Trends in maternal deaths from epilepsy in the United Kingdom: a 30-year retrospective review

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Abstract

Objective: Neurological diseases remain the second most common cause of maternal mortality from indirect causes, according to the last United Kingdom confidential enquiry into maternal death. The maternal mortality rate from epilepsy is reported as 0.61 per 100,000 maternities. The aim of this study was to analyse the trends and causes of maternal death from epilepsy in the UK over the last 30 years. Information on sub-standard care associated with fatalities was also consolidated to inform guidance and clinical care by obstetricians and physicians caring for pregnant women with epilepsy.

Study design: A retrospective review of 10 triennial confidential enquiry into maternal death reports (1979–2008) was performed, encompassing 21,514,457 maternities. Late and coincidental deaths were not included in the analyses.

Results: Between 1979 and 2008, there were 92 maternal deaths from epilepsy. The proportion of total maternal deaths from epilepsy over 30 years is 3.7% (95% CI 3.0–4.5), which showed an increasing trend. Sudden unexpected death in epilepsy remains the single greatest cause of maternal death from epilepsy followed by aspiration of gastric contents during seizures and drowning during bathing.

Conclusion: All women with epilepsy should be looked after by specialist combined obstetric and medical or neurological teams in pregnancy to improve maternal and fetal outcomes.

Keywords

Maternal mortality, high-risk pregnancy, neurology

Introduction

According to the last United Kingdom confidential enquiry into maternal death (CEMD) report, 261 women died directly or indirectly related to pregnancy, with a mortality rate of 11.39 per 100,000 maternities.¹ The maternal death rate in the UK has decreased dramatically over the last three decades, despite the challenges of rising birth rates, maternal age and co-morbidities. This has been due to an impressive reduction in deaths from direct obstetric causes, including obstetric haemorrhage, ectopic pregnancy and venous thromboembolism. However, there has been a significant increase in deaths from indirect causes such as pre-existing or new onset medical and psychiatric conditions. The leading cause of maternal death remains cardiac disease; the second is neurological disease. Even with improving nationwide surveillance of maternity services, childbearing women are still subject to short- and long-term morbidity and mortality, of which epilepsy can be one of the most devastating.

Although epilepsy is often thought of as a relatively benign disease, it carries a 20-fold increased risk of sudden death compared with the general population.² Sudden unexpected death in epilepsy (SUDEP) is defined as “the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death of a patient with epilepsy with or without evidence of a seizure, excluding documented status epilepticus, and in which postmortem examination does not reveal a structural or toxicological cause of death”.³ Accepted practice is to classify all such deaths when there has been an autopsy as ‘definite SUDEP’ and those in which there has been no autopsy as ‘probable SUDEP’. A general population-based study of SUDEP observed an incidence of 0.35 per 1000 person-years,² with much higher rates in intractable cohorts.⁴ In patients with chronic refractory epilepsy who attend epilepsy referral centres, SUDEP is the leading cause of premature death, accounting for 10–50% of all deaths.^{5–12} It is not known whether pregnancy increases the risk of SUDEP. There is a surprising lack of awareness among patients and healthcare professionals of this increased risk of sudden death.

Adab et al.¹³ estimated a 10-fold increase in mortality in pregnancy in the UK in women with epilepsy (WWE) compared to women without epilepsy in pregnancy, but data is limited.

The aim of this study was to analyse the trends and causes of maternal death from epilepsy in the UK over the last 30 years. Information on sub-standard care associated with fatalities was also consolidated to inform guidance and clinical care by obstetricians and physicians caring for pregnant women with epilepsy.

Methods

A retrospective review of 10 triennial CEMD reports was performed, encompassing the 30-year period from 1979 to 2008.^{1,14–22} The 10th revision of the International Classification of Diseases, Injuries and Causes of Death (ICD 10) defines a maternal death as ‘the death of a woman while pregnant or within 42 days of termination of pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes’. The current system of confidential enquiries started in 1952, just 4 years after the inception of the National Health Service (NHS). Before that, maternal deaths were reported to the Ministry of Health on an ad hoc basis. From 1985 to 1987 onwards, a single report was published triennially for the whole of the UK. For the first time in 1988, statistics were calculated using total number of maternities (not births). Maternities are defined as the number of pregnancies that results in a live birth at any gestation or stillbirths occurring at or after 24 completed weeks of gestation and are required to be notified by law. The report stated that change in the denominator did not have a large effect on resulting comparison statistics. Since the introduction of a new Office for National Statistics (ONS) computer program in 1993, all conditions given anywhere on the death certificate are now coded,

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enabling a more extensive search of death entry information to identify all conditions listed that suggest a maternal death. In the past, this has helped in improving case ascertainment, with a number of previously unreported deaths being identified. The ONS does not service Scotland; instead, cases are ascertained from the General Register Office for Scotland, the Reproductive Health Programme of NHS Quality Improvement Scotland and the clinical community.

The main objective of the CEMD has been to monitor causes of maternal death, improve safety and reduce mortality using a system of anonymized case records and regional and national assessors, with review, standardization and recommendations. In the CEMD, all cases are reviewed by expert panels. Determinations of causes of death include data from coroners' postmortem reports. Maternal mortality rate (MMR) is calculated as the number of direct and indirect deaths per 100,000 maternities.

All of the CEMD reports from the last 30 years were examined for the incidence and cause of maternal death from epilepsy in UK. We also looked at other parameters including timing of maternal death, anti-epileptic drugs (AED) used, pre-pregnancy counselling and referral to specialist service during pregnancy; however, full information regarding these factors was only available in the most recent CEMD

report. Late and coincidental maternal deaths from epilepsy as well as women who died with epilepsy but whose primary cause of death was due to another morbidity were excluded from analysis, in order to calculate proportional maternal epilepsy deaths in parallel with CEMD maternal mortality ratios. We were then able to look for trends in epilepsy deaths in pregnancy. This methodology has previously been successfully used to look at deaths from cerebrovascular events in pregnancy.²³

Results

Between 1979 and 2008, out of 21,514,457 maternities, there were 92 maternal deaths from epilepsy. The rate of maternal death from epilepsy is 0.43 per 100,000 maternities. The proportion of total maternal deaths from epilepsy over 30 years is 3.7% (95% CI 3.0–4.5), which showed an increasing trend. The numbers and rates of death are shown in Table 1.

SUDEP was the single greatest cause of maternal death from epilepsy, particularly in the last 15 years followed by aspiration of gastric contents during seizures and drowning during bathing (see Table 2). Causes of maternal death were not documented in 15 cases.

Table 1. Maternal death from epilepsy in the UK (1979–2008).

Year	Maternities	Maternal deaths	Deaths from epilepsy	Percentage of epilepsy-related deaths/maternal deaths	Rate of epilepsy-related deaths per 100,000 maternities
2006–2008	2,291,493	261	14	5.36	0.61
2003–2005	2,114,004	295	11	3.72	0.52
2000–2002	1,997,472	261	13	4.98	0.65
1997–1999	2,123,614	242	9	3.71	0.42
1994–1996	2,197,640	268	19	7.08	0.86
1991–1993	2,315,204	228	6	2.63	0.25
1988–1990	2,360,309	238	9	3.78	0.38
1985–1987	2,268,766	223	3	1.34	0.13
1982–1984	1,903,096	209	7	3.34	0.36
1979–1981	1,942,859	268	1	0.37	0.05
Total	21,514,457	2493	92	3.7 (95% CI 3.0–4.5)	0.43

Source: Confidential Enquiries into Maternal Death.

Table 2. Causes of maternal death from epilepsy in the UK (1979–2008).

Year	SUDEP	Hypoxic brain injury	Trauma	Bathing	Aspiration of Stomach contents	Acute asphyxia	Cardio-respiratory failure	Not documented
2006–2008	11	1	1	1				
2003–2005	6							5
2000–2002	4 (+5 ^a)				3			1
1997–1999	1 (+2 ^a)	1		3	1			1
1994–1996	9			1	9			
1991–1993				1	1		2	2
1988–1990					4		1	4
1985–1987		1						2
1982–1984				2	1	2	2	
1979–1981		1						
Total	38	4	1	8	19	2	5	15

SUDEP: sudden unexpected death in epilepsy.

^aPossible SUDEP.

Source: Confidential Enquiries into Maternal Death.

Table 3. Timing of maternal death from epilepsy during pregnancy and postpartum in UK (1979–2008).

Year	During pregnancy					Post delivery/miscarriage/TOP
	Total	First trimester	Second trimester	Third trimester	Not documented	
2006–2008	9				9	5
2003–2005 ^a						
2000–2002 ^a						
1997–1999	7	2	4	1		2
1994–1996	14	3	1	10		5
1991–1993	6	0	0	3	1	2
1988–1990	8	1	1	4	2	1
1985–1987	3	0	1	2		0
1982–1984	2	0	1	1		4
1979–1981	1	0	0	1		0

^aNot recorded.

Source: Confidential Enquiries into Maternal Death.

The concept of SUDEP was first mentioned in the 1994–1996 CEMD report.¹⁹

The majority of the deaths occurred during pregnancy, particularly in the third trimester, as shown in Table 3. However, one-third of the maternal deaths in the most recent CEMD report occurred postpartum.

It was difficult to calculate the proportion of maternal death from epilepsy, who had sub-therapeutic levels of anti-convulsants in their blood during pregnancy and at the time of death, as there was no common quantitative denominator across the CEMDs. In the last triennium,¹ 9 of the 14 women who died from epilepsy were taking lamotrigine. Blood levels were not checked during pregnancy for any of these women, although the lamotrigine dose was increased in three. Comprehensive data was not available in the previous CEMD reports on how many women had anti-convulsant blood levels monitored during pregnancy or measured at the time of death, how often they were performed during pregnancy and whether the levels were in the therapeutic range or not. The reports also lack data on the type of AEDs prescribed for these women. However, it has been highlighted repeatedly in several CEMD reports that in the majority of women, no action has been taken even if the drug levels were found to be sub-therapeutic. In most women where anti-convulsant levels were checked at the time of death, they were found to be either sub-therapeutic or not detectable.

The role of autopsy including histology of any tissues and ancillary blood tests to identify anti-convulsant and other drugs is crucial in establishing the cause of death in these patients and is particularly important in the case of SUDEP to address the critical question of alternative diagnoses to epilepsy. In the last CEMD report,¹ all women with epilepsy had autopsies by approved methodologies. These were not quantified in the older reports and no data is available on what proportion of women with epilepsy had autopsies in comparison to the total number of autopsies undertaken during that time period.

Several CEMD reports have emphasized that women with epilepsy should be referred for pre-pregnancy counselling and have specialist care in pregnancy from a consultant obstetrician and a neurologist or physician with interest in epilepsy and pregnancy. In spite of major developments in NHS in the last 30 years, there has been little improvement in this area with only 6 of the 14 women with epilepsy received pre-pregnancy counselling and of the 11 women who had sought antenatal care, only 6 were referred to a healthcare provider with an interest in epilepsy according to the last triennial report.¹ These were not quantified in the previous reports.

It was not possible to calculate the percentage of maternal deaths from epilepsy, which were due to sub-standard clinical care, as these were reported sporadically across the CEMDs. The most common themes commented on by the CEMD reports were failure to recognize

the need for referral to specialist service, inadequate treatment with AEDs and a lack of appropriate follow-ups.

Discussion

This is the largest study reviewing the trends and proportion of maternal death from epilepsy from the longest uninterrupted series of enquiries into maternal deaths, encompassing over 21 million maternities between 1979 and 2008. Although rare, 3.7% (approximately 1 in 27) of maternal deaths were attributable to epilepsy. The number of women with epilepsy among the 2,291,493 maternities is unknown. Use of an observed rate of approximately 0.6%^{24,25} based on studies in the UK gives an estimated death rate from epilepsy among women with epilepsy (mostly SUDEP) during or shortly after pregnancy of the order of 1 per 1000 women. As previously calculated, this is approximately 10 times higher than in women without epilepsy.²⁶

The MMR and the proportion of maternal death from epilepsy have increased gradually over the last three decades. This may represent a rise in epilepsy-related deaths or may be a reflection of improved case ascertainment. It is in keeping with the worrying trend identified in the most recent CEMD report.¹ The report states that most maternal deaths in the UK now occur in women with pre-existing or new onset medical and psychiatric conditions ('indirect causes'). The leading cause of maternal death remains cardiac disease; the second is neurological disease. The number of maternal deaths due to indirect causes has significantly increased over the last two decades. Furthermore, most of these deaths are associated with sub-standard care and in one-third of cases this is classified as major sub-standard care, where different care might have prevented death of the mother.

Our study revealed that SUDEP is by far the commonest cause of maternal death from epilepsy in the last 15 years. This is also the commonest cause of death amongst the general population with epilepsy and the epidemiological studies showed that it occurs most commonly in patients with chronic epilepsy with poorly controlled seizures. Although SUDEP has been recognized since the 19th century, only in the past two decades has the full extent and risk of this event been established. Thus it is likely that SUDEP was under-reported in the earlier years of the confidential enquiry and not necessarily registered as an epilepsy-related death. SUDEP usually occurs when the seizures are not witnessed and often at night. Several different mechanisms probably exist and most research has focused on seizure-related respiratory depression, cardiac arrhythmia, cerebral depression and autonomic dysfunction. Data from a pooled analysis of risk factors indicate that the higher the frequency of tonic-clonic seizures, the higher the risk of SUDEP. Furthermore, risk of SUDEP is also elevated in male patients,

patients with long-duration epilepsy and those on polytherapy for epilepsy. It is not known whether this risk is further increased during pregnancy. SUDEP is uncommon in those with good seizure control. More knowledge and awareness is needed surrounding this area among healthcare professionals and the general population.

Drowning during bathing is the third most common cause of maternal death from epilepsy in our study. Some women with epilepsy or undiagnosed syncope are still unaware of the very rare but real risk of drowning while bathing unattended. A shower is preferable and the bathroom door should remain unlocked.¹ Although most women with epilepsy are aware of this, pregnancy gives an opportunity for this to be re-emphasized, often together with discussions about issues related to parenting including not bathing their baby alone.²⁷

Overall, the majority of the deaths occurred during the third trimester and this trend has not changed over the last 30 years. The high proportion in the third trimester is likely to be due to multiple factors, such as the sleep deprivation and reduction in AED levels.

Failure to measure AED levels in maternal blood has been reported in several CEMD reports. It is clearly established that free drug levels of many AEDs falls in all three trimesters of pregnancy because of altered pharmacokinetics, which includes increased plasma volume and enhanced renal and hepatic drug clearance. These changes are particularly marked with lamotrigine use during pregnancy. Compared with other AEDs used as monotherapy, women exposed to lamotrigine monotherapy in pregnancy were more likely to have deterioration in seizure control from the first to the second or third trimesters and more generalized tonic-clonic seizures (GTCS) potentially related to reduced drug levels.^{28–31} The other possibility is that lamotrigine for some women is inferior to other AEDs (especially valproate) in controlling GTCS. These would suggest the possibility that lamotrigine may be associated with epilepsy-related death in and around pregnancy; however, conversely, there appears not to have been any consistent increase in such deaths in parallel with the increasing use of the drug. Between 1993 and 2008, there was a substantial increase in the use of lamotrigine from 2% to 17%.³² The National Institute for Health and Clinical Excellence (NICE) recommendations regarding the treatment of epilepsy²⁷ advice that routine monitoring of anti-convulsant levels is not recommended in pregnancy but with the important caveat that monitoring of anti-convulsant drug levels may be useful for dose adjustment if seizures increase or are likely to increase. It has been recommended in the last CEMD report that all health care professionals caring for women with epilepsy in pregnancy should be aware of the likely fall in lamotrigine levels in pregnancy and that they should take account of this in their management plans.¹

AED levels in blood at autopsy were either sub-therapeutic or undetectable in most women who died from epilepsy. It is difficult to draw conclusions from these small numbers, especially as epilepsy is controlled by clinical response to therapy and not by the drug levels; but it is possible that some mothers are stopping their medications against medical advice because they were anxious about congenital fetal malformations or are non-compliant because of complex social circumstances. From this study, it is difficult to conclude whether there is a strong correlation between drug levels during pregnancy or immediate postpartum period and at autopsy as only a few women had their drug levels measured during pregnancy and at the time of death.

This study has highlighted the repeated failure to refer these potentially high-risk women to specialist combined obstetric and medical or neurological service as early in pregnancy as possible, despite the recommendation of several CEMD reports. CEMD has defined this as sub-standard care; however, it should be noted that no strong evidence exists showing improved outcomes with such care. The reasons for failure to refer are likely to be multiple. In some cases the obstetric and midwifery team do not appear to have perceived maternal epilepsy as a high-risk condition. In addition, medical care is advancing rapidly and patterns of the delivery of care in the UK have changed over the years.¹ It has also been acknowledged that it may be very difficult to treat these women effectively even in a specialist clinic as many of them will have difficult and complex social circumstances that were likely to cause them to be

excluded from mainstream healthcare provision.¹ Healthcare providers should be aware that women with epilepsy who also live in difficult social circumstances are at particular risk of poor seizure control and require additional effort to ensure their disease is well controlled.

Considering pre-pregnancy counselling, while there is an intuitive feeling that such counselling will be beneficial, again there is limited evidence supporting this. Obstetricians and midwives alone cannot reduce epilepsy-related maternal deaths; they need support from physicians and general practitioners. An expansion in the number of obstetric physicians could potentially be a positive step towards reducing deaths from medical disorders in pregnancy, with their knowledge of both medical conditions and physiological changes in pregnancy.³³

Limitations of the CEMD are that it does not report denominator data or morbidities from epilepsy and hence it is not possible to estimate case-fatality ratio. Also, the CEMD might have underestimated deaths prior to the introduction of a standardized case ascertainment system. Only since 1993 has specialized ONS computer software been available to match death records of women of fertile age living in England and Wales with birth registrations up to 1 year previously. This allowed links between birth and death notifications to be highlighted, thus avoiding missed recognition of some maternal deaths, particularly towards the end of the puerperium, which might not previously have been reported to maternity teams or otherwise wrongly coded at death certification. It was also difficult to analyse the numerical trends as older reports do not have the same degree of detail about pre-pregnancy counselling, referral to specialist service, anti-convulsant levels and autopsies.

In conclusion, this is the largest study to date examining the incidence of epilepsy and the proportion of maternal deaths attributed to epilepsy in the UK. While rare, epilepsy accounted for 1 in 27 UK maternal deaths over 30 years. The incidence of maternal death from epilepsy has increased over the last 30 years, which might reflect a mismatch between women's services and increasing maternity challenges. Sub-standard care features especially in regard to lack of referral to specialist service, inadequate treatment with anti-convulsants and appropriate follow-ups. All women with epilepsy should be looked after by specialist combined obstetric and medical or neurological teams in pregnancy to improve maternal and fetal outcomes.

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Ethical approval

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Guarantor

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Contributorship

DK was involved with reviewing the CEMACE reports, data collection, interpretation of results and writing the manuscript. SW reviewed the draft and approved the final version of the manuscript.

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