnancy outcome, SLE flare, and disease progression.

In addition to patients with a prior diagnosis of SLE, there is also the subgroup of patients who have new diagnosis of SLE during pregnancy. Patients with a new diagnosis of SLE tend to have more severe disease and worse outcomes.[10] Within this group of patients, LN and renal flares appear to be a highly common manifestation, with subsequently poorer outcomes, both in terms of its effects on pregnancy as well as on SLE activity and disease state.[18]

Chapter 3: Materials and Methods

A review was performed of the available literature with regards to lupus nephritis and pregnancy in developing countries using PubMed and Google Scholar. Studies included spanned the timeline from 1999 to 2016, with older studies not being included given advances in the management of SLE resulting in better outcomes during pregnancy. The studies discussed consist of primarily single center retrospective case reviews, although a prospective case series[19] was also included, due to the overall paucity of publications regarding SLE and pregnancy. Developing countries were defined using the United Nations list of developing nations created by the Department of Economic and Social Affairs.[20]

The amount of available information in the studies varied based on geographic location and available laboratory resources. All included studies utilized the 1997 American College of Rheumatology classification criteria for diagnosis of SLE[2], and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score[21] to diagnose lupus flare. Outcomes and complications are defined as the following terms. Miscarriage or spontaneous abortion (SAB) as fetal loss <24 weeks gestation, IUFD as fetal loss >24 weeks gestation, pre-term as viable delivery <37 weeks gestation, proteinuria as > 0.5 g protein/24h, pre-eclampsia as blood pressure >140/90 mm Hg and proteinuria developed >20 weeks gestation, eclampsia as pre-eclampsia with seizure, IUGR as fetal weight <10 percentile, and APS as presence of anti-phospholipid antibodies and history of thrombosis or multiple early pregnancy loss.

Given the differences in information available in the included studies, the available data is not consistent for all studies. Data that was consistently available across all included papers (see Appendix 1) was analyzed to determine if there was any correlation between active disease and flare, presence of LN and flare, active disease and pregnancy outcome (live birth and fetal loss), and LN and pregnancy outcome (live birth and fetal loss). Additionally, data was divided by geographic region as available, to look for any trends in the variables mentioned above. The geographic regions used were India, Southeast Asia, and Africa (with a subset for Sub-Saharan Africa). No studies were found for South America.

Data sets for each study contained variable population sizes, so percentage of patients with active disease, LN, and flare were calculated to allow a more standardized comparison (Appendix 2). Similarly, the percentages of live births and fetal loss from total pregnancies were calculated (fetal loss did not include medical termination, as the legality and ability to obtain termination differs from nation to nation). Data was charted using Microsoft Excel 2013, and analyzed for any correlation.[19,22-32]

Chapter 4: Results and Discussion

Relation of Active Disease to Flare and Pregnancy Outcomes

Active disease prior to conception and during pregnancy was not found to have any relationship to SLE flare based on the studies analyzed (Figure 1). Data from Ku et al and Mbuli et al was not included in the analysis, as the number of patients with active SLE at conception was unavailable for these studies. While there are studies illustrating this relationship in the literature from developed countries[11], it is possible that this effect may have a genetic component. Other factors that might affect the data for the relationship between disease activity at conception and flare rate are immunosuppressive drug regimen, environmental factors, co-morbidities, organ systems involved in SLE, age at diagnosis, number of prior flares, and available health care or diagnostic resources. More studies are needed to better understand the effects of active disease on flare rate, as the data remains inconclusive.

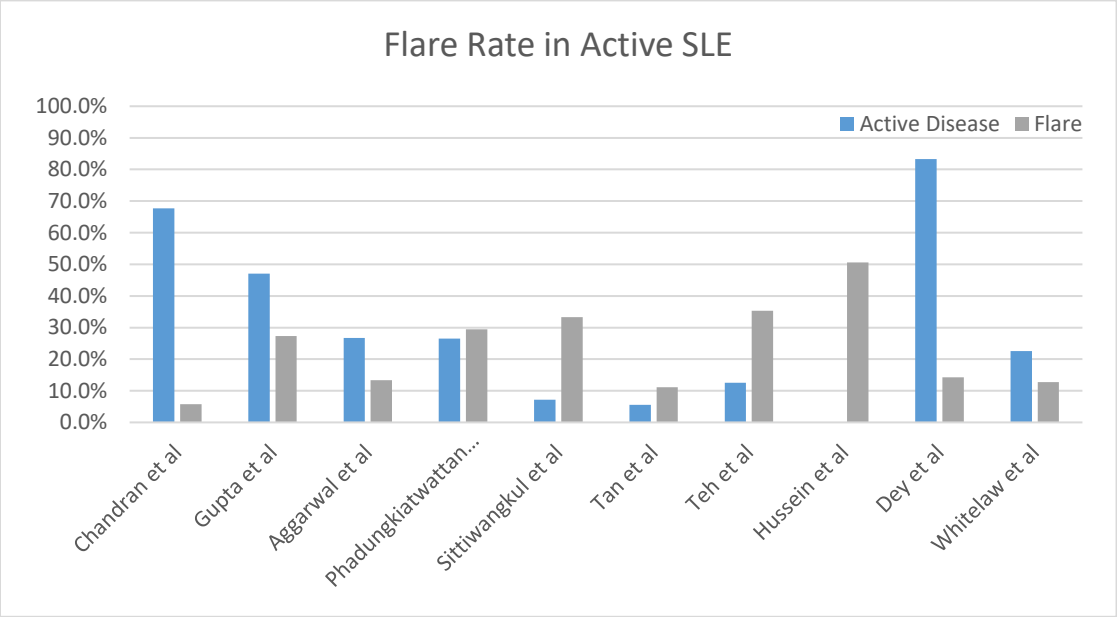

FIGURE 1 – FLARE RATE RELATED TO RATE OF ACTIVE SLE AT CONCEPTION

The relationship of active disease at conception was also examined in comparison to live birth rate (Figure 2) and fetal loss (Figure 3), to determine if any correlation could be found in the included studies.

Again, data from Ku et al and Mbuli et al were not included in the analysis, as active disease at conception was not included in the results of these two studies.

Based on the studies analyzed, there does appear to be a correlation between active disease at conception and live birth rates. For the majority of studies analyzed, the higher rates of active disease at conception, the lower the live birth rate. There was one exception to this general trend – seen in Dey et al. There was a very high active disease at conception rate (83.3% for N=7), and a subsequently lower live birth rate (57.1%), however the birth rate was still higher than seen in Chandran et al and Gupta et al (46.2% and 45.5% respectively) despite lower rates of active disease (67.7% and 47.1% respectively) at conception in both of those studies. This effect could be attributed to the small population studied in Dey et al (N=7) compared to the larger populations studied in Chandran et al (N=52) and Gupta et al (N=33). Other contributing factors could be genetic differences, co-morbidities (e.g. APS), immunosuppressive regimen, age at diagnosis and number of prior flares.

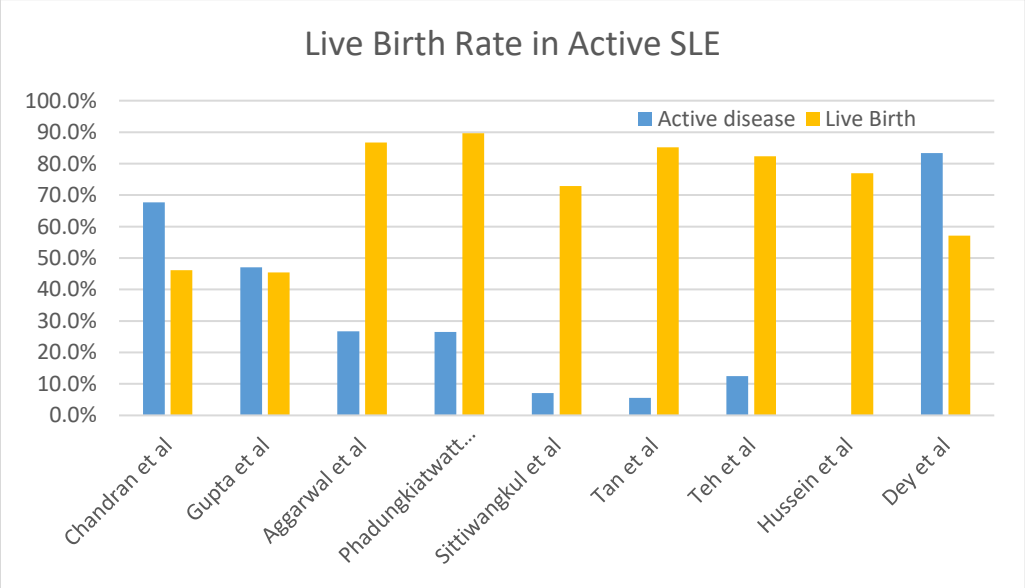

FIGURE 2 – LIVE BIRTH RATE RELATED TO THE RATE OF ACTIVE SLE AT CONCEPTION

When the fetal loss rate was compared to the rate of active SLE at conception, there was not a correlation between the two. Instead it appears there may be a baseline rate of fetal loss seen in patients with SLE that is unrelated to rates of active disease at conception. It should be noted that fetal loss rate includes

only SAB and IUFD, it does not include medical terminations performed for flare or severe disease. The fact that termination data is not included could explain the lack of correlation between active disease and fetal loss, especially since there is a correlation between active disease at conception and live birth. In the case of severe flare threatening the mother's life, or poorly controlled disease, medical termination may be indicated. Since medical termination is not legal in every country, and the data was unknown in several studies, this factor could not be included in the analysis, and its effects are unknown. More studies are needed, ideally including data on terminations for severe disease and flare, to fully understand the relationship between active disease at conception and fetal loss.

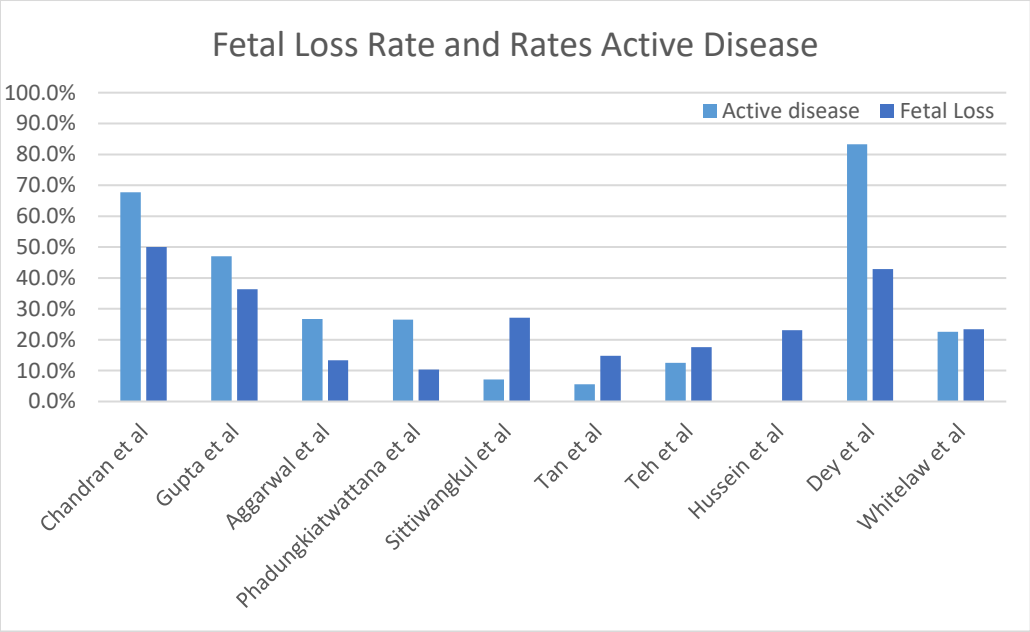

FIGURE 3 – RATE OF FETAL LOSS COMPARED TO THE RATES OF SLE ACTIVITY AT CONCEPTION

The studies themselves reported the following in regards to whether there was a statistically significant relationship between disease activity at conception and risk of flare, live birth rates, or fetal loss (Table 1).

Study	Active Disease and Flare	Active Disease and live Birth	Active Disease and Fetal Loss	LN and flare	LN and fetal loss
Chandran et al	significant	significant	significant	no	no
Mbuli et al	no	no	no	significant	significant
Whitelaw et al	no	no	no	no	no
Sittiwangkul et al	no	no	no	significant	significant
Dey et al	no	no	no	no	no
Ku et al	no	significant	significant	significant	no
Teh et al	--	--	--	--	--
Phadungkiatwattana et al	significant	no	no	significant	no
Hussein et al	no	no	no	significant	no
Aggarwal et al	no	no	no	significant	no
Tan et al	--	--	--	--	--
Gupta et al	no	no	no	no	no

TABLE 1 – SIGNIFICANCE OF RELATIONSHIPS BETWEEN SLE ACTIVITY AND FLARE, LIVE BIRTH, AND FETAL LOSS RATE

A majority of the studies reported that there was no significant relationship between active disease state at conception and flare, live birth or fetal loss. Most studies reported a significant relationship between LN and flare rate (Tan et al and Teh et al did not include any information about the relationships between disease activity or LN and flare or pregnancy outcomes), but did not find a significant relationship between LN and fetal loss. Overall though the data is inconclusive with regards to the relationships between disease activity or LN and flare or pregnancy outcome. More research is needed to understand these relationships.

Relation of Flare Rate to Pregnancy Outcomes

The flare rate was compared to the pregnancy outcomes (live birth and fetal loss) for the studies included. There does not appear to be any correlation between flare rate and the live birth rate (Figure 4). There was not much reported on any correlation between flare rate and live birth rate in the literature, presumably because both are typically viewed as outcomes, flare rate as a maternal outcome and live birth rate as a fetal outcome.

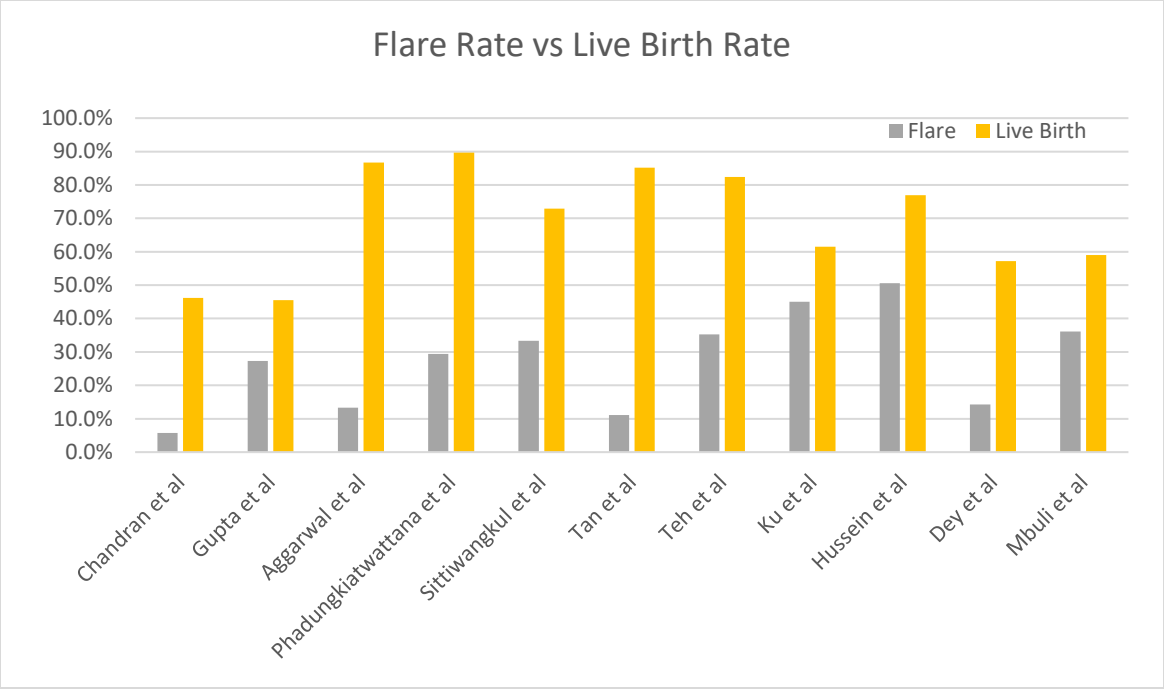

FIGURE 4 – RELATIONSHIP BETWEEN SLE FLARE RATE AND LIVE BIRTH RATE

When the flare rate and rate of fetal loss were compared, no correlation was found (Figure 5). Again, it should be noted that fetal loss rate did not include any terminations to treat severe flare. Overall, flare does not appear to have any effect on the fetal outcome with regards to pregnancy. As with flare rate and live birth, there was not much reported in the literature about a relationship between flare rate and fetal loss, for presumably the same reason.

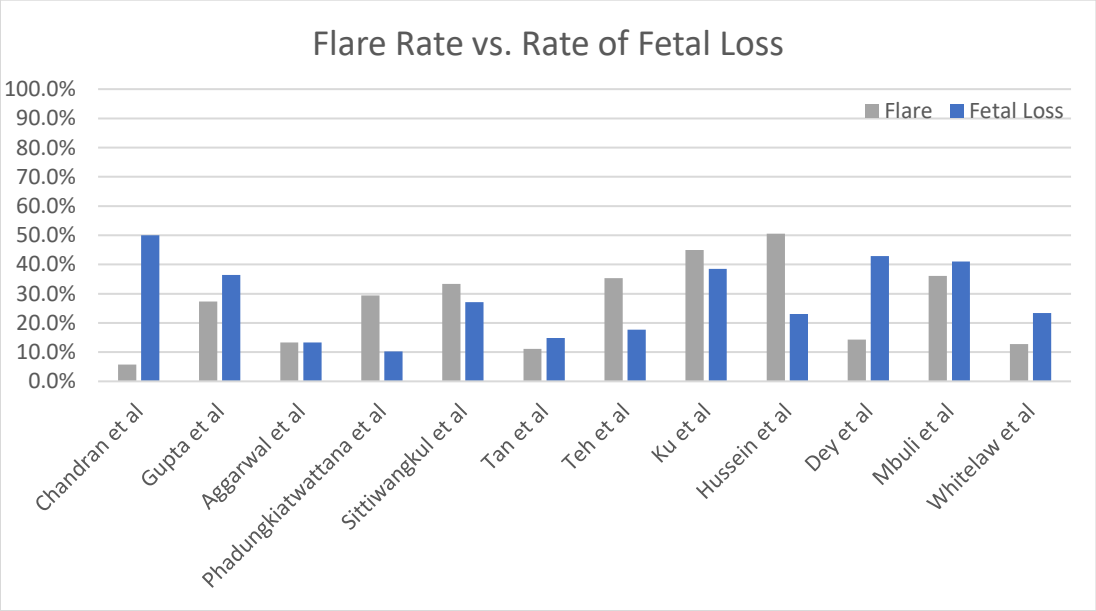

FIGURE 5 – RELATIONSHIP BETWEEN SLE FLARE RATE AND RATE OF FETAL LOSS

Relation of LN to Flare Rate and Pregnancy Outcome

When the overall rate of LN and flare rate were compared (Figure 6) for all the included studies, there appears to be a correlation between the two. Namely, higher rates of LN within the population appear to be correlated with higher rates of SLE flare. Of the studies included, 5 studies did not fit this overall trend: Chandran et al, Gupta et al, Tan et al, and Dey et al, and Whitelaw et al. These 5 studies had a greater than 15% (the standard deviation for overall flare rates across all 12 studies) difference between the rate of LN and the flare rate, which was used as the cutoff for a relationship. In addition, the studies themselves reported if there was a significant relationship between LN and flare rate (Table 1). In most of the studies, a trend of increased flare is seen with increased rates of LN. Tan et al did not report anything in their paper about a correlation between LN and flare rate (Table 1). The other 4 studies reported no significant relationship between the two. Many factors could impact this relationship, most notably genetic or geographic differences, immunosuppressive regimen, the use of aspirin and hydroxychloroquine, age at diagnosis, prior history of flares, disease state at conception, severity of disease, comorbidities, or degree of renal insufficiency. The use of aspirin and hydroxychloroquine during pregnancy are of particular interest as both have been shown to improve maternal and fetal outcomes. Most of the studies did not report on the number of patients using these therapies, so it is possible that the studies with lowered flare rates had widespread use of hydroxychloroquine (which reduces risk of flare[10]).

With regards to the impact of genetics on flare rate, Mbuli et al found that their patients of black African ancestry had a significantly higher flare rate compared to patients of mixed ancestry. They did not report on the proportion of black African patients with LN and subsequent flare rates. Other studies have reported on genetic differences between populations in Asia having greater severity of SLE, as well as higher proportions of LN.[33] As such, though there appears to be an overarching relationship between LN and the risk of flare, there are likely genetic factors that impact and alter this relationship. More studies

are necessary to fully understand the trend, and hopefully to elucidate the impact of geographic and genetic differences in LN and subsequently the relationship between LN and flare rate during pregnancy.

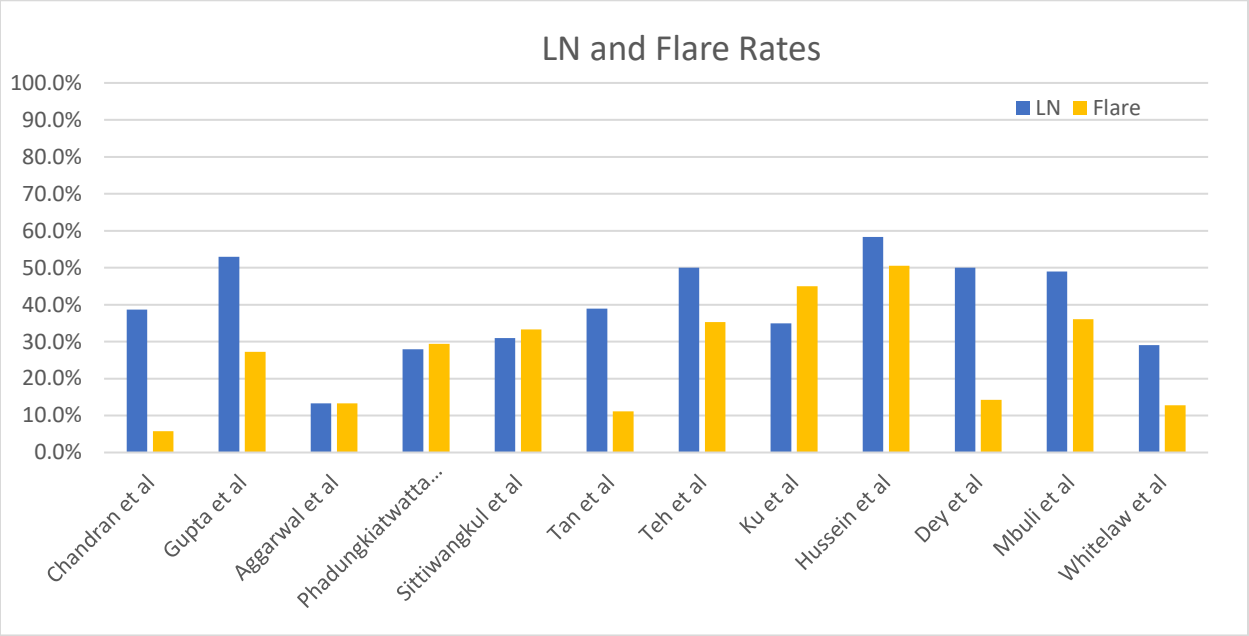

FIGURE 6 – RELATIONSHIP OF LN AND SLE FLARE RATE

When the rates of LN were compared to fetal loss rates (Figure 7), there appears to be a correlation between the two. Increased rates of fetal loss were seen within populations with higher rates of LN. The exceptions seen were in Phandungkiatwattana et al, Tan et al, Teh et al, and Hussein et al, where high rates of LN in these 4 studies were not necessarily correlated with high rates of fetal loss. Still of the 12 studies, the majority followed the general trend of higher rates of LN being correlated with higher rates of fetal loss. It should be noted again that fetal loss did not include any medical termination for severe disease or treatment of flare. As LN appears to be correlated to flare, the lack of termination data could significantly impact the understanding of any relationship between LN and fetal loss. Interestingly, while many studies noted a correlation between LN and increased rates of fetal loss, only two reported that this was a statistically significant – Mbuli et al and Sittiwangkul et al. Multiple reasons exist for this, including small populations in the studies (ranging from N=7 to N=109), genetic differences between populations, the use of aspirin and hydroxychloroquine during pregnancy, other immunosuppressive

therapy, disease activity at conception, etc. The use of aspirin and hydroxychloroquine during pregnancy are of particular interest as both have been shown to improve maternal and fetal outcomes. Most of the studies did not report on the number of patients using these therapies, it is possible that the studies with lower rates of fetal loss in LN may have had high usage of both drugs. Aspirin reduces the risk of pre-eclampsia, which has subsequent significant effects on fetal outcomes, including fetal loss. Hydroxychloroquine also impacts the risk of pre-eclampsia, as well as complete heart block, both of which impact the rate of fetal loss. Disease activity and degree of renal insufficiency are also notable variables that could have a significant effect on fetal outcomes, particularly renal insufficiency. Further studies including these other variables are needed to understand the relationship between LN and fetal loss.

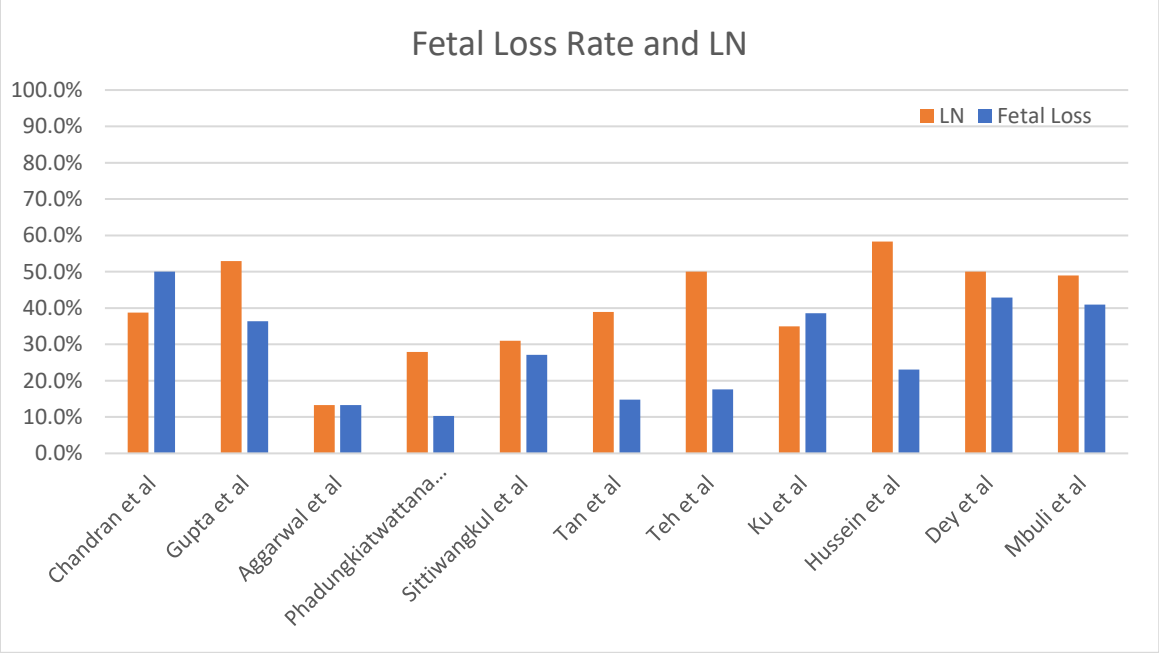

FIGURE 7 – RELATIONSHIP OF LN TO RATE OF FETAL LOSS

When the rate of LN and was compared to the rate of fetal loss (Figure 8), a correlation was observed. Higher rates of LN were correlated with lower live birth rates. This effect was less pronounced in Hussein et al, Dey et al, and Mbuli et al (all studies from Africa), but still present. Given that the effect was less pronounced in African studies, a genetic component to this effect is more likely. This fits with the

observation that LN has a correlation with fetal loss. Whether or not these relationships are significant is unknown, as this was not reported in the studies included in this review. Further data is needed to understand the relationship between LN and pregnancy outcomes.

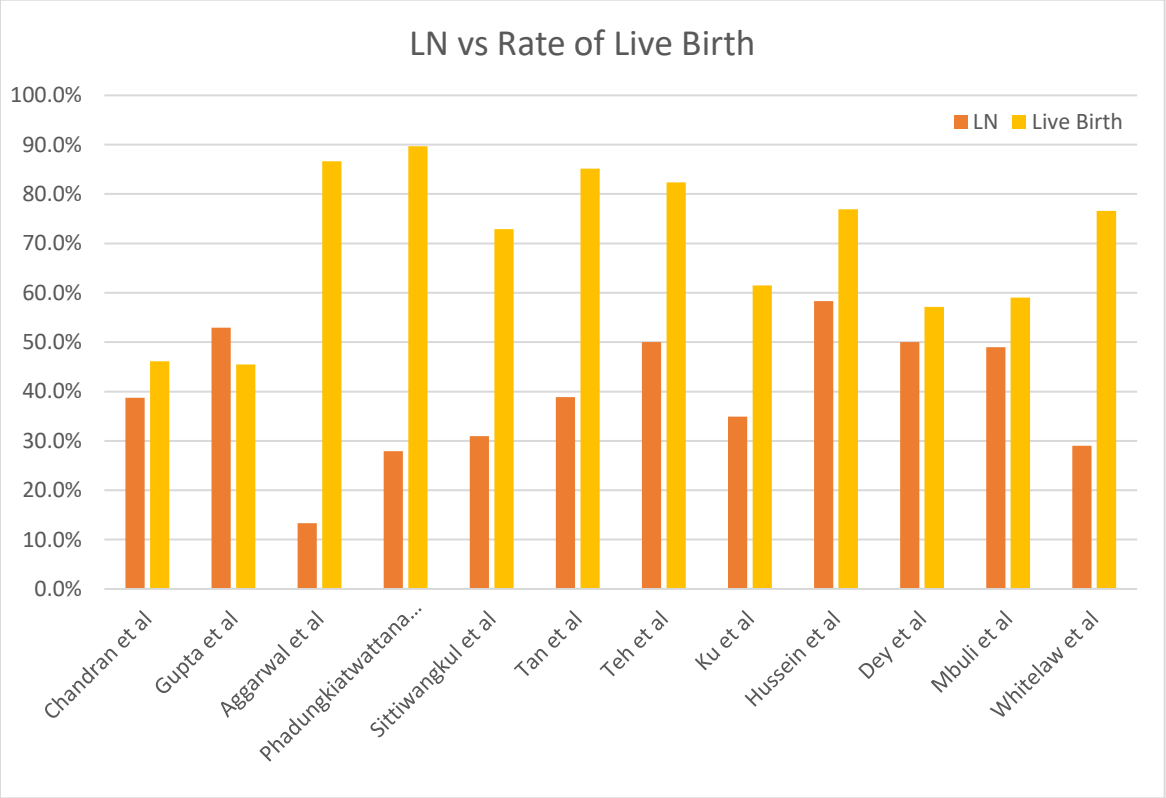

FIGURE 8 – RELATIONSHIP OF LN TO LIVE BIRTH RATES

Geographic Trends

In addition to the relationships between active disease at conception, LN, flare, live birth rate, and fetal loss, the data was examined for any geographic trends. Within the geographic regions, the following general trends were noticed. It appears that live birth rate was considerably lower in India compared to other regions (Table 2), and the rate of active disease at conception was relatively higher (Table 3). Dey et al is an exception to this trend. The other noticeable trend regarding the Indian population compared to the rest of the world is that the rate of pre-eclampsia was relatively lower (Table 4).

The lower birth rate in India could be attributed to numerous factors, including access to prenatal and obstetric care, access to rheumatologic care, higher rates of active disease at conception, genetic differences, cultural or financial barriers to accessing care, and availability and access of immunosuppressive medication. While Aggarwal et al had a live birth rate more comparable to the other studies, their study included a significantly smaller population (N=15) when compared to Chandran et al (N=55) and Gupta et al (N=33). Thus, numerous factors could explain the overall lower birth rates seen in the Indian population compared to the other studies. Further research controlling for these variables would be needed to determine if there is a genetic component to these outcomes.

Region	**Study**	**Live Birth**
India	Chandran et al	46.2%
	Gupta et al	45.5%
	Aggarwal et al	86.7%
Southeast Asia	Phadungkiatwattana et al	89.7%
	Sittiwangkul et al	72.9%
	Tan et al	85.2%
	Teh et al	82.4%
China	Ku et al	61.5%
Africa	Hussein et al	76.9%
	Dey et al	57.1%
	Mbuli et al	59.0%
	Whitelaw et al	76.6%

TABLE 2 – LIVE BIRTH RATES BY GEOGRAPHIC REGION

The higher percentage of active disease at conception in the Indian studies could be explained by cultural differences between geographic regions, particularly since India is a single country (no other studies were found for the subcontinent), while the other regions encompass multiple countries (with the exception of Ku et al for China). Genetic components may also play a role, as could the health care systems and access to care. Active disease at conception would [in theory] be related to the availability and accessibility of immunosuppression and rheumatologic care, cultural norms regarding pregnancy and fertility, as well as patients' access to family planning services and contraception. With women's healthcare, particularly in regards to family planning, there is a strong intersection with cultural attitudes and norms, all of which

would impact the ability of patients to plan for pregnancy during disease remission – assuming that their disease was diagnosed prior to presentation for prenatal care. As such, numerous factors could affect the higher rates of active disease at conception seen in the Indian population. More research controlling for the many variables is needed to determine which factors affect the higher rates of active disease at conception in the Indian population.

Region	Study	Active disease
India	Chandran et al	67.7%
	Gupta et al	47.1%
	Aggarwal et al	26.7%
Southeast Asia	Phadungkiatwattana et al	26.5%
	Sittiwangkul et al	7.1%
	Tan et al	5.6%
	Teh et al	12.5%
China	Ku et al	--
Africa	Hussein et al	0.0%
	Dey et al	83.3%
	Mbuli et al	--
	Whitelaw et al	22.6%

TABLE 3 – RATES OF ACTIVE SLE BY GEOGRAPHIC REGION

The lower rates of pre-eclampsia seen within the Indian population are particularly interesting, given the lower overall live birth rate, as well as the higher rates of active disease at conception. Per the literature, higher rates of active disease at conception are associated with a greater risk of developing pre-eclampsia.[8,10,11] Pre-eclampsia also increases risk of fetal loss.[10] Given that the Indian studies have higher rates of active disease at conception and lower rates of live birth, a higher percentage of patients with pre-eclampsia would be expected. It is possible that there is a genetic component to explain this trend. The underlying etiology to pre-eclampsia is poorly understood[10], thus more research is needed to elucidate the pathophysiology and mechanisms of pre-eclampsia, as well as to establish if there is a statistically significant geographic difference in pre-eclampsia rates for SLE patients.

Region	Study	% of Pre-eclampsia
Africa	Hussein et al	13%
	Mbuli et al	20%
	Whitelaw et al	26%
	Dey et al	--
China	Ku et al	--
Southeast Asia	Tan et al	22%
	Teh et al	24%
	Phadungkiatwattana et al	21%
	Sittiwangkul et al	0%
India	Aggarwal et al	13%
	Chandran et al	8%
	Gupta et al	3%

TABLE 4 – RATES OF PRE-ECLAMPSIA BY GEOGRAPHIC REGION

The other noticeable trend along geographic lines was that the SLE flare rate appeared to be higher in Asia (both Southeast Asia and China) compared to India and Africa (Table 5), although Hussein et al is an exception. There is a possible genetic component to this effect, as previous studies have noted more severe disease in Asian patients, as well as higher rates of LN[33], which could relate to higher flare rates. Other factors that could be related to the higher flare rates seen in the Asian studies are the use of hydroxychloroquine during pregnancy, the disease severity, immunosuppressive regimen, prior history of flares, and access to rheumatologic care, none of which were reported in the studies. More research is needed to determine if there is a statistically significant difference in flare rates across geographic regions. No other trends were noted.

Region	Study	% Flare
India	Aggarwal et al	13.3%
	Chandran et al	5.8%
	Gupta et al	27.3%
Southeast Asia	Tan et al	11.1%
	Teh et al	35.3%
	Phadungkiatwattana et al	29.4%
	Sittiwangkul et al	33.3%
Asia	Ku et al	45.0%
Africa	Dey et al	14.3%
	Hussein et al	50.5%
	Mbuli et al	36.1%
	Whitelaw et al	12.8%

TABLE 5 – RATE OF SLE FLARE BY GEOGRAPHIC REGION

Chapter 5: Conclusion

Overall, there is a general paucity of data in regards to lupus nephritis and pregnancy in developing nations. There are numerous reasons for this paucity of research, including fewer resources, reduced access to care, decreased funding for research, financial barriers to care, provider shortage, underdiagnosis, and cultural differences. These studies do demonstrate that good outcomes are possible with appropriate care and coordination of providers, even in low resource settings. This is of significant benefit to patients. Hopefully, with time, more research can be conducted in developing nations to optimize care and outcomes for these patients.

Chapter 6: Impact of Global Health

My experiences in India, as well as those prior to medical school, have shaped my path in medicine and my future career. Witnessing and participating in the delivery of medicine within different health care systems has given me a drive to approach my patients with cultural humility and adaptability to their circumstances, whatever it may be. Health is not the result of only individual choices and genetics, but of a patient's social and environmental situation too.

My summer in India helped me improve my medical Hindi significantly, which made me more confident and comfortable when communicating with patients. It was an excellent exercise in the challenges that come with practicing global health as well as doing global health research. All global health work is reliant on partnerships – which require continuous maintenance. Things are prone to change in this dynamic environment, so flexibility, communication, and humility are key. The incredible opportunities I had in Delhi helped me uncover my fascination with surgery, altering my career path – I likely would never have considered a surgical specialty otherwise.

Rotating in Bangalore was also an interesting challenge, albeit in a different form than my summer in Delhi. It was a hand-on experience in the difficulties faced when one cannot speak directly with one's patients, and the communication and cultural gaps that arise because of this language barrier. In addition, my time in Bangalore was a surprise exercise in ethics, one in which the importance of partnerships and clarity of communication became key. Mutual respect, the ability to empathize, and cultural sensitivity are all incredibly important to navigating these situations. I am grateful for the lessons I have learned through these experiences.

Acknowledgements

I am incredibly grateful to the UT Southwestern Office of Global Health for its support in my endeavors. In particular, I would like to thank Dr. Nilum Rajora, my global health mentor for all her expertise, guidance, and encouragement, as well as Dr. Rasha Babakir for her help and support. I would also like to thank Dr. Fiemu Nwariaku and Dr. Ramesh Saxena for their help in my research. I am indebted to Dr. Sushila Kataria in the Department of Internal Medicine at Medanta the Medicity. Above all, I am grateful to my family and friends for being there with me every step of the way.

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