Maternal Near Miss in Patients with Systemic Lupus Erythematosus

Arlley Cleverson Belo Silva (arlleyc@hotmail.com)
Paulista School of Medicine - Federal University of São Paulo (EPM – UNIFESP)
Sue Yazaki Sun
Paulista School of Medicine - Federal University of São Paulo (EPM – UNIFESP)
Felipe Favorette Campanharo
Paulista School of Medicine - Federal University of São Paulo (EPM – UNIFESP)
Letícia Tiemi Morooka
Paulista School of Medicine - Federal University of São Paulo (EPM – UNIFESP)
José Guilherme Cecatti
University of Campinas (UNICAMP)
Rosiane Mattar
Paulista School of Medicine - Federal University of São Paulo (EPM – UNIFESP)

Research Article

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Abstract

Introduction: Systemic lupus erythematosus (SLE) may cause irreversible organ damage. Pregnancy with coexisting SLE may have severe life-threatening risks. Severe maternal morbidities (SMM) include maternal death, maternal near miss (MNM), and potentially life-threatening conditions (PLTC). This study aimed to determine the prevalence of SMM in patients with SLE and analyze the parameters that contributed to cases of greater severity.

M**ethods:** This is a cross-sectional retrospective study from analysis of data retrieved from medical records of pregnant women with SLE treated at São Paulo Hospital , Brazil, from 2005 to 2015. The pregnant women were divided in control group without complications, group with PLTC, and group with MNM.

Results: Out of 149 pregnancies, there were 14 cases of MNM (9.4%), 56 cases of PLTC (37.6%), and no maternal death. The maternal near miss rate was 112.9 per 1,000 live births. The majority of PLTC (83.9%) and MNM (92.9%) cases had preterm deliveries with statistically significant increased risk compared with control group [p=0.0042; OR (95% CI): 12.05 (1.5-96.6) for MNM group and p=0.0001; OR (95% CI): 4.84 (2.2-10.8) for PLTC group]. SMM increases the risk of longer hospitalization [p<0,0001; OR (95% CI): 18.8 (7.0-50.6) and p <0.0001; OR (95% CI): 158.17 (17.6-1424,2) for PLTC and MNM, respectively], newborns with low birth weight [p=0.0006; OR (95% CI): 3.67 (1.7-7.9) and p=0.0009; OR (95% CI): 17.68 (2-153.6) for PLTC and MNM group, respectively] as well as renal diseases [PLTC (58.9%, 33/56; p = 0.0069) and MNM (78.6%, 11/14; p = 0.0026)]. MNM cases presented increased risk for neonatal death [p=0.0128; OR (95% CI): 38.4 (3.3-440.3)], stillbirth and miscarriage [p=0.0011; OR (95% CI): 7.68 (2.2-26.3)].

Conclusion: SLE was significantly associated with severe maternal morbidity, longer hospitalizations, and increased risk of poor obstetric and neonatal outcomes, such as prematurity, neonatal death, miscarriage and fetal loss.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease of multifactorial etiology and involving different systems; thus, it presents diverse clinical manifestations with periods of exacerbations and remissions of signs and symptoms, which may progress to irreversible organic damage [1]. However, there have been improvements in therapeutic strategies over the last decades due to increasing knowledge of the disease pathophysiology [2–4].

SLE is diagnosed most often in women of child-bearing age [5–6]. Maternal and fetal complications, including miscarriage, fetal death, prematurity, premature rupture of ovular membranes, preeclampsia, acute fetal distress and intrauterine growth restriction can occur during gestation in patients with SLE [7]. Conception is recommended within 6 months of disease remission, as this and other factors, such as

absence of chronic hypertension and renal insufficiency, are related to a lower rate of active disease during gestation and a better obstetric outcome [6–8].

The maternal mortality ratio is one of the most important indicators in assessing the quality of obstetric practice and perinatal care. Furthermore, researchers worldwide have been studied the prevalence of severe maternal morbidity as assessment tool in maternal health care. The Maternal Morbidity Working Group of the World Health Organization (WHO) defined uniform criteria in view of identifying cases of severe maternal morbidity (SMM), potentially life-threatening conditions (PLTC) and maternal near miss (MNM) [9].

The main purpose of this study was to evaluate the association of SLE with severe maternal morbidity and mortality. Although several studies have reported on the link between SLE and maternal morbidity, to the best of our knowledge, there are no studies specific to pregnant patients with systemic lupus erythematosus and SMM, according to the WHO criteria [9]. The secondary aim was to compare sociodemographic, obstetric, perinatal characteristics, and maternal morbidity features between patients.

Material And Methods

Study design

This was a cross-sectional, retrospective study of pregnant patients with systematic lupus erythematosus cared from January 2005 to December 2015 in the prenatal care unit and labor ward of São Paulo Hospital from the Universidade Federal de São Paulo – Escola Paulista de Medicina, a tertiary referral service in Brazil. Data collection, held between 2017 and 2018, was conducted separately by two researchers in order to check the consistency of data extracted from medical records of pregnant women with SLE and their newborns.

Pregnant patients with SLE were divided into three groups: without complications (control group: CG), with potentially life-threatening conditions (PLTC) and patients with maternal near miss (MNM), according to the WHO criteria [9]. Study variables included sociodemographic features, clinical and obstetric history, prenatal care, mode of delivery, gestational age at childbirth, days of hospitalization, and obstetric outcome. Birth conditions (Apgar score at 5 minutes and birth weight) and neonatal outcome were included.

Statistical analyses

The collected data were analyzed using IBM® SPSS® Statistics version 23.0 (Armonk, NY, USA). Descriptive analysis was performed using frequency and percentage for the categorical variables; for continuous variables, mean, standard deviation, minimum, median, and maximum were used. The Chi-square, Fisher exact test and Likelihood ratio test were used to compare the variables. P value < 0.05 were considered statistically significant, and odds ratios (OR) were estimated with their 95% confidence interval.

Ethical approval

The study was approved by the Ethics Review Board of Universidade Federal de São Paulo, under CAAE number 56744616.0.0000.5505. The need for informed consent was waived due to the retrospective design of the study. However, all of the authors signed a document guaranteeing the confidentiality and secrecy of data in order to preserve the anonymity of patients.

Results

The initial sample consisted of 169 pregnant patients with SLE. Twenty cases were excluded, six because childbirth did not occur at São Paulo Hospital and 14 due to unavailable records. The final 149 cases were divided into 3 groups: no complications control group (CG) (n=79, 53%); PLTC (n=56 cases, 37.6%); and MNM (n=14, 9.4%) (Figure 1).

The mean age of participants was 29 years, with the majority of patient ages ranging between 26 to 35 years (51%, 76/149 of pregnancies).

The maternal near miss rate was 112.9 per 1,000 live births; there were no cases of maternal death. There were no statistically significant differences in sociodemographic features or obstetric characteristics (number of pregnancies, parity and number of prenatal visits) among the three groups (Table 1).

Descriptive analysis revealed that the PLTC criteria “Prolonged hospital stay” was the most identified within all cases of SMM, both the MNM (85.7%, 12/14) and PLTC (62.6%, 35/56) groups. The duration of hospital-stay during pregnancy, delivery, and postpartum was above 8 days in the PLTC (60.7%, 34/56) and MNM (92.9%, 13/14) groups, significantly greater than the CG (7.6%, 6/79) [p<0,0001; OR (95% CI): 18.8 (7.0-50.6) and p <0.0001; OR (95% CI): 158.17 (17.6-1424,2) for PLTC and MNM, respectively]. (Table 2 and 3) In the MNM group, the length of hospitalization was greater than 21 days in over half of the patients. The second most frequent PLTC criteria was hypertensive complications such as severe hypertension, severe preeclampsia and HELLP syndrome, identified in 55,4% (31/56) and 64,3% (9/14) of PLTC and MNM groups, respectively.

Delivery after 37 weeks occurred in 16.1% and 7.1% of the PLTC and MNM groups compared to 48.1% of the CG. Consequently there was increased risk of preterm delivery both in the MNM group [p=0.0042; OR (95% CI): 12.05 (1.5-96.6)] and PLTC group [p=0.0001; OR (95% CI): 4.84 (2.2-10.8)] (table 2 and 3). Additional analysis demonstrated that in MNM group 71.5% (10/14) were associated with delivery before 27 weeks compared to 16.4% in the CG (p<0.001) and in the PLTC group 70% (39/56) delivered between 28 and 37 weeks compared to 35.4% (28/79) in the CG (p<0.001). Only 28.6% (4/14) of the cases in the MNM group resulted in take-home babies versus 83% (44/53) and 81.8% (63/77) in the PLTC and CG groups, respectively. A total of 57.1% of the MNM group (8/14) resulted in stillbirth and miscarriage compared to 18.2% (14/77) in the CG. Therefore there is increased risk of pregnancy loss in the MNM group [p=0.0011; OR (95% CI): 7.68 (2.2-26.3)] (table 3). Moreover there is higher chance of late neonatal death than neonatal hospital discharge in MNM cases [p=0.0128; OR (95% CI): 38.4 (3.3-440.3)] (table 3).

The PLTC group had four cases (7.5%) of early neonatal death, however when compared with the neonatal hospital discharge rate there was no significantly increased risk of neither neonatal death nor miscarriage/stillbirth. Additional analysis demonstrated that newborns from the PLTC group weighed less than 1500 g in 28% (15/54) of the cases compared to 6% (4/67) in the CG (p = 0.0016) as well as half of the MNM newborns (4/8) weighed less than 1000 g, compared to 1.5% (1/67) in the CG (p = 0.0003). Taking into account low birthweight babies, it was noted increased risk in both PLTC group [p=0.0006; OR (95% CI): 3.67 (1.7-7.9)] (table 2) and MNM group (p=0.0009; OR (95% CI): 17.68 (2-153.6)] (Table 3).

The presence of systemic impairment and antibodies due to SLE were assessed in this study with statistically significant results. Renal disorder was more prevalent in the PLTC (58.9%, 33/56; p = 0.0069) and MNM (78.6%, 11/14; p = 0.0026) groups than in the CG (35.4%, 28/79). In addition, hematological disorders were more frequent in the MNM group (71.4%, 10/14) than in the CG (40.5%; 32/79). There was a lower percentage of cutaneous impairment in the MNM group (64.3%, 9/14) compared with the control group (82.3%, 65/79) (Table 4).

Table 5 shows the MNM criteria that defined each of the 14 MNM cases. The criteria most frequently seen were “creatinine ≥ 3.5 mg/dl” and “dialysis for acute renal failure”, with at least one of these criteria present in half of the cases.

Discussion

A relationship between SLE and pregnancy complications has been previously established. The purpose of the present study was to evaluate the association of SLE with SMM according to the WHO standardized definitions and criteria [9], as well as compare sociodemographic, obstetric, perinatal characteristics, and maternal morbidity features in this cohort.

The elevated incidence rate of MNM in this study (112.9 cases per 1,000 live births) demonstrates that SLE has as a severe impact on pregnancy. The range of MNM incidence rates (per 1,000 live births) in the general population according to the WHO criteria is 9.35 to 13.5 in Brazil and Latin American countries [10-15], 5.9 in the United States of America [16], and 21.5 in Rwanda [17]. Additionally, the PLTC and MNM groups revealed a higher frequency of complications, such as prematurity, stillbirth, miscarriage, neonatal death, low birth weight, and a longer period of hospitalization. We identified a high association between SMM and maternal and fetal complications, including low birth weight, neonatal death, fetal loss, and miscarriage, correlating with previous reports [7, 18-23]. Prematurity was one of the most significant complications, with the majority of pregnancies in the MNM group delivering earlier than 27 weeks (71.5%), with statistically significant increased risk of preterm delivery in both MNM and PLTC groups.

Patients in both SMM groups had a statistically significant longer hospitalization period, with the main criteria "Prolonged hospital stay (> 7 days)". Therefore, we emphasize the importance of applying strategies that improve the health care of these patients. Better prenatal follow-up may lower the risk of complications, likely decreasing long-term hospitalization, and reducing social and economic costs,

which benefit public national health systems. As previously mentioned, among the 70 patients with SMM, 56 presented with PLTC and 14 with MNM. Thus, it could be argued that theoretically 80% of the PLTC cases were identified and reversed before evolving to maternal near miss cases. This analysis directly reflects service assistance quality and can be useful in audits as well as subsequent implementations and improvements in health care [24].

The association of renal impairment and severe maternal morbidity among the patients indicated that the presence of lupus nephritis during gestation is a relevant factor for developing complications. Cases with positive antiphospholipid antibodies or anti-phospholipid antibody syndrome associated with SLE also had a higher risk of developing PLTC. Several studies have indicated the presence of previous lupus nephritis, chronic hypertension, and positive antiphospholipid antibodies, such as anticardiolipin antibody and lupus anticoagulant, to be predictors of poor obstetric and neonatal outcomes in patients with SLE [7,8,18-20,25-27].

There were two unexpected results in this study, one was the relation between hematological impairment and a higher percentage of MNM compared to control group. The other one was the association of cutaneous criteria (malar rash, discoid rash and photosensitivity) with a lower percentage of cases with SMM. Such relationships have not been found in previous studies regarding lupus during pregnancy. In order to understand the first finding, the 10 MNM cases with hematological criteria were analyzed individually and it was found that in 7 of them there was also nephritis, with the presence of laboratory and management criteria "Creatinine ≥ 3,5 mg / dl " and "Dialysis for acute renal failure ", respectively. Therefore, nephritis was believed to be a bias factor for this result. No bias factor was identified for the second unexpected finding; therefore, cutaneous criteria in SLE patients might be considered a weak sign for SMM and poor obstetric outcomes. However, new studies should be performed to define this relationship more clearly.

This retrospective study has some limitations. As this study was based on existing medical records, some data was missing. Additionally, although we selected a 10-year period for this study to provide an adequate number of patients, in the future, a larger sample size and the collection of prospective data may provide more representative results.

Conclusion

The findings of the current study demonstrated a strong and significant association between SLE and SMM. Cases of SMM had longer hospitalization and a higher risk of poor obstetric and neonatal outcomes, such as prematurity, miscarriage, fetal loss, and neonatal death. The presence of chronic or acute renal impairment was a significant factor in the evolution of SMM. We believe that the development of SMM in this population might be avoided through appropriate preconception planning, good disease control, absence of disease activity (especially of the renal system), along with specialized prenatal, perinatal, and postpartum care carried out by a multi-professional team.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Review Board of Universidade Federal de São Paulo, under CAAE number 56744616.0.0000.5505. The need for informed consent was waived by the Ethics Review Board due to the retrospective design of the study. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, ACBS, upon reasonable request.

Competing interests

The authors report no conflict of interest**.**

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Authors' contributions

All authors reviewed and approved the final version of the manuscript.

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Tables

Table 1. Sociodemographic and obstetric characteristics between groups of complications of pregnancies with systemic lupus erythematosus.

Characteristics	Group			p value	p value
	PLTC	MNM	No Complication	No complication PLTC	No complication MNM
Age (years)					
15 a 25	16 (28.6%)	9 (64.3%)	25 (31,6%)	0.2335[c]	0.0647[a]
26 a 35	34 (60.7%)	4 (28.6%)	38 (48,1%)		
>35	6 (10.7%)	1 (7.1%)	16 (20,3%)		
(n)	56	14	79		
Ethnic origin[d]					
White	34 (66.7%)	9 (75%)	37 (53.6%)	0.1507[c]	0.1677[c]
Other	17 (33.3%)	3 (25%)	32 (46.4%)		
(n)	51	12	69		
Education[e]					
None	6 (11.3%)	2 (18.2%)	9 (15%)	0.9241[c]	0.9121[a]
Primary school	14 (26.4%)	2 (18.2%)	17 (28.3%)		
High school	28 (52.8%)	6 (54.5%)	29 (48.3%)		
University	5 (9.4%)	1 (9.1%)	5 (8.3%)		
(n)	53	11	60		
Marital status[f]					
With partner	42 (79.2%)	9 (69.2%)	50 (69.4%)	0.2193[c]	1.0000[b]
No partner	11 (20.8%)	4 (30.8%)	22 (30.6%)		
(n)	53	13	72		

No of pregnancies					
1	25 (44.6%)	6 (42.9%)	24 (30.4%)	0.0895[c]	0.3679[b]
≥ 2	31 (55.4%)	8 (57.1%)	55 (69.6%)		
(n)	56	14	79		
Parity					
0	29 (51.8%)	6 (42.9%)	31 (39.2%)	0.1484[c]	0.7989[c]
≥ 1	27 (48.2%)	8 (57.1%)	48 (60.8%)		
(n)	56	14	79		
Prenatal visits					
0	8 (14.3%)	6 (42.9%)	15 (19%)	0.1638[a]	0.0549 [a]
1 – 5	12 (21.4%)	4 (28.6%)	14 (17.7%)		
6 – 12	25 (44.6%)	4 (28.6%)	41 (51.9%)		
13 – 18	8 (14.3%)	0 (0%)	9 (11.4%)		
>18	3 (5.4%)	0 (0%)	0 (0%)		
(n)	56	14	79		

Abbreviations: MNM, maternal near miss; PLTC, potentially life-threatening condition.

Statistically significant when $p < 0.05$.

[a]Likelihood Ratio Test; [b]Fisher Exact test; [c] X^2 test adjusted for cluster effect; [d]Missing values of 17 women; [e] Missing values of 25 women; [f]Missing values of 11 women; [g] Ectopic pregnancy case xcluded from the statistical analysis

Table 2. Hospitalization time, obstetric and neonatal outcomes between PLTC and control groups of pregnancies with systemic lupus erythematosus.

Characteristics	Group		p value	OR (95% CI)
	PLTC	No complication		
Hospital Stay (days)			**<0.0001**	18.8 [7.0- 50.6]
< 8 (ref)	22 (39.3%)	73 (92.4%)		
≥ 8	34 (60.7%)	6 (7.6%)		
(n)	56	79		
GA at delivery (weeks)			**0.0001**	4.84 [2.2- 10.8]
<37	47 (83.9%)	41 (51.9%)		
≥ 37 (ref)	9 (16.1%)	38 (48.1%)		
(n)	56	79		
Outcome/Mode of delivery				
Miscarriage	1 (1.9%)	12 (15.2%)	0.1301[a]	5.78 [0.7- 49.3]
Cesarean section	41 (74.5%)	40 (50.6%)	0.0774	0.47 [0.2- 1.0]
Vaginal (ref)	13 (23.6%)	27 (34.2%)		-
(n)	55[b]	79		
Neonatal outcome				
Neonatal death <7 days	4 (7.5%)	0 (0%)	0.0975[a]	12.84 [0.2-57.7]
Neonatal death ≥ 7 days	2 (3.8%)	0 (0%)	0.5275[a]	7.13 [0.1-25843.3]
Miscarriage/Stillbirth	3 (5.7%)	14 (18.2%)	0.1916	0.31 [0.083-1.1]
Hospital discharge (ref)	44 (83%)	63 (81.8%)		-
(n)	53	77		
Birthweight (grams)				
≤ 2500	32 (59.3%)	19 (28.4%)	**0.0006**	3.67 [1.7-7.9]
> 2500	22 (40.7%)	48 (71.6%)		
(n)	54[c]	67[d]		

Abbreviations: PLTC, potentially life-threatening condition; GA, Gestational Age.

Statistically significant when $p < 0.05$.

[a] Fisher Exact test

[b] Ectopic pregnancy case excluded from the stastitical analysis

[c] Missing values of 1 case of miscarriage

[d] Missing values of 12 cases of miscarriage

Table 3. Hospitalization time, obstetric and neonatal outcomes between MNM and control groups of pregnancies with systemic lupus erythematosus.

Characteristics	Group		p value	OR (95% CI)
	MNM	No complication		
Hospital Stay (days)			**<0.0001**	158.17 [17.6- 1424.2]
< 8 (ref)	1 (7.1%)	73 (92.4%)		
≥ 8	13 (92.9%)	6 (7.6%)		
(n)	14	79		
GA at delivery (weeks)			**0.0042**	12.05 [1.5- 96.6]
<37	13 (92.9%)	41 (51.9%)		
≥ 37 (ref)	1 (7.1%)	38 (48.1%)		
(n)	14	79		
Outcome/Mode of delivery				
Miscarriage	6 (42.9%)	12 (15.2%)	0.0899[a]	0.22 [0.05-1.04]
Cesarean section	5 (35.7%)	40 (50.6%)	0.5687	0.89 [0.20- 4.0]
Vaginal (ref)	3 (21.4%)	27 (34.2%)		-
(n)	14	79		
Neonatal outcome				
Neonatal death ≥ 7 days	2 (14.3%)	0 (0%)	**0.0128[a]**	38.4 [3.3- 440.3]
Miscarriage/Stillbirth	8 (57.1%)	14 (18.2%)	**0.0011**	7,68 [2.2- 26.3]
Hospital discharge (ref)	4 (28.6%)	63 (81.8%)		
(n)	14	77	-	
Birthweight (grams)			-	
≤ 2500	7 (87.5%)	19 (28.4%)	**0.0009**	17,68 [2- 153.6]
> 2500	1 (12.5%)	48 (71.6%)		
(n)	8[b]	67[c]		

Abbreviations: MNM, maternal near miss; GA, Gestational Age.

Statistically significant when p < 0.05.

[a] Fisher Exact test

[c] Missing values of 6 cases of miscarriage

[d] Missing values of 12 cases of miscarriage

Table 4. Systemic impairment and positive antibodies between group of complications of pregnancies with systemic lupus erythematosus.

	Group			p value	p value
Systemic impairment	PLTC	MNM	No Complication	No complication	No complication
	n =56	n =14	n =79	PLTC	MNM
Renal disorder	33 (58.9%)	11 (78.6%)	28 (35.4%)	**0.0069**	**0.0026**
Cutaneous disorder	36 (64.3%)	9 (64.3%)	65 (82.3%)	**0.0177**	0.1521 [a]
Arthritis	39 (69.6%)	9 (64.3%)	57 (72.2%)	0.7513	0.5385 [a]
Serositis	11 (19.6%)	2 (14.3%)	13 (16.5%)	0.6332	1.0000 [a]
Blood disorder	28 (50%)	10 (71.4%)	32 (40.5%)	0.2741	**0.0321**
Neurologic disorder	4 (7.1%)	3 (21.4%)	8 (10.1%)	0.7606[a]	0.3619[a]
Antibodies					
Anti DNA	19 (33.9%)	3 (21.4%)	21 (26.6%)	0.3571	1.0000[a]
Anti Smith (Sm)	10 (17.9%)	2 (14.3%)	15 (19%)	0.8677	1.0000 [a]
Anticardiolipin	11 (19.6%)	1 (7.1%)	6 (7.6%)	**0.0376**	1.0000 [a]
Lupus anticoagulant	4 (7.1%)	1 (7.1%)	0 (0%)	**0.0278** [a]	0.1505 [a]
AntiRo	15 (26.8%)	2 (14.3%)	27 (34.2%)	0.3607	0.2120 [a]
Anti La	4 (7.1%)	0 (0%)	5 (6.3%)	1.0000 [a]	1.0000 [a]
Antinuclear	47 (83.9%)	11 (78.6%)	62 (78.5%)	0.4291	1.0000 [a]
Anti RNP	14 (25%)	3 (21.4%)	20 (25.3%)	0.9667	1.0000 [a]

Abbreviations: MNM, maternal near miss; PLTC, potentially life-threatening condition.

Statistically significant when $p < 0.05$.

[a]Fisher Exact test.

Table 5. Description of the criteria present in each maternal near miss case according to WHO criteria.

Patient	Age (y)	Criteria		
		Clinical	Laboratory	Management
Case 1	31	-	-	Hysterectomy following infection or hemorrhage
Case 2	28	Shock	-	Transfusion of ≥ 5 units of red cells
Case 3	25	Clotting failure	Lactate > 5 / Platelets < 50 000	Transfusion of ≥ 5 units of red cells
Case 4	20	-	-	Transfusion of ≥ 5 units of red cells
Case 5	24	Respiratory rate > 40 or <6/min	Lactate > 5	-
Case 6	24	-	Oxygen saturation < 90% for ≥ 60 minutes / Lactate > 5	Intubation/ventilation for ≥ 60 min not related to anesthesia
Case 7	22	-	Creatinine ≥ 3.5mg/dl	Dialysis for acute renal failure
Case 8	32	-	Creatinine ≥ 3.5mg/dl	Dialysis for acute renal failure
Case 9	37	-	Creatinine ≥ 3.5mg/dl	Dialysis for acute renal failure
Case 10	25	-	Creatinine ≥ 3.5mg/dl	Dialysis for acute renal failure
Case 11	27	-	Creatinine ≥ 3.5mg/dl	-
Case 12	19	-	-	Dialysis for acute renal failure
Case 13	22	-	Creatinine ≥ 3.5mg/dl / Lactate > 5	-
Case 14	22	-	Lactate > 5	-

Figures

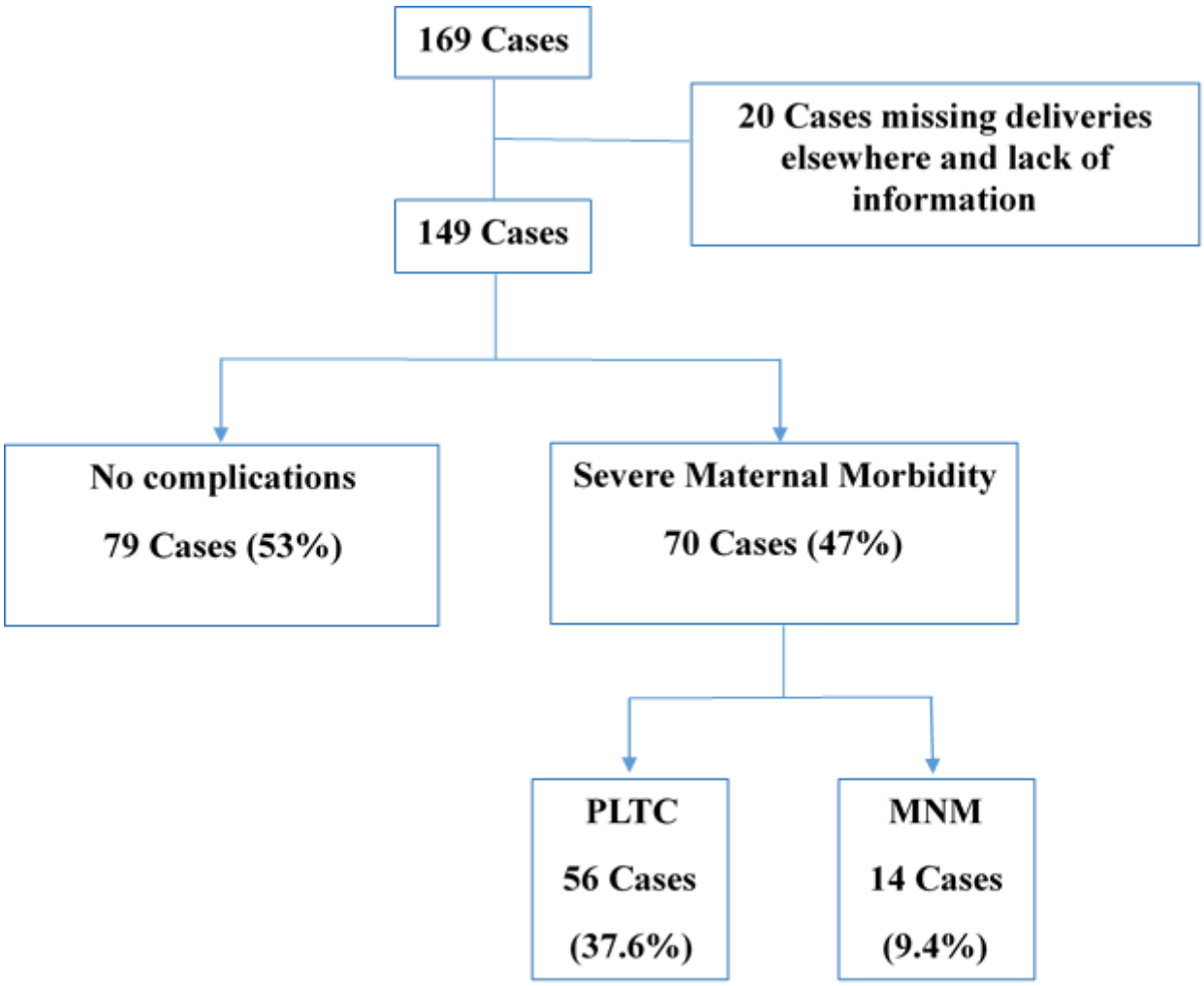

Figure 1

Flow chart of inclusions. PLTC, potentially life-threatening conditions; MNM, maternal near miss