Afr. J. Med. Med. Sci. (2019) 48, 207-215

Pregnancy outcome in Nigerians with systemic lupus erythematosus: case series and literature review

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Abstract

Background: Pregnancy has been reported to constitute a high risk in lupus patients. However, with the emergence of potent disease modifying antirheumatic drugs (DMARDs), pregnancy outcome has become more favorable in this group of patients. There is thus a need to report the Nigerian experience so as to add to the body of knowledge. There has been no report on pregnancy outcome among Nigerian lupus patients.

Objective: To describe the maternal and fetal outcomes among pregnant female systemic lupus erythematosus [SLE] patients attending Lagos State University Teaching Hospital (LASUTH), Lagos, Nigeria.

Methods: A retrospective case series of pregnancy outcome in systemic lupus erythematosus (SLE) patients between the years 2011 to 2015. Data about demography, symptoms during pregnancy, blood pressure, investigations, treatment, route of delivery and pregnancy outcome were collected from patients' case record files. Data was analyzed using descriptive statistics.

Results: The outcome of 15 pregnancies in 12 lupus patients were reported. The outcome of the pregnancies were eight live births from elective cesarean section (CS), three live births via spontaneous vaginal delivery, a stillborn following vaginal delivery, an intrauterine fetal death from intrauterine growth restriction, a spontaneous abortion, and a maternal mortality. Mean birth weight was 2.8kg (SD+/-0.5). Active disease and hypertension were observed in 2 pregnancies each, while lupus nephritis was present in 5 pregnancies. Only one of the patients was hospitalized before delivery due to a flare of lupus nephritis. Antiphospholipid syndrome occurred in 1 of the pregnancies. There was no occurrence of a flare post-delivery, neither was there any case of neonatal lupus syndrome nor congenital heart block.

Conclusion: Pregnancy in patients with SLE is still associated with a risk of poor outcome in Nigeria, but with the appropriate timing and management, it is possible to have a good outcome. Cooperation with an Obstetrician experienced in high risk pregnancies is also essential. A high index of suspicion is recommended in patients with recurrent spontaneous abortions and/or unexplained deterioration in renal function, even in the absence of typical skin lesions of lupus and/or arthritis.

Finally, since the management of SLE in pregnancy is cost intensive, the development of favorable health insurance policies by the government to enable the common man to benefit from standard health care will ease the burden of cost of management on patients.

Keywords: *Systemic lupus erythematosus, pregnancy, maternal outcome and fetal outcome.*

Abstrait

Contexte : La grossesse a été signalé à constituer un risque élevé chez les patientes atteintes de lupus. Cependant, avec l'émergence de médicaments antirhumatismaux (DMARD) puissants, l'issue de la grossesse est devenue plus favorable chez ce groupe de patientes. Il est donc nécessaire de rendre compte de l'expérience Nigériane afin de compléter le corpus de connaissances. Aucun résultat de grossesse n'a été signalé chez les patientes atteintes de lupus Nigérian.

Objectif : Pour décrire les résultats maternels et fœtaux chez les patientes enceintes atteintes de lupus érythémateux disséminé (LES) à l'Hôpital d'Enseignement Universitaire de l'État de Lagos (LASUTH) à Lagos, Nigéria.

Méthodes : Une série de cas rétrospectifs sur l'issue de la grossesse chez les patientes atteintes de lupus érythémateux systémique (LES) entre 2011 et 2015. Les données sur la démographie, les symptômes pendant la grossesse, la pression artérielle, les investigations, le traitement, la voie d'accouchement et l'issue de la grossesse ont été recueillies des dossiers des patientes. Les données ont été analysées à l'aide de statistiques descriptives.

Résultats : Les résultats de 15 grossesses chez 12 patientes atteintes de lupus ont été rapportés. Les résultats de la grossesse ont été huit naissances vivantes issues d'une césarienne élective (CS), trois naissances vivantes via un accouchement vaginal

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spontané, un mort-né après un accouchement vaginal, une mort fœtale intra-utérine due à une restriction de croissance intra-utérine, un avortement spontané et une mortalité maternelle. Le poids moyen à la naissance était de 2,8 kg (ET +/- 0,5). Une maladie active et une hypertension ont été observées dans 2 grossesses chacune, tandis que la néphrite lupique était présente dans 5 grossesses. Un seul des patients a été hospitalisé avant l'accouchement en raison d'une poussée de néphrite lupique. Le syndrome des anti-phospholipides est apparu dans une des grossesses. Aucune poussée n'a été constatée après l'accouchement, ni aucun syndrome de lupus néonatal ni aucun bloc cardiaque congénital.

Conclusion : La grossesse chez les patientes présentant un LES est toujours associée à un risque de résultats médiocres au Nigéria, mais avec un temps et une gestion appropriée, il est possible d'obtenir de bons résultats. La coopération avec un obstétricien expérimenté dans les grossesses à haut risque est également essentielle. Un indice de suspicion élevé est recommandé chez les patientes présentant des avortements spontanés récurrents et / ou une détérioration inexpliquée de la fonction rénale, même en l'absence de lésions cutanées typiques du lupus et / ou de l'arthrite.

Enfin, comme la gestion de LES pendant la grossesse est coûteuse, le développement de politiques d'assurance maladie favorables par le gouvernement permettant à l'homme du commun de bénéficier de soins de santé standard allégera le fardeau des coûts de la gestion pour les patientes.

Mots clés: *Lupus érythémateux disséminé , grossesse, évolution maternelle et évolution fœtale*

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease which predominantly affects females of child bearing age [1]. The disease has been uncommonly reported in African blacks unlike among African –Americans [1]. However, recent encounters with new cases show that it may not be rare. The frequency as reported by Adelowo *et al* in Nigeria was 5.28%of 1250 rheumatologic cases seen in a private rheumatology clinic over a period of 6 years [1]. Its actiology is unknown. However, environmental factors, hormones, genetic composition and immunological aberrations have been implicated in its pathogenesis [2].

Pregnancy outcome in SLE refers to both maternal and fetal results of pregnancy in lupus patients. The frequency of pregnancy in lupus patients is similar to that of females without the condition [3], meaning that SLE has no negative effect on fertility.

The pathogenesis of complications in lupus pregnancies include clinical or subclinical inflammation, hormonal dysfunction (increased estrogen and prolactin), immune alterations (a shift to T helper 2 cell cytokines production) and the presence of autoantibodies [4]. There is thus impaired early placental development leading to poor vascularization, which then results in placental ischemia and endothelial damage. Known complications of pregnancy in SLE are preeclampsia, eclampsia, intrauterine growth restriction, small for gestational weight babies, premature delivery and increased pregnancy loss [5]. Factors that lead to poor pregnancy outcomes are lupus nephritis [6], secondary antiphospholipid syndrome [5,6], hospitalization or a lupus flare inpregnancy [5,7], thrombocytopenia [8,9] and high blood pressure [7]. It is thus important for SLE patients to delay pregnancy for at least 6 months after disease stability [10,11]. SLE does not affect fertility [12], neither is pregnancy contraindicated in lupus but there could be adverse fetal and maternal outcome if disease is not properly managed [13].

Maternal and fetal morbidities and mortalities have been documented among pregnant SLE patients in Western World [14]. However, there is paucity of reports of pregnancy outcomes among pregnant SLE patients in Africa. There is a considerable number of SLE patients in Nigeria [1,15] and we do not know the pregnancy outcome among our patients. Hence, we intend to study the pregnancy outcome in SLE patients in Lagos State University Teaching Hospital (LASUTH), Lagos, Nigeria.

Materials and methods.

This is a five year retrospective case series of pregnancy outcome in SLE patients in LASUTH between 2011and 2015. Patients were diagnosed as having SLE if they fulfilled at least 4 out of the 11 1982 revised ACR criteria [16]. All subjects had antenatal care, delivery and postnatal care in the obstetric department of LASUTH. They were collectively managed by the rheumatologist and the obstetrician.

Data about demography, symptoms during pregnancy, blood pressure, investigations, treatment, route of delivery, and pregnancy outcome were gathered from patients' case record files.

They had regular clinic follow ups, at least once monthly in most cases and serial monitoring of their full blood count, erythrocyte sedimentation rate [ESR], serum creatinine, urinalysis and microscopy, urine protein creatinine ratio and serology. Serial

obstetric ultrasound scans and doppler scan of the placental circulatory bed were also done if indicated and affordable. Hypertension was defined as blood pressure ≥140/90mmHg [17], preeclampsia as a new onset blood pressure of ≥140/90mmHg with proteinuria of >300mg/24hours after the 20th week of gestation [18], lupus nephritis as proteinuria >500mg/+++ or elevated serum creatinine or presence of casts in urine or decreased eGFR or biopsy proven renal disease [19].

A flare was defined as the occurrence of new symptoms and sign and/or laboratory results which necessitate an increase in the dose of therapy or a change or addition of an immunosuppressant or necessitating admission [20].

Intrauterine fetal death (IUFD) was defined as the death of a fetus in the uterus after the age of viability (28weeks) [21,22], intrauterine growth retardation (IUGR) as a fetal weight below the 10th percentile for a gestational age as determined by an ultrasound scan, preterm birth as birth before 37 completed weeks and low birth weight as that which is below 2.5kg [21].

Antiphospholipid syndrome was defined by Sapporo criteria as presence of at least one clinical and one laboratory (serologic) criteria. The serologic criteria is elevation in titer of any of the antiphospholipid antibodies done 12 weeks apart and the clinical criteria is any pregnancy morbidity or a history of thrombosis [23].

Results

A total of 15 pregnancies in 12 SLE patients were reviewed. One of the patients was pregnant on 3 occasions and another twice.

Demography and clinical features

The mean age of the subjects was 31.8years (SD=+/-2.04). Polyarthralgia (n-2), skin rash (n-1) and facial swelling (n-1) were the symptoms recorded during pregnancy. Blood pressure ranged between 110/60mmHg and 180/120mmHg. Five pregnancies were documented in patients with an active disease while the remaining had a quiescent disease for at least 6 months before conception.

Laboratory Investigations.

Erythrocyte sedimentation rate (ESR) was done during all pregnancies and was elevated in 14 pregnancies (mean=66.4±35.4). The least hemoglobin concentration was 8g/dl. Platelet count was normal in all patients. Elevated serum creatinine and reduced estimated glomerular filtration rate [eGFR] were documented in 3 pregnancies. None of the patients had casts in their urine but proteinuria was recorded in 11 pregnancies, ranging from trace to +++. Urine albumin creatinine ratio [UACR] was done in 4 of pregnancies and was elevated in half of them.

Results of serology show anti-nuclear antibody [ANA] had highest titer being 1: 640, while C_3 was low in both patients in whom it was assayed for. The table below shows the results of serology done in all pregnancies.

One patient had renal biopsy done before pregnancy which revealed class V lupus nephritis. None of the patients with positive anti Ro/SSA or anti La/SSB had fetal electrocardiogram and fetal echocardiography.

The disease was stable in 10 patients for at least 6months prior to pregnancy. Five patients had lupus nephritis, of whom the disease was quiescent in two. Antiphospholipid syndrome was present in 1 patient while2 patients had poorly controlled hypertension.

Treatment offered.

All the patients were placed on either prednisolone tablets or methyl prednisolone tablets and hydroxychloroquine before and during pregnancy. The maximum dose of prednisolone was 10mg, however majority (8 patients) had methyl prednisolone tablets instead. Intravenous methyl prednisolone was administered to one patient at an estimated gestational age of 20 weeks, when she had a flare. This was done on an outpatient basis. In-patient care was necessitated for a patient who had a flare of lupus nephritis in pregnancy. Four patients who had been on azathioprine before they got pregnant also continued throughout pregnancy. All patients were placed on low dose aspirin until 32weeks gestational age. One patient, who fulfilled the Sapporo criteria for antiphospholipid syndrome had daily subcutaneous low molecular weight heparin in addition to aspirin till an estimated gestational age of 32 weeks. Fetal electrocardiograph and echocardiography could not be done in these patients due to financial constraint. Only two patients were placed on blood pressure lowering drugs.

Pregnancy outcome

There were 10 term deliveries. One case of intrauterine growth restriction which later resulted in intrauterine fetal death was recorded while another pregnancy resulted in preterm delivery of a low birth weight neonate. Spontaneous abortion and still birth occurred in 1 pregnancy each.

Table 1: Demography and obstetric history.

Patient	Age (yrs)	Parity	Past medical History	Time of Diagnosis	Blood Pressure (mm/Hg)	Pregnancy Outcome	Outcome of Labour	Outcome of Care
1.	30	$G_1P_0^{+0}$non alive	Inactive disease for More than 6 months	3 years before pregnancy	110/60	Term delivery	Cesarean section	Mother alive and healthy
2a.	31	$G_1P_0^{+0}$non alive	Active disease	1 year before pregnancy	110/80	Term delivery	Cesarean Section	Mother alive
2b.	32	$G_2P_1^{+0}$1 alive	Active disease		130/90	Pregnancy loss at 6 weeks		Mother alive
2c.	33	$G_3P_1^{+1}$1 alive	Inactive disease for 6 months		120/90	Term delivery	Cesarean section	Mother alive
3	32	$G_1P_0^{+0}$non alive	Inactive disease for more than 6 months	10 years before pregnancy	130/84	Term delivery	Cesarean section	Mother alive
4a	31	$G_1P_0^{+0}$	Active disease	During pregnancy (10 weeks)	180/120	IUGR then IUFD at 32 weeks	Spontaneous vaginal delivery	Mother alive
4b	33	$G_2P_1^{+0}$non alive	Active disease		140/94	Pretem delivery at 28 weeks	Spontaneous vaginal delivery	Mother alive
5	32	$G_2P_1^{+0}$1 alive	Inactive disease for more than 6 months	1year before pregnancy	120/80	Term delivery	Cesarean section	Mother alive
6	37	$G_8P_2^{+5}$2 alive	5 pregnancy losses, each before 10 weeks within 2 years	1year before pregnancy	110/70	Term delivery	Cesarean section	Mother alive
7	31	$G_1P_0^{+0}$non alive	Inactive disease for more than 6 months	1year and 6 months before pregnancy	110/70	Term delivery	Spontaneous vaginal delivery	Mother alive
8	30	$G_3P_{02}^{+0}$2 alive	Inactive disease for more than 6 months	4 years before the index pregnancy	120/80	Term delivery	Spontaneous vaginal delivery	Post- delivery flare

9	34	$G_1P_0^{+0}$non alive	Inactive disease for more than 6 months	2 years before pregnancy	120/80	Term delivery	Cesarean section	Mother alive
10	31	$G_1P_0^{+0}$non alive	Inactive disease for more than 6 months	1year and 4 months pregnancy	110/70	Term delivery	Cesarean section	Mother alive.
11	29	$G_2P_1^{+0}$1 alive	Inactive disease for more than 6 months	6years before pregnancy	140/90	Still birth at term	Spontaneous vaginal delivery	Mother alive
12	32	$G_2P_1^{+1}$ non alive	Past pregnancy loss before 10 weeks	During pregnancy	150/100	Maternal death at 28 weeks		Maternal death

Table 1.1: Laboratory parameters

Serial No.	Hb (11.5-6.5g/dl)	Plt (150-450*10⁹/1)	ESR(0-20mm/hr)	Urea (2.1-7.1mmol/1)	Creatinine (53-97µmol/l)	UACR (<0.5/g Cr)	Hematuria	Proteinuri	eGFR (ml/min)
1.	10.0	267	30	5.36	81.8	NA	No	No	NA
2a	10.4	189	130	1.1	50	NA	No	+	>89
2b.	10	NA	NA	NA	NA	NA	NA	NA	NA
2c.	10.7	176	66	1.2	48	NA	No	Trace	>89
3	13.9	292	34	3.2	104	1.66	No	+++	62
4a	9.0	288	90	3.5	101	NA	Yes	++	63
4b	9.0	312	78	3.1	97	1.8	Yes	++	65
5	11.3	253	66	4.5	72	NA	Yes	+	NA
6	10.6	222	55	NA	81.8	NA	Yes	Trace	NA
7	10.3	343	110	8.6	90.9	NA	No	Trace	NA
8	9.3	157	101	2.0	51	0.4	No	No	>89
9.	11.8	309	8	2.4	44	NA	No	No	>89
10	10.3	200	29	NA	40	0.2	No	Trace	>89
11	10.0	232	34	NA	NA	NA	Yes	Trace	>89
12	8.0	200	78	9	178	NA	No	+++	NA

Key: NA – Not available

Table 2: Results of serology

Serial. No	C_3	ANA	Anti dsDNA	Anti-Smith	AntiR_0 SSA	AntiL_a SSB	Lupus anti-coagulation	Anti-cardio-lipin	Anti β_2GP_1
1.	NA	1:640	Negative	NA	Positive	Positive	NA	Negative	Negative
2.	NA	1:640	Positive	NA	Positive	Negative	NA	Negative	Negative
3	NA	1:320	Positive	NA	-VE	Negative	Negative	Positive	Positive
4	NA	1:640	Positive	NA	NA	NA	NA	Negative	Negative
5	NA	1:160	Negative	NA	NA	NA	NA	NA	NA
6	Low	1:80	Negative	NA	Negative	Positive	Negative	Positive	Positive
7	NA	1:320	Negative	NA	Negative	Negative	Negative	Negative	Negative
8	Low	1:640	Negative	NA	Negative	Negative	Negative	Negative	Negative
9	NA	1:640	NA	NA	NA	NA	NA	NA	NA
10	NA	1:320	NA	NA	NA	NA	NA	NA	NA
11	NA	Negative	Negative	Positive	Positive	Positive	NA	NA	NA
12	NA	1:640	Positive	NA	NA	NA	NA	NA	NA

Key: NA – Not available

Maternal outcome

There was no flare post-delivery, while there was no hospitalization during puerperium. Maternal mortality occurred during one pregnancy at an estimated gestational age of 28 weeks.

Table 1.3 shows fetal and maternal outcomes in our pregnant lupus patients.

Table 1.3: Fetal and Maternal Outcome.

Outcome	Frequency
Live births	11
Abortion	1
Maternal mortality	1
Stillborn	1
IUFD	1
Hospitalization during pregnancy	1

Discussion

Our series, the first in Nigeria and second in West Africa, showed that adverse fetal and maternal outcomes are common in pregnant lupus patients. The observed maternal outcomes were one case of maternal death from active lupus nephritis in pregnancy and a case of secondary anti-phospholipid syndrome. Whilst we documented high frequency of live births, we observed a stillborn following vagina delivery; an intrauterine fetal death from preterm delivery; fetal death from maternal mortality; and a spontaneous abortion as adverse fetal outcomes.

Although, the frequency of fetal loss in the first South African series was 3 fetal deaths (42.9%) in 7 pregnancies in Korle bu Teaching Hospital, Ghana [24] , this report contrasts 4 fetal losses (26.6%) in 15 pregnancies documented in this series. Moreover, a controlled study by Georgiou *et al* in Greece found fetal loss of 22% in 59 pregnancies among 47 lupus patients [25] while fetal loss of 30.7%(n-17) was recorded in 52 pregnancies among Indian lupus patients [26]. In a prospective study in America, Clouse also reported a threefold increase in fetal loss in pregnant lupus patients [14].The differences in the frequency of fetal loss in various studies may be attributable to varying sample size and study design adopted by various authors.

Spontaneous abortion was one of the causes of fetal loss in this series and it was documented in one pregnancy (6.7%). However, it was reported in 15% of pregnancies in Middle East [7] and none was recorded in lupus pregnancies in South Africa [27] and Ghana [24]. Furthermore, in South Africa series, there were two cases (4.3%) of therapeutic abortions due to maternal request [27]. The major predisposing factor for spontaneous abortion identified in our study was the presence of an active disease in the index patient. A high disease activity has been linked to poor pregnancy outcome in studies from developed countries [14].

Intrauterine growth retardation with an eventual fetal demise was observed in one pregnancy (6.7%). In a population-based study by Chen *et al*, they observed that SLE patients were more prone to IUGR than pregnant non SLE patients (28.5% vs 17.5%) [5]. In addition, IUGR was recorded in 32% of lupus pregnancies by Aly *et al* [7] and in 14% of

South African lupus pregnancies by Whitelaw *et al* [27]. Hypertension, placental thrombosis and infarction have been shown to predispose to adverse fetal outcomes including IUGR [7]. The patient in our study was one of the two who had poorly controlled hypertension in addition to lupus nephritis. Aly *et al* also reported a preponderance of hypertensive subjects among their cohorts [7].

Still birth was observed in 6.7% (n=1) of the pregnancies in our study .In European patients, still birth was recorded in 2% of their pregnancies [25] while none was documented among Arab patients in the Middle East [7]. This could be explained by the fact that all patients in the Middle East study were in remission before onset of pregnancy. The index case here had positive anti Ro/SSA and anti La/SSB, markers of congenital heart blocks in fetus and neonates of lupus mothers. However, she defaulted from regular clinic visit and as such, never had fetal M mode echocardiography and fetal electrocardiography to monitor this complication.
Maternal death was documented in one pregnancy in this study. The reported case in this study had a flare of lupus nephritis in pregnancy which eventually led to her death at an estimated gestational age of 28weeks.Several reports have shown that active lupus nephritis during pregnancy is a major predictor of both fetal and maternal outcomes [28,29,25].

Term deliveries were observed in 66.7% (n=10) of pregnancies with a low proportion of preterm birth(n-1, 6.7%).Similarly, previous studies from developing countries have shown Higher frequency of term delivery in comparison with pre-term delivery [7,24].

Over half of our patients (52.7%) opted for elective caesarian section after being counseled on the risk of post-partum flare after the stress of spontaneous vaginal delivery. This was comparable to the 57.1% cesarean section rate reported by Dey *et al* in Ghana [24] and 53% by Aly *et al* in the Middle East [7], though for specific obstetric indications.

There was no record of neonatal lupus or confirmed congenital heart block in our study despite the positivity of the predisposing auto-antibodies in a quarter of the patients screened. This is not unexpected as the incidence of congenital heart block in the first affected pregnancy is 2% [30,31]. This increases to 16 -20% with subsequent pregnancies [30]. These auto-antibodies cross the placenta at around 16 to 26weeks gestational age and cause neonatal lupus syndrome which is characterized by skin, hepatic, hematologic and cardiac manifestations. All the organ affectations are reversible within 6 to 8 months of life with the clearance of maternal antibodies except the cardiac manifestations which result in congenital heart block, cardiomyopathy and congestive cardiac failure. The most feared cardiovascular manifestation is a complete heart block. This is usually preceded by low grade conduction defects such as a prolonged PR interval on fetal electrocardiogram. Cardiac manifestations occur when the conducting system of the heart is attacked by the implicated antibodies between weeks 18 and 24 of gestation. Treatment with fluorinated steroids could reverse the spectrum if commenced early at the stage of prolonged PR interval. Hydroxychloroquine has also been found to reduce the risk of occurrence of cardiac manifestation in neonates of mothers positive for anti Ro/SSA and anti La/SSB [32].

Antiphospholipid syndrome was diagnosed in one pregnancy while the antiphospholipid antibodies were elevated in 2 patients without APS. These antibodies can be found in 1-5% of the normal population and 12-30% of SLE patients [23]. Adelowo *et al* reported 5 cases of APS in 66 SLE patients in 2009 in Nigeria [33]. Another study outside Africa showed that 38% of lupus pregnancies in the Middle East were associated with APS [7]. This highlights the fact that secondary antiphospholipid syndrome may not be rare in SLE. Moreover; we might have under-estimated the frequency of APS due to our patients' inability to afford APS screening tests. The case in this study had aspirin and heparin in pregnancy and delivered a live baby at term after a previous history of 5 consecutive spontaneous abortions before diagnosis.

Conclusion

Fetal and maternal complications are common in Nigerian pregnant lupus patients but with an appropriate timing and management, it is possible to have a good outcome. Cooperation with an Obstetrician experienced in high risk pregnancies is also essential. A high index of suspicion is recommended in patients with recurrent spontaneous abortions and/or unexplained deterioration in renal function, even in the absence of typical skin lesions and/or arthritis.

Finally, since the management of SLE in pregnancy is cost intensive, the development of favorable health insurance policies by the government to enable the common man to benefit from standard health care will ease the burden of cost of management on patients.

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