

Maternal mortality among women with sickle cell disease in Jamaica over two decades (1998–2017)

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Summary

Background Sickle cell disease (SCD) affects 2.8% of Jamaican antenatal women. Between 1998–2007 their maternal mortality ratio was 7–11 times higher than women without these disorders. We aim to determine if outcomes improved between 2008 and 17 amid declining fertility and changes in referral obstetric care.

Methods Maternal deaths in Jamaica's maternal mortality surveillance database (assembled since 1998) with SCD reported as underlying or associated cause of death were compared to those without known SCD, over two decades from 1998 to 2017. Social, demographic and health service variables were analysed using SPSS and EpiInfo Open.

Findings Over the two decades from 1998 to 2017, 806 (74%) of the 1082 pregnancy-associated deaths documented by the Jamaican Ministry of Health and Wellness were maternal deaths. The maternal mortality ratio (MMR) did not statistically change over the two periods for women with ($p = 0.502$) and without SCD ($p = 0.629$). The MMR among women with and without SCD in 2008–17 was 378.1 ($n = 41$) and 89.2/100,000 live births ($n = 336$) respectively, an odds ratio of 4.24 (95% CI: 3.07–5.87). When deaths due to their blood disorders were excluded, risk remained elevated at 2.17 (95% CI: 1.36–3.32). There was an upward trend in direct deaths over the two decades (p [trend]=0.051).

Interpretation MMRs were unchanged over two decades for Jamaicans with SCD. The high contribution to maternal mortality by women with SCD may explain some of the persistently higher mortality experience of women in the African diaspora. Multi-disciplinary evidence-based strategies need to be developed and tested which improve survival for women with SCD who want to have children.

Funding No external funding was provided.

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Keywords: Jamaica; Sickle Cell Disease; Maternal Deaths; Surveillance; Direct Deaths

Introduction

Sickle cell disease (SCD) is a genetic disorder principally affecting persons of African ancestry, but also populations from India,¹ the Middle East,² and the Mediterranean.³ The most common variants include homozygous SCD (HbSS), and the heterozygotes sickle-hemoglobin C disease (HbSC) and sickle β -thalassaemia (HbS β -Thal). SCD is the most common genetic disorder in Jamaica; one in ten persons carry the sickle gene and 6/

1000 newborns have either HbSS or HbSC disease.^{4,5} In New York State maternal ethnicity correlated with SCD incidence (SS, SC or S β -Thal), with rates ranging from 0.32% among infants of US-born African-American women to 0.48% in babies of Caribbean women to 1.28% in the progeny of West African mothers.⁶

SCD is associated with high, but improving, lifetime morbidity and premature mortality.⁷ In 2001, a Jamaican specialist SCD clinic estimated life expectancy in their patients of 53 (males) and 58.5 (females) years.⁸ Survival to 40 years in 2018 was 55.5% (95% CI 48.7–61.7%)⁹ but may be lower in the wider community. A clear twenty-year gap exists with the general population, whose life expectancy (2018) was 73.6 (males) and 78.5 (females) years.¹⁰

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EClinicalMedicine
2022;43: 101238

Published online xxx

<https://doi.org/10.1016/j.eclinm.2021.101238>

eclinm.2021.101238

Research in Context

Evidence before this study

Global evidence documents that women with sickle cell disease (SCD) are at excess risk of maternal death compared to women without these genetic disorders, but little long-term data exist on whether or how survival has improved over time. We searched PubMed for articles published in English from 1998 to August 2021, using search terms “sickle cell disease”, “pregnancy”, “maternal mortality”, “antenatal care”, “trends”, “African diaspora”, “developing countries,” and “Americas.” Two of three papers represented our work.

Added value of this study

This study compiles twenty years of evidence from a middle-income, western hemisphere country and discusses the challenges of affected women on whom little research effort has been directed at improving their obstetric outcome. These findings should stimulate development of evidence-based specialist services for pregnant women with SCD in all four health regions in Jamaica, and developed and developing countries.

Implications of all the available evidence

Efforts must focus on equitably closing the two-fourfold maternal survival gap for women with SCD. Greater research investment is needed to develop and test specific models of antenatal care which improve maternal and neonatal survival. Models should include input from haematologists and maternal-foetal specialists during pregnancy and access to neonatologists at delivery. Trial evidence should lead to global guidelines for their care. Newborn screening should be universal in settings where the SCD gene exists.

As more women with SCD survive into the reproductive ages, childbearing risks emerge. Sergeant et al. recruited a cohort of persons with SCD at birth. When the women were compared to normal controls, females with HbSS disease had later median age at menarche (15.4 versus 13.0 years) and first pregnancy (23.7 versus 20.1 years).^{11,12} Toward the end of their reproductive life cycle, of 163 desired pregnancies, 34% ($n = 56$) ended in miscarriage; 8% (14) were stillborn and just 57% ($n = 93$) were liveborn. There were four maternal (three indirect) and one late maternal deaths.¹³

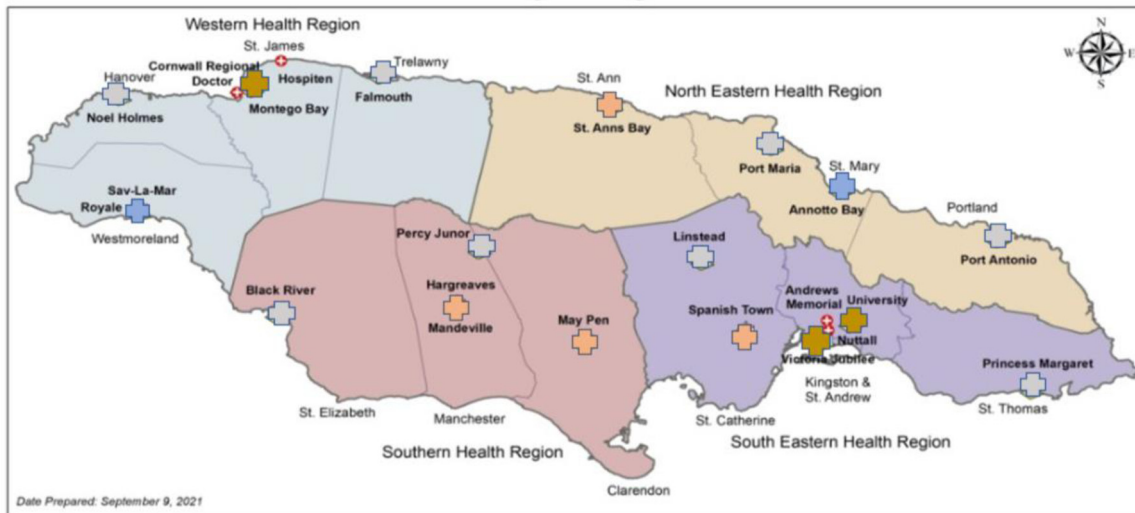
SCD complications affect every organ system.¹⁴ In pregnancy, women with SCD experience higher rates of both medical and obstetric complications of pregnancy than those without this disorder. In addition to vaso-occlusive crises (VOCs), they were more likely to develop urinary tract infections and the hypertensive disorders (pregnancy-induced hypertension, puerperal hypertension) than AA controls matched for age and parity.¹⁵ A meta-analysis of 16 studies of pregnancy

outcomes and SCD in both low and high income countries found higher pooled odds ratios (OR) for pre-eclampsia (OR 2.05, 95% CI 1.47–2.85) and eclampsia (OR 3.02, 95% CI 1.20–7.58). Babies were more often born preterm (OR 1.25, 95% CI 1.03–1.52),¹⁵ growth restricted (OR 2.79, 95% CI 1.85–4.21), low birthweight (OR 2.00, 95% CI 1.42–2.83) and experienced perinatal death (OR 3.76, 95% CI 2.34–6.06).¹⁶ Their pooled odds of maternal death was 10.91 (95% CI 1.83–65.11, $p = 0.009$).¹⁶

In France (1996–2009), the maternal mortality ratio (MMR) among women with SCD was 454 [95% CI 254–750]/100,000 live births (15/3300) versus 9.4 [95% CI 8.8–10.0]/100,000 for women without these conditions; 87% (13/15) died from SCD complications; only two died from direct causes (amniotic fluid embolism, chorioamnionitis).¹⁷ In Jamaica (1998–2007), MMRs of 719 and 78 per 100,000 respectively were noted but with a different cause profile; 40% (17/42) died from SCD complications; 24% (10/42) other medical conditions, while 29% (12/42) were direct deaths.^{18–21} When deaths attributed to SCD were excluded, women with SCD were 4–6 times as likely to experience maternal death than non-SCD women,¹⁸ challenging health care providers to manage this chronic disease alongside childbearing.

Public services for Jamaican mothers and babies are delivered through 300+ primary care centres and 20 hospitals in four health regions (West: Westmoreland, Hanover, St James, Trelawny; North-East: St Ann, St Mary, Portland; South: St Elizabeth, Manchester, Clarendon and South-East: St Catherine, Kingston, St Andrew and St Thomas). inpatient obstetric/neonatal services (see Fig. 1), occur at three levels of care. Tertiary hospitals providing a full range of specialty services, including intensive care units (ICUs) are limited to Kingston/St Andrew (KSA) and St James. Referral hospitals offer obstetric and pediatric services in St Mary, St Ann, Westmoreland, Manchester, Clarendon, and St Catherine. In the remaining parishes, deliveries are attended by midwives in general hospitals, with surgical support if emergency Caesarean sections are needed (St Thomas, Portland, Trelawny, Hanover, St Elizabeth). Optimal outcomes require timely clinical identification of patients at high risk of severe morbidity and transfer to better equipped institutions prior to deterioration. The majority (95%) of births between 2013 and 17 occurred in public hospitals (183,962) with 2.5% (4545) and 2.4% (4348) respectively in private hospitals or the community. From 1998 to 2017, annual registered births declined by 26%, from 46 690 to 34 426.

In 2014, Jamaica began deployment of obstetricians trained as maternal-foetal medicine (MFM) specialists in KSA, St Catherine, St James and Manchester and coincided with the introduction of high dependency units (HDUs) in St James (4 beds), St Ann (3 beds), Manchester (2 beds), KSA (2 beds) and Clarendon (1



Legend

Symbol	Public hospitals by level of care	Colour code	Health regions
	Tertiary hospital, ICU & HDU		Western region
	Referral hospital, HDU		North east region
	Referral hospital, <u>no</u> HDU		Southern region
	General hospital		South east region

Figure 1. Distribution of public hospitals attending births in Jamaica, by region and level of care available, 2021.

bed). As women with SCD require highly specialized care, we will examine whether mortality differed both by region of residence and by the highest level of care in their parish of residence (tertiary, referral, general midwifery).

With over 10 years since the first review, we examine whether changes in obstetric care, including addition of the MFM subspecialty, and declining fertility have reduced likelihood of pregnancy and improved maternal survival for this very high-risk population. We aim to describe the epidemiology of maternal deaths among women with and without SCD for the decade 2008–2017 compared to 1998–2007 in Jamaica. Specific objectives are to:

1. Describe the socio-demographic (age, geographic access to care), and obstetric experience (fertility, complications of pregnancy, perinatal outcome) of SCD women experiencing maternal death compared to non SCD women who also died.
2. Determine the immediate and underlying causes of death (COD) and whether these have changed among these two groups of women and over the decades 1998–2007 and 2008–2017.
3. Identify whether access to health service factors may be associated with risk of dying.

Methods

The study utilizes secondary data from Jamaica’s national maternal mortality surveillance system which seeks to identify and document all maternal deaths on the island. Instituted in 1998 by the Ministry of Health and Wellness (MOHW),²² it employs both passive reporting and active surveillance to identify events. This maternal mortality surveillance database is compiled to inform public policy and develop appropriate interventions. Health care providers may report suspected maternal and late maternal deaths to the MOHW, however public health officers actively review deaths in women of reproductive age in obstetric and non-obstetric areas of public hospitals, private facilities and the community for evidence of pregnancy within a year of death.

Suspected cases are investigated by the local health team and reviewed at regional and national levels. Retrospectively available data assessed include information from permanent antenatal and postnatal service records (primary care centres; hospital high risk outpatient clinics) and inpatient facilities (antepartum admission; labor, delivery and puerperal care). Over 80% of maternal deaths undergo necropsy and postmortem findings are included. The primary care team also visit with the next-of-kin at home to compile qualitative evidence on access to care; compliance with referral and clinical advice; and signs and symptoms preceding death.

Multi-disciplinary teams review the available evidence and seek to reach consensus on the underlying and immediate causes of death and avoidable factors. Where co-morbidities exist, the condition initiating the chain of events leading to the immediate COD is selected. For example, if obstetric hemorrhage (a direct cause) co-occurred with a VOC and the immediate cause was due to haemorrhagic shock and not SCD stigmata (kidneys, lungs, gall bladder, spleen), the underlying COD would be assigned to the direct versus the indirect condition.

Cases are classified as direct, indirect or coincidental (not pregnancy related) and maternal (pregnancy to 42 days after pregnancy ends) or late maternal, (43–364 days after delivery).²² Among decedents with SCD, 88% were maternal and 12% late maternal deaths; no coincidental deaths were identified (Table 1). Data presented are restricted to maternal deaths between 1998 and 2017 (Fig. 2). We excluded late maternal deaths, women whose cause of death could not be determined or whose deaths were not considered as

pregnancy-related. Maternal deaths (pregnancy to six weeks after pregnancy ended) with evidence of SCD (HbSS, HbSC or HbSβ-Thal) are compared to women without known SCD (sickle cell trait (HbAS) or HbAA) in their medical history.

Estimating births among Jamaican women with sickle cell disease

Jamaica's birth registration process records maternal age, parity, parish of residence, place of delivery but no medical indicators. To estimate how many births occur to women with SCD, we consulted the MOHW for summary results of anemia screening at first antenatal (AN) visits, including identification of HbSS/HbSC disease. Data for selected years between 2009 and 2015 report, on average, that 2.8% of women had SS/SC disease (Appendix 1). Secondly, the University Hospital of the West Indies (UHWI), a tertiary teaching hospital, provides AN care to women who must present in the first trimester and pay for care. Of 1688 women screened Jan 2019–Jun 2021,

Sickle cell status and category of pregnancy associated death	1998–2007		2008–2017		Total	
All women	N and MMR^a		N and MMR^a		N and MMR^a	
All pregnancy associated deaths^b	547		535		1082	
Maternal deaths ^c	428		378		806	
Total registered live births	459 803		387 252		847 055	
MMR per 100,000 LB (95% CI)	93.1 (84.5–102.2)		97.6 (88.1–107.8)		95.2 (88.7–101.9)	
Women with any SCD^c	N	Percent	N	Percent	N	Percent
Direct/indirect	42	89.4	41	85.4	83	87.4
Late direct/indirect	5	10.6	6	12.5	11	11.6
Late coincidental	0	–	1	2.1	1	1.1
Subtotal	47	100	48	100	95	100
	N and MMR^a		N and MMR^a		N and MMR^a	
Proportion of maternal deaths to women with SCD (maternal deaths: SCD/all deaths)	9.8%		10.8%		10.3%	
Births to women with SCD (2.8% of registered live births)	12 873		10 843		23,717	
MMR – SCD (95% CI)	326.2 (241.5–440.7)		378.1 (278.9–512.6)		350.0 (282.4–433.6)	
Women without any SCD^d	N	Percent	N	Percent	N	Percent
Direct/indirect	386	77.2	336	69.0	722	73.2
Late direct/indirect	86	17.2	92	18.9	178	18.0
Coincidental (accidents/violence)	15	3.0	36	7.4	51	5.2
Late coincidental	0	–	10	2.0	10	1.0
Cause not known	13	2.6	13	2.7	26	2.6
Subtotal	500	100	487	100	987	100
Births to non SCD women (97.2% registered live births)	446 930		376 409		823 338	
MMR – non SCD (95% CI)	86.4 (78.1–95.4)		89.2 (80.2–99.3)		87.7 (81.5–94.3)	
Crude OR range with 95% CIs(MMR – SCD vs non SCD)	3.78 (2.75–5.20)		4.23 (3.02–5.80)		4.00 (3.18–5.02)	
Yates corrected chi-square (p value)	P<0.0001		P<0.0001		P<0.0001	

Table 1: Pregnancy associated deaths, by sickle cell status of the decedents and World Health Organization (WHO) category of death, 1998–2017: Jamaica.

^aMMR = maternal mortality ratio ([direct and indirect maternal deaths/live births] * 100,000).

^bDirect, indirect and coincidental deaths during pregnancy and up to one year after pregnancy ends.

^cDirect and indirect deaths during pregnancy and up to 6 six weeks after pregnancy ends.

^dInclude HbSS, HbSC, HbSβ-Thal.

^eInclude women who carry the trait (HbAS).



Figure 2. Case selection process – Jamaica maternal mortality surveillance database, 1998–2017.

164 (9.7%) had sickle trait (AS), and 23 (1.4%) had a sickling disorder (SS, 13; SC, 5; S β -Thal, 5).

Lubeck et al. suggest that chronic disorders like SCD which reduce life expectancy by as much as 22 years, impact lifetime earning potential. In early life, educational potential may not be realized due to limited school attendance and learning resulting from repeated illness episodes; while shorter life expectancy truncates working years. Family income may be indirectly affected if parents/caregivers are unable to work while caring affected children, combined with the negative opportunity costs of seeking care at facilities.²³ Given the potential economic impact and, relatively more affected women accessing cost-free public AN care services, we applied the 2.8% prevalence to the registered livebirths to estimate births to women with SCD (see Table 1) so as to calculate cause-specific MMRs.

Data analysis and presentation

Causes of death (COD) are coded using the International Classification of Diseases (ICD-10), 10th edition.²⁴ The underlying COD are summarized using the ICD-MM guidelines for maternal mortality. For the immediate COD, organ system dysfunction criteria from the World Health Organization (WHO)²⁵ were used.

Data were summarized using IBM SPSS Statistics (Version 22, Armonk, NY). For continuous variables, histograms were compared to the normal distribution. If variables were normally distributed, means and standard deviations were compared using t-tests. If skewed, Mann-Whitney U tests were applied to test for differences between medians and IQRs. Probability values (p-values) less than 0.05 were considered statistically significant. MMRs were compared using odds ratios (mid-p exact two-tailed test) using EpiInfo Open (OpenEpi

Collection of Epidemiologic Calculators, Version 3.0: Revised April 6, 2013). Reporting is consistent with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.²⁶

As these are retrospective data gleaned from clinical records, missing data reflect what clinicians thought necessary to record during care. We have no reason to believe that there are biases in what may be missing. The highest prevalence of missing data was for gestation at the end of pregnancy and reflect whether women had known and reported, a priori, their last menstrual period or if a pelvic ultrasound had been done (available data: 73% and 81% among women with SCD for 2008–17 and 1998–2007 respectively; and 67% and 81% of women not known to have SCD). For most other variables, 90% or more of cases had available data for socio-demographic and health service variables. The amount of missing data for each variable may be determined by comparing the grand total of cases (N) at the top of columns for each table to variable sub-totals. Cases with missing data were excluded from analysis.

As the dataset only includes pregnancy related deaths but lacks information on women who survived their pregnancies, we could not adjust the maternal mortality ratios using multivariate methods for variables such as age and parity. Social, obstetric and health service variables significantly correlated on univariate analysis with sickle cell status were however evaluated using logistic regression to determine which were independent predictors of maternal death among women with SCD compared to women without these disorders.

Ethics and confidentiality

The proposal received Ethics approval from the University of the West Indies, Mona Campus Research Ethics Committee, (Protocol #: CREC-MN.195, 20/21) and the

Ministry of Health and Wellness, Jamaica (Protocol #: 2021/12). As secondary data, informed consent does not apply. Following evidence of ethics approval, de-identified data were made available to investigators and have been treated in the strictest confidence.

Role of the funding source

No funding was received for the study. AM-B had access to the case reports. The MOHW team had no role in the study design or analysis of the data. The MOHW co-authors contributed to interpretation of the data and approved the final manuscript. AM-B and MA had principal access to the final database. MA and AM-B decided to submit of the paper for publication.

Results

Pregnancy associated deaths and SCD in Jamaica

Over the two decades from 1998 to 2017, 806 (74%) of the 1082 pregnancy-associated deaths documented by the MOHW were maternal deaths (Fig. 2/Table 1). The MMR did not statistically change over the two periods for women with ($p = 0.502$) and without SCD ($p = 0.629$). Women with SCD averaged 10.3% of maternal deaths (range: 9.8%–10.8%) but were 2.8% of antenatal attendees, a fourfold risk of death (OR 4.00; CI: 3.18–5.02) compared to women not known to have these disorders. Over the twenty years, most SCD maternal deaths were associated with HbSS (83%; 69) or HbSC (16%; 13) disease. HbS β -Thal was linked to only one (1%) maternal death in 2014.

Social, obstetric and health care factors associated with maternal and perinatal outcome

Social, obstetric and health care indicators. Table 2 compares social, obstetric, health care and perinatal outcome by sickle cell status for both decades. Between 2008 and 2017, there were no significant socio-demographic differences between women with and without SCD; and fertility differences by SCD status from the earlier decade did not persist. For 1998–2007 there were suggestions that more women with SCD died in the southeast region ($p = 0.076$) and in parishes with tertiary care ($p = 0.020$). This was no longer evident in the recent period and may have been an artifact of access to care, as more cases may have been then identified in these settings. In the latter decade, like the earlier one, more women with SCD were seen in high-risk antenatal clinics (55% [21/41] vs 28% [87/309]) but fewer in the private sector (5%; 2/41; 12% [38/309]) than women without SCD ($p = 0.001$). More of all women with complications were admitted antenatally in the recent decade ($p = 0.003$) but at higher rates for women with SCD in both periods (2008–17; SCD 88%;

30/34), non-SCD 65% (185/287), $p = 0.005$ compared to 1998–2007, 38% (16/42) and 24% (90/381) respectively ($p = 0.004$). All women with SCD in the later decade delivered at a referral hospital, under obstetric management.

Maternal outcome. Around a quarter of women died undelivered (SCD: 27.5%; 11/40), one in three at term (33.3%; 12/36), similar to non-SCD women (24.7%; 81/328 and 28%; 92/328 respectively); $p = 0.220$. All died in hospital, but women with SCD were more likely (33%; 13/41) to die in an intensive care (ICU) or high dependency unit (HDU) than women not known to have SCD (12%; 39/337), $p = 0.004$. postmortem rates increased overall to 87% (249/286) in the later decade versus 78% (268/343) in the earlier period ($p = 0.004$) and did not vary by SCD status ($p = 0.788$).

Perinatal outcome. No differences in perinatal indicators (gestation, birthweight) were observed among the groups ($p = 0.812, 0.425; 2008–17; or over time$ ($p = 0.311, 0.940$ respectively: 1998–2007). In the recent decade, the pregnancies of women with SCD women ended at a median of 35.2 (IQR 28.5–38.0) weeks gestation and their live born babies averaged 2.51 (IQR 1.58–3.13) kg. Of the SCD cohort who delivered, there were two spontaneous abortions (5%), five stillbirths (13%), and 22 live births (55%), twelve of which were preterm. $p = 0.220$. See Table 2.

Underlying and immediate causes of maternal death by sickle cell status

In the recent decade, the MMR among women with SCD was 4.24 times higher than among non-SCD women (Table 3). After excluding deaths due to their sickling disorder, their maternal death risk remained 2.17 times higher. Underlying conditions of significance were direct deaths generally (OR 2.74 [1.6–4.3], $p = 0.0003$), especially the hypertensive disorders of pregnancy (OR 4.27 [1.9–8.5], $p = 0.001$), obstetric emboli (OR 4.82 [1.4–11.5], $p = 0.006$) and obstetric infections (OR 9.9 [1.4–41.5], $p = 0.026$). Respiratory complications were the most significant immediate causes of death (OR 7.8 [4.2–13.6]; $p < 0.0001$). Metabolic derangements (OR 7.72 [2.9–17.9]; $p = 0.0002$) preceding death included renal failure, electrolyte imbalance, dehydration, and hepatic failure. Infectious (OR 4.03 [1.4–9.5]; $p = 0.013$) and cardiovascular processes (OR 4.08 [1.59–9.01]; $p = 0.006$) were other significant immediate causes of death.

Changes in causes of maternal death among women with sickle cell disease over two decades

When outcomes among SCD decedents were compared by decade (Table 4), the upturn in direct deaths (OR

Social, health care and perinatal indicators	2008-17			1998-2007						
	SCD maternal deaths [N=41]	Other maternal deaths [N=337]	P value [χ^2]	SCD maternal deaths [N=42]	Other maternal deaths [N=386]	P value [χ^2]				
<i>Social and obstetric indicators</i>										
Age in years (mean \pm SD, n)	28.4 \pm 6.8 [41]	29.7 \pm 7.1 [337]	0.252	27.4 \pm 5.6 [42]	29.3 \pm 7.1 [386]	0.103				
Gravidity (median [IQR]; n)	3 [1-4]; 37	3 [2-4]; 312	0.933	3 [2-3]; 40	3 [2-5]; 314	0.032				
Parity (median [IQR]; n)	1 [0-2]; 37	2 [1-3]; 312	0.655	1 [0-2]; 40	2 [0-3]; 314	0.005				
Region of residence (n, %)	41	100	337	100	0.837	42	100	385	100	0.076
- South east	18	43.9	170	50.4		28	66.7	175	45.5	
- North east	5	12.2	30	8.9		4	9.5	55	14.3	
- West	8	19.5	63	18.7		4	9.5	59	15.3	
- South	10	24.4	74	22.0		6	14.3	96	24.9	
Highest level hospital in parish of residence (n, %)	41	100	337	100	0.490	42	100	384	100	0.020
- Tertiary care	16	39.0	110	32.6		23	54.8	128	33.3	
- Referral obstetric care	17	41.5	173	51.3		14	33.3	174	45.3	
- Midwifery care	8	19.5	54	16.0		5	11.9	82	21.4	
<i>Health care indicators</i>										
Antenatal (AN) care	38	100	309	100	0.001	35	100	302	100	<0.0001
- None reported	6	15.8	52	16.7		5	13.9	62	20.0	
- Primary health care	9	23.7	135	43.3		6	17.8	105	34.8	
- Hospital, high risk	21	55.3	87	27.9		22	62.9	79	26.2	
- Private doctor	2	5.3	38	12.2		2	5.6	56	18.6	
Referred during pregnancy	32	100	276	100	0.087	31	100	252	100	0.612
- Yes	24	75.0	152	59.4		25	80.6	193	76.6	
- No	8	25.0	104	40.6		6	19.4	59	23.4	
Antepartum admission	34	100	287	100	0.005	42	100	381	100	0.040
- Yes	30	88.2	185	64.5		16	38.1	90	23.6	
- No	4	11.8	102	33.5		26	61.9	291	76.4	
Total AN visits (median [IQR]; n)	4 [2-7]; 37		3 [1-7]; 303		0.467	4 [2-9]; 35		2 [1-4.25]; 302		<0.0001
Place of death	40	100	337	100	0.004	42	100	384	100	0.004
- Intensive care/high dependency unit	13	32.5	39	11.6		13	31.0	42	10.9	
- Tertiary hospital	17	42.5	141	41.8		15	35.7	147	42.8	
- Referral hospital	8	20.0	106	31.5		9	21.4	95	38.0	
- General hospital	1	2.5	21	6.2		3	7.1	69	17.8	
- Home/other	1	2.5	30	8.9		2	4.8	34	8.8	
Post-mortem done	36	100	250	100	0.727	36	100	307	100	0.956
- Yes	32	88.9	217	86.8		28	77.8	240	78.2	
- No	4	11.1	33	13.2		8	22.2	67	21.8	
<i>Infant health indicators</i>										
Gestation at end of pregnancy (median [IQR]; n)	35.2 [28.5-38.0]; 30		36 [25.5-38.0]; 225		0.812	34.5 [27.25-38.0] 34		34 [24.0-38.0]; 312		0.311
Perinatal outcome	40	100	328	100	0.220	38	100	363	100	0.758
- Died undelivered	11	27.5	81	24.7		11	26.3	97	26.7	
- Early foetal loss	2	5.0	49	14.9		4	10.5	64	17.6	
- Stillbirth	5	12.5	48	14.6		5	13.2	53	14.6	
- Preterm livebirth	12	30.0	58	17.7		7	18.4	49	13.5	
- Full-term livebirth	10	25.0	92	28.0		12	31.6	100	27.5	
Birth weight (median, [IQR]; n)	2.51 [1.58-3.03]; 13		2.60 [1.89-3.13] 97		0.425	2.63 [1.87-3.28]; 18		2.68 [1.86-3.27]; 165		0.940
Potentially viable fetuses (\geq 28wks)	25	100	190	100	0.663	23	100	183	100	0.245
- Survived neonatal period	17	68.0	118	62.1		18	78.3	117	63.9	
- Neonatal death/stillbirth	8	32.0	72	38.9		5	21.7	66	36.1	

Table 2: Maternal deaths among women with and without sickle cell disease, by socio-demographic characteristics, access to health care and perinatal outcome: 2008-2017 versus 1998-2007.

Causes of death	Sickle cell maternal deaths		All other maternal deaths		Crude OR (95% CI)	P value ^a
	N	MMR [95% CI]	N	MMR [95% CI]		
All underlying causes of death	41	378.1 [278.9–512.5]	336	89.3 [80.2–99.3]	4.24 (3.03–5.82)	<0.0001
Total excluding blood disorders	21	193.7 [126.7–295.7]	335	89.0 [80.0–99.0]	2.17 (1.36–3.32)	0.001
Medical (indirect) deaths	23	212.1 [141.4–318.1]	108	28.7 [23.8–34.6]	7.40 (4.52 – 11.17)	<0.0001
<i>Non-communicable diseases</i>	21	193.7 [126.7–295.7]	71	18.9 [15.0–23.8]	10.29 (7.16–16.54)	<0.0001
Blood disorders	20	184.5 [119.4–284.7]	1	0.26 [0.04–1.50]	695.6 (128.3–14,570)	<0.0001
Cardiovascular	1	9.2 [1.62–52.2]	35	9.3 [6.7–12.4]	0.99 (0.078–5.16)	0.907
Endocrine	0	–	6	1.6 [0.73–3.48]	–	–
Malignancy	0	–	14	3.72 [2.21–6.04]	–	–
Other NCDs	0	–	15	3.98 [2.41–6.42]	–	–
<i>Non-obstetric infections</i>	2	18.4 [5.06–74.3]	37	9.8 [7.1–13.5]	1.87 (0.30 – 6.57)	0.298
HIV/AIDS	0	–	14	3.72 [2.21–6.04]	–	–
Respiratory infections	2	18.4 [5.06–74.3]	13	3.45 [2.02–5.91]	5.34 (0.81 – 20.85)	0.072
Other infections	0	–	10	2.66 [1.44–4.89]	–	–
Obstetric (direct) deaths	18	166.0 [105.0–262.3]	228	60.6 [53.2–68.9]	2.74 (1.64 - 4.34)	0.0003
Hypertensive disorders	8	73.8 [37.5–145.5]	65	17.3 [13.5–22.0]	4.27 (1.91 – 8.54)	0.001
Obstetric hemorrhage	2	18.4 [5.06–74.3]	51	13.5 [10.3–17.8]	1.36 (0.22 - 4.69)	0.624
Abortive outcomes	1	9.2 [1.62–52.2]	39	10.4 [7.6–14.2]	0.89 (0.04 - 4.60)	0.987
Obstetric infections	2	18.4 [5.06–74.3]	7	1.86 [0.90–3.84]	9.92 (1.41 - 41.57)	0.026
Obstetric embolism	5	46.1 [9.7–107.9]	36	9.5 [6.9–13.2]	4.82 (1.67 - 11.57)	0.006
Other direct	0	–	30	7.9 [5.5–11.3]	–	–
Immediate causes of death	41		336			
Infectious	5	46.1 [19.7–107.9]	43	11.4 [8.4–15.3]	4.03 (1.41 - 9.56)	0.013
Respiratory	16	147.5 [90.8–239.6]	71	18.8 [14.9–23.7]	7.83 (4.42 - 13.24)	<0.0001
Hematologic	4	36.9 [14.3–94.8]	79	21.0 [16.8–26.1]	1.75 (0.54 - 4.38)	0.287
Cardiovascular	6	55.3 [25.3–120.7]	51	13.5 [10.3–17.8]	4.08 (1.59 - 9.01)	0.006
Metabolic	6	55.3 [25.3–120.7]	27	7.1 [4.9–10.4]	7.71 (2.90 - 17.92)	0.0003
Cerebral	3	27.6 [9.4–81.3]	42	11.1 [8.25–14.5]	2.48 (0.60 - 7.15)	0.168
No immediate cause stated	1	9.2 [1.62–52.2]	23	6.1 [4.07–9.16]	1.50 (0.07 – 8.08)	0.638
Estimated births		10 843		376 409		

Table 3: Underlying and immediate cause specific maternal mortality ratios (MMR) per 100,000 livebirths, by sickle cell status, Jamaica: 2008–2017.

^aMid-p exact two-tailed test, Epi-Info Open.

1.78 [0.85–3.80], $p = 0.122$) or the hypertensive disorders of pregnancy (OR 3.16 [0.86–14.7], $p = 0.083$) did not achieve statistical significance. The upward movement in direct deaths among women with SCD was of borderline significance (p [trend]=0.051) when evaluated over four five-year periods while in the non-SCD population indirect deaths also trended up (p [trend]=0.022). See Fig. 3. The only important change in the immediate COD over time was a 2.37-fold increase (CI 1.01–5.87; $p = 0.043$) in terminal respiratory events.

Multivariate analysis

We evaluated the seven social, obstetric and health service variables significantly correlated on univariate analysis with sickle cell status to determine the independent predictors of maternal death among women with SCD compared to those without these conditions. With no differences in outcome over time (Table 4), data for all

twenty years were used. Only two were retained confirming that with 47% ($N = 39/83$) of deaths in women with SCD due to complications of their disorder, they were in total 44% less likely to die from direct complications of pregnancy (95% CI 0.24–0.81; $p = 0.009$) than women without these genetic anomalies. After accounting for source of antenatal care, pre-delivery admission and number of antenatal visits, the only health service variable of import was that women with SCD were more than three times as likely (OR=3.37 [1.17–9.71]; $p = 0.024$) to die in an ICU or HDU than a general hospital. See Table 5.

Discussion

Across Jamaica between 2008 and 17, women with SCD were 4.24 times more likely to die in association with pregnancy than women without these disorders, with a

Underlying and immediate causes of death	2008-2017		MMR	1998-2007		MMR	Crude OR (95% CI)	P value ^b
	N	%		N	%			
All underlying causes of death	41	100	378.1	42	100	326.3	1.16 (0.75 - 1.78)	0.572
Total, excluding blood disorders	21	51.2	193.6	18	42.8	139.8	1.38 (0.73 - 2.63)	0.314
Medical (indirect) causes	23	56.1	212.1	30	71.4	233.0	0.91 (0.52 - 1.56)	0.739
NCDs	21	51.2	193.6	26	61.9	202.0	0.95 (0.53 - 1.70)	0.890
Blood disorders	20	48.8	184.4	24	57.1	186.4	0.98 (0.53 - 1.79)	0.975
Cardiovascular	1	2.4	9.2	1	2.4	7.8		
Other indirect	0	-	-	1	2.4	7.8		
Non-obstetric infections	2	4.9	18.4	4	9.5	31.1	0.59 (0.07-3.46)	0.581
HIV/AIDS	0	-	-	3	7.1	23.3		
Respiratory infections	2	4.9	18.4	0	-			
Other non-obstetric infections	0	-	-	1	2.4	7.8		
Obstetric (direct) causes	18	43.9	166.0	12	28.5	93.2	1.78 (0.85 - 3.80)	0.122
Hypertensive disorders of pregnancy	8	19.5	73.8	3	7.1	23.3	3.16 (0.86 - 14.76)	0.083
Obstetric haemorrhage	2	4.9	18.4	3	7.1	23.3	0.79 (0.09 - 5.32)	0.825
Abortive outcomes	1	2.4	9.2	3	7.1	23.3	0.39 (0.01 - 3.71)	0.466
Obstetric infections	2	4.9	18.4	0	-			
Obstetric embolism	5	12.2	46.1	2	4.8	15.5	2.96 (0.58 - 22.1)	0.201
Other direct	0	-	-	1	2.3	7.8		
Immediate causes of death	41	100		42	100			
Infectious	5	12.2	46.1	10	23.8	77.7	0.59 (0.18 - 1.72)	0.352
Respiratory	16	39.0	147.6	8	19.0	62.1	2.37 (1.02 - 5.87)	0.043
Hematologic	4	9.8	36.9	8	19.0	62.1	0.59 (0.15 - 1.96)	0.410
Cardiac	6	14.6	55.3	7	16.6	54.4	1.01 (0.32 - 3.14)	0.970
Metabolic	6	14.6	55.3	4	9.5	31.1	1.78 (0.48 - 4.31)	0.387
Cerebral	3	7.3	27.7	4	9.5	31.1	0.89 (0.16 - 4.31)	0.895
No immediate cause stated	1	2.4	9.2	1	2.3	7.8	1.18 (0.03-46.3)	0.914
Estimated births	10 843	12 873						

Table 4: Changes in the underlying and immediate causes of maternal death among women with sickle cell disease over two decades, Jamaica: 2008-17 and 1998-2007, MMR^a per 100,000 live births

^a Maternal mortality ratio
^b Mid-p exact two-tailed test, Epi-Info Open.

persistent 2.17-fold risk after complications of their blood disorders were excluded as these disorders profoundly alter the physiology of their circulatory, respiratory, and immune systems. The multivariate analysis confirmed their higher risk of indirect death due to sickle cell crises and the greater need for intensive or high dependency care to manage these complications in pregnancy.

When pregnancy outcomes among the latest SCD decedents were compared to women from the Jamaican sickle cell birth cohort, experiences were remarkably similar. Lewis et al. report that of 163 non-terminated pregnancies, 57% ($n = 93$) resulted in live births,¹³ which is comparable to the 55% of live births in the latest series. Some variation in global maternal and perinatal mortality rates may be due to differences in SCD genotypes, other co-morbidities, maternal age and parity however in both developed and developing countries risk differences are similar between SCD and non-SCD women.^{27,28} Where close foetal monitoring occurs during labor, with timely intervention, no excess risk of

foetal mortality has been noted,²⁵ however MMRs six times higher than in the non-SCD population have been noted.²⁹ The still-birth rate of 12.5% among our SCD maternal deaths is similar to the 10% observed by Thame et al. (2007) among Jamaican SCD mothers who survived.³⁰

Pregnancy outcomes have not improved for Jamaican women over two decades regardless of sickle cell status, with direct deaths trending upward for women with SCD. Among non-pregnant women of reproductive age, obesity prevalence increased with age from 29% among adolescents to 80% for women 35 years and older.³¹ The prevalence of overweight and obesity in SCD is also on the rise,³² including in Jamaica,³³ and its effects on pregnancy related morbidity and mortality will need to be monitored closely. As more women delay childbearing, they are also more likely to present in pregnancy with cardiovascular and metabolic disorders, such as the hypertensive disorders of pregnancy, thromboembolic disorders, heart disease and diabetes mellitus.²⁰

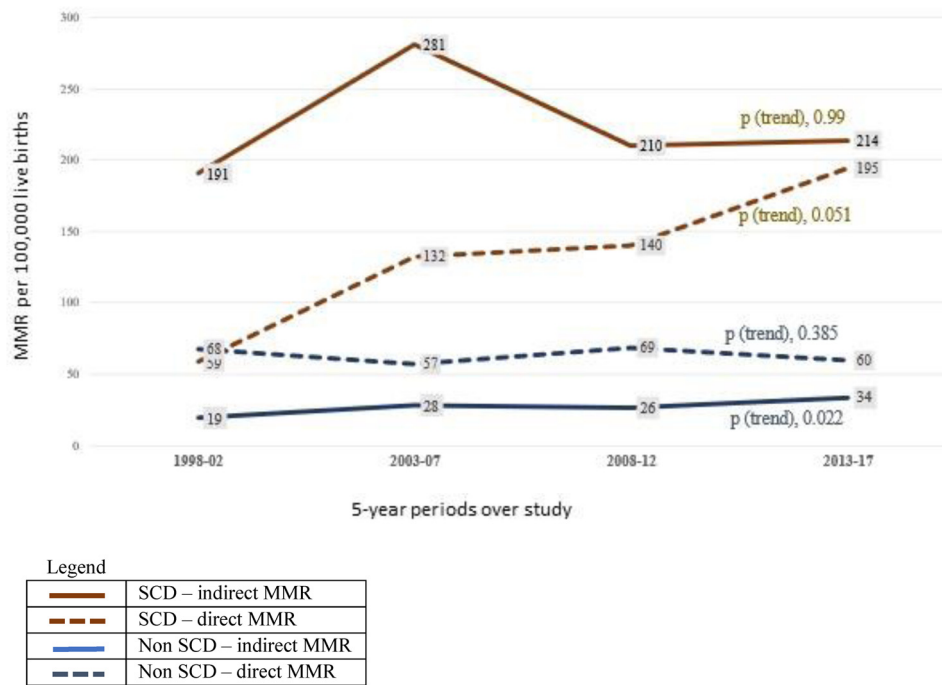


Figure 3. Direct and indirect maternal mortality trends, by sickle cell status: Jamaica, 1998–2017 maternal mortality ratios (MMR) per 100,000 live births.

Variable ^b	Odds Ratio	95% confidence interval	P value
Category of maternal death			
- Indirect	1 (ref)		
- Direct	0.44	0.24 – 0.81	0.009
Place of death			
- General hospital	1 (ref)		
- Referral hospital	1.15	0.45 – 2.97	0.767
- ICU/HDU	3.37	1.17 – 9.71	0.024

Table 5: Demographic and health service factors associated with risk of maternal death among women with sickle cell disease compared to women not known to have these disorders,^a Jamaica: 1998–2017.

^aCases with complete information included in the model: sickle cell disease (69%, 57/83); women not known to have sickle cell disease (64%, 461/723).

^bVariables entered: maternal age, parity, source of antenatal care, antepartum admission, category of maternal death [direct vs indirect] and place of death as categorical variables; and number of antenatal visits as continuous.

Black women are 3–4 times more likely to die of pregnancy related deaths compared to white women³⁴ and the presence of SCD may partially explain this elevated maternal mortality. Global strategies to improve outcomes among persons with sickling disorders are further plagued by barriers and ethical issues.³⁵ Social and economic impediments to equitable, high quality care especially present challenges for populations of African ethnicity. In settings where drug abuse co-exists with structural racism and poverty, the need for opioids to manage pain is often met with resistance.³⁶ On the other hand, opioid related disorders have been described to be higher among SCD pregnant woman than in those

without SCD and significantly impact maternal sepsis and other pregnancy outcomes.³⁷

Where community prevalence is high, newborn or school-age screening enable early identification, access to specialist care and appropriate management, improving both child survival and prevalence.³⁸ Providing information on genetic risk to carriers (sickle cell trait) may allow informed reproductive choice including pregnancy avoidance, prenatal genetic diagnosis, and the difficult decision to terminate an affected foetus. While England, Wales and Scotland offer antenatal screening for sickle cell disease and thalassemia to women whose families originated outside of northern Europe and the

United Kingdom (including Africa, the Caribbean and South Asia),³⁹ one study found that only 64% of fathers presented for partner screening, limiting informed reproductive choice prenatally.³⁵ In Jamaica, knowledge of one's status and subsequent counselling showed no effect on choice of partner.³⁸

Routine antenatal screening in low-income countries is variable but more consistent in high income settings. Screening early in pregnancy enables referral for appropriate care, which needs to be sensitive to local culture, values, and beliefs. Genetic screening of partners is offered but not well accepted in Jamaica, and prenatal genetic diagnosis is rare. Birth of affected children to sickle cell trait (AS) couples may stimulate future reproductive choice counselling. Where medical termination of pregnancy is either unavailable or unacceptable, ethical care and maternal survival require access to high quality antenatal, intrapartum and postpartum care.

While population prevalence of SCD in Jamaica is estimated below one percent, based on newborn screening,⁴ the average prevalence of 2.8% in the antenatal population is of interest. Given Jamaica's relatively low total fertility rate (TFR) of 2.0 in 2021,⁴⁰ but more adverse perinatal outcomes among women with SCD, these women may be attempting pregnancy more often to achieve a live birth. The higher SCD prevalence among residents of the southeast (SE) region (3.9%) versus 1.3–2.8% in the other three regions (See Appendix 1) may reflect migration into this region to access the specialist Sickle Cell Unit at the UHWI. Brazil also reports wide variations in SCD and mortality across their five geographic regions.^{41,42} These variations may simply reflect and correlate with historical agrarian economic activity where descendants of African servitude settled.

Jain et al. (2019) suggest that SCD affects fertility through delayed menarche, chronic inflammation, oxidative stress and lower levels of female hormones.⁴³ The non-persistence of fertility differences between women with and without SCD from the first decade must be interpreted against a backdrop of replacement fertility. In the United States, Barfield et al. also did not observe any parity differences.⁴⁴ In the Congo however, lower fertility (gravidity) and fecundity (parity) are evident in a setting where the TFR is 5.9.²⁷

Pregnancy in women with SCD requires multi-disciplinary co-management by a sickle cell expert (or hematologist) and a MFM specialist, with a paediatrician to advise on and manage perinatal complications. These and other inexpensive interventions such as routine monitoring of oxygen saturation can improve neonatal and maternal survival even in low resource settings.⁴⁵

The antenatal team can anticipate increased occurrence of painful crises, venous thromboembolism (VTE) and infections, alongside pregnancy complications such as preeclampsia/eclampsia, preterm labor,

prematurity, intra-uterine growth retardation (IUGR), and fetal demise. The relative risk of 2.42 (1.75–3.39) for preeclampsia among women with SCD in the UK⁴⁶ is within our estimate of 4.27 (1.91–8.54); $p = 0.001$. With respiratory conditions and sepsis⁵ a large component of morbidity and mortality, pneumococcal prophylaxis including vaccinations should be considered in the antenatal care package. Despite the risk of VTE in this population,⁴⁷ there is little evidence on the prophylactic use of anticoagulant agents in pregnancy.

Therapeutic interventions have evolved beyond managing painful crises to include curative procedures such as bone marrow transplant, gene therapy, and gene editing. Given the systematic inequity endured by the affected population, many of these novel strategies will be beyond their reach, especially in developing countries.³⁶ A systematic review by Sins et al. of controlled clinical trials of pharmaco-therapeutic interventions to reduce VOCs in SCD patients found that the most promising interventions to reduce VOC frequency or hospitalizations were the oral antioxidants L-glutamine and ω -3 fatty acids, and the intravenous antiadhesive agent, crizanlizumab. Due to intervention heterogeneity however, no meta-analysis could be performed to measure possible benefits.⁴⁸ Neither L-glutamine nor crizanlizumab are available in Jamaica, however.

Blood transfusions used to treat acute anemia, acute chest syndrome or stroke have insufficient evidence to recommend their prophylactic use in SCD pregnancies,⁴⁹ however Whittington et al. indicate advantages of not delaying use until an emergency occurs.⁵⁰ A retrospective review of Burkina-Faso women who (a) received at least one exchange transfusion, (b) required an emergency blood transfusion, or (c) had no transfusion at all, found that of 164 women (53, 32 and 79 respectively), third trimester pregnancy complications were less prevalent ($p < 0.0001$) in the exchange transfusion (58.5%) than the emergency transfusion (78.5%) or no transfusion group (91.1%). Maternal mortality was also lower (5.7%; 12.5%; 12.6%; [$p = 0.009$] respectively). Preterm birth and early neonatal death were less common in the first group (15.1%; 1.8%) than the second (40.6%; 23.1%) or third (32.9%; 7.6%). They concluded that prophylactic blood transfusion should be considered in managing pregnant women with SCD.⁵¹ One intervention requiring large scale clinical trials is the therapeutic use of erythrocytapheresis during pregnancy which has shown benefit.⁵² The BASCARE (Baskent Sickle Cell Medical Care Development Program) program in Turkey reported that no foetal or maternal deaths occurred in pregnancies where carefully conducted prophylactic automatic erythrocyte exchange was employed.⁵³ Ogu and colleagues and Sins et al. highlight the burden of maternal complications in SCD and the relatively small number of clinical trials objectively evaluating strategies to improve outcome.^{36,48}

Evidence-based clinical guidelines need to be developed and tested to ensure they improve maternal and perinatal outcome prior to national implementation. They should address primary, secondary and tertiary prevention for women with chronic co-morbidities. Gaps in care speak to the need for the sustained implementation (development, equipment, staff, training, supplies) of maternal-foetal medicine units (MFMUs) which address:

1. Primary prevention:
 - a. Pre-conception counselling
 - b. Health promotion of evidence-based strategies to reduce the occurrence of VOCs, VTE, infections (medical and obstetric)
 - c. Postpartum contraceptive services.
2. Secondary prevention:
 - a. Pre- and postnatal multi-disciplinary care, supported by weekly meetings of senior representatives from obstetrics (MFM), hematology, neonatology, intensive care and other specialists relevant to the optimal management of women under care. For each case, a comprehensive care plan should be outlined to guide optimal outcomes for mother and baby.
 - b. Comprehensive health promotion to ensure that women recognize and act on early signs and symptoms of developing preeclampsia/eclampsia, VTE and infection. Messages must include where to seek timely and appropriate care.
 - c. Services should continue into the extended postpartum period (beyond the usual six weeks) until women can be effectively re-integrated into the general health system.
3. Tertiary prevention:
 - a. Joint management by MFM obstetricians, intensive care and other consultants as indicated, to oversee care of women needing high dependency and intensive care.
 - b. Intensive review of all adverse maternal and perinatal outcomes to address avoidable factors.

Although women with SCD largely benefit from care and delivery at tertiary facilities, the quality and consistency of care may be negatively impacted by human, technical and infrastructural resource limitations due to financial constraints and high turnover of managerial and professional staff, especially doctors and ICU nurses. Access to a social worker to address non-clinical needs, will ensure sustained improvements in outcomes.

The study explores maternal deaths among women with SCD. We may have missed some community deaths, but this was unlikely for hospital deaths. Some

cases may have been misclassified, under-estimating their mortality experience. Results speak only to women who died; some of the experience of mothers who survived their pregnancy may be different. For the 1998–2007 study there was greater uncertainty in the estimated population at risk, we only had access to UHWI prevalence data however public sector data were available for this study. This limits the comparability of the risk ratios between the two studies. We however recalculated risk ratios for the earlier period and included them in this report.

Women who died from SCD in Jamaica between 2008 and 17 were more likely to be admitted antepartum than women in the previous decade. Compared to women without SCD, they were at higher risk of death from direct causes such as preeclampsia/eclampsia and obstetric embolism as well as both obstetric and non-obstetric infections, despite access to high-risk AN clinics, delivery in referral hospitals and greater access to ICU/HDU care. The growing prevalence of obesity, which increases with age among childbearing women who increasingly delay childbearing, must be addressed within the care strategies.^{4†}

Management by regional specialist multi-disciplinary teams is recommended to improve the effectiveness of care for reproductive age women with chronic diseases. Teams should include disease-specific consultants, including haematologists for women with SCD. Targeted newborn screening is recommended to identify children with SCD born to the 10% of parents who carry the trait to promote their successful development.

Declaration of interest

We the authors have no conflicts of interest.

Data sharing statement

Deidentified data may be shared on approval by the MOHW, Jamaica; and the Ethics Committee of the University of the West Indies, Mona, on submission of a Data Use Agreement specifying the uses of the data to be shared.

Funding

This study received no external funding.

Authors' contributions

MA conceptualized the paper in collaboration with AM-B. AH, L-AJ and LC participated in the data compilation, regional and national reviews of cases. AM-B and MA analysed the data and prepared the first draft. All authors contributed to the interpretation of the results and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101238.

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