Maternal deaths in the UK: pre-eclampsia deaths are avoidable

Being pregnant in the UK has never been safer. The latest Confidential Enquiries into Maternal Deaths and Morbidity\(^1\) reported that fewer than one in 10,000 women died in or around pregnancy in the UK during 2012–14 (241 women within the triennium), the lowest rate recorded since such surveillance began in 1952 in England and Wales. This maternal mortality rate is lower than age-matched male death rates (5–17 per 10,000 population for men aged 20–44 years in England and Wales, 2014) such that a man is more likely to die while his partner is pregnant than she is.\(^2\)

Several important messages emerge from the latest Confidential Enquiries into Maternal Deaths and Morbidity: cardiac disease is the leading cause of indirect maternal death, while thrombosis and thromboembolism continues to feature as a major issue and is the leading cause of direct deaths. Suicide is, however, the leading cause of direct maternal deaths within a year after the end of pregnancy.\(^1\) Two-thirds of maternal mortality is due to a medical or mental health condition. Therefore, the need for specialist care for women with pre-existing medical and mental health problems is clearly still a vital concern.

In addition to ongoing surveillance of triennial maternal deaths, the report examined deaths related to cardiovascular and hypertensive diseases, early pregnancy problems, and critical care between 2009 and 2014. Indirect maternal deaths, related to underlying conditions exacerbated by pregnancy, are increasingly important and now represent 59% of total maternal deaths; 153 women died from heart disease between 2009 and 2014, representing about a third of all maternal deaths.\(^2\) Specialist multidisciplinary care for women with known heart disease, particularly with prosthetic valves, together with prompt action when women present with chest symptoms or breathlessness remain key to avoiding further deaths. Health-service provision must also focus on pre-pregnancy counselling, and uptake of contraception and provision of termination services to limit future mortality among women with known heart disease. Other causes of death both indirect and direct (resulting from obstetric complications of pregnancy) have been stable, with the exception of pre-eclampsia, which has substantially reduced since the last report and is now the least represented category (figure).

Only two women died from pre-eclampsia and eclampsia during pregnancy in the UK during 2012–14.\(^1\) In the previous two reports, there were 19 and ten maternal deaths from pre-eclampsia in 2006–08 and 2009–11, respectively.\(^1\) This reduction is remarkable since hypertensive diseases have consistently been a leading direct cause of death in pregnancy. Maternal deaths from pre-eclampsia have been associated with substandard care,\(^3\) suggesting they are avoidable. In the latest Confidential Enquiries into Maternal Deaths and Morbidity, fewer than one woman per million women died from hypertensive-related disorders during pregnancy in the UK and there was less than one such death per year.\(^1\)

The low rate of maternal deaths from pre-eclampsia in the UK is in stark contrast with the global setting where an estimated 40,000 women die each year from this condition,\(^4\) which equates to about five deaths every hour. The proportion of maternal deaths from hypertensive disorders of pregnancy is 2.8% in the
UK (2011–13); 7.4% in the USA (2011–13); and 14% globally (2013).4

Deaths from hypertensive diseases of pregnancy are largely due to treatable pathology, the elements of which are important to define if other countries are to emulate the reduction in the UK. The largest triennial fall in maternal deaths from these diseases in England and Wales occurred between the 1950s (200 deaths) and 1970s (fewer than 40 deaths); this reduction was related to improved surveillance, diagnosis, and timely delivery. From the 1980s onwards, the confidential enquiries showed that deaths in women with hypertensive diseases of pregnancy were related to pulmonary oedema and intracerebral events, particularly haemorrhage. The subsequent introduction of fluid-restricting management protocols meant pulmonary oedema was no longer a cause of maternal death in the UK in 2002.6 Intracerebral haemorrhage remained a fairly common cause of death, and substandard care was often associated with inadequate treatment of severe hypertension, a likely causative factor.6

Have further improvements in management caused this latest reduction in deaths? Pre-eclampsia can be partly prevented by prophylactic use of low-dose aspirin.7 Since 2010, aspirin has been routinely recommended for higher risk women by the UK National Institute for Health and Care Excellence,8 which also underlines the judicious use of antihypertensive medication with lower target thresholds (now to less than 150/100 mm Hg). The use of anticonvulsant therapies has increasingly been introduced into practice for women with preeclampsia in the past few decades, after trials showed the efficacy of magnesium sulfate for the prevention of eclamptic fits.9 More recently, planned delivery as treatment of severe hypertension, a likely causative factor.6

In the latest Confidential Enquiries into Maternal Deaths and Morbidity about a quarter of pregnant women who died in 2012–14 were born outside the UK, but maternal death rates were similar in these women and those born in the UK (8.85 vs 7.87 per 100 000 maternities; relative risk 1.12; 95% CI 0.80–1.56),1 even when their origins were from a low-income setting, which suggests that universal pregnancy care provision, rather than background demographics, influence the reduction of maternal mortality rates. Antenatal care and many therapeutic and management interventions for pregnancy hypertensive disorders can be provided at relative inexpensive cost and are potentially available in low-income settings. The challenge is implementation.

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Research misconduct and the INTERGROWTH-21st study

On Oct 20, 2016, a statement appeared on the WHO website, announcing that “An independent review commissioned by WHO has found that research ethics misconduct occurred in a study on foetal growth standards.”¹ The study in question was the INTERGROWTH-21st study, led by researchers at the University of Oxford, UK, funded by the Bill & Melinda Gates Foundation (BMGF), and reported in several journals, including our own.²⁻⁵ Such a judgment by the world’s foremost global health agency was serious, casting damaging light on a study of international importance.

On Nov 16, 2016, we wrote to Ian Smith, Executive Director of the Office of the WHO Director-General, to request a copy of the review report, but were told that it was confidential and had been supplied only to the University of Oxford, BMGF, and the UK General Medical Council, which was considering whether to open an investigation of its own.

We then wrote, on Nov 23, 2016, to the researchers, Stephen Kennedy and José Villar at the University of Oxford, to request their response to the review’s findings. We subsequently received a letter from the University’s Registrar, Ewan McKendrick, reiterating the history of the dispute, which (as we were aware) dates back to 2008 and has been the subject of previous investigations by the University of Oxford, the Committee on Publication Ethics (COPE), and other journals. In brief, the dispute surrounds allegations of plagiarism and disputes over intellectual ownership concerning two research protocols with joint origins: those of the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) and the WHO Multicentre Study for the Development of Growth Standards from Fetal Life to Childhood. Both protocols were drawn up in response to a 1995 WHO Expert Committee report⁶ that recommended, among other things, “Assessment and development of fetal growth reference data suitable for international applications”. Both protocols also built on the methods of the WHO Multicentre Growth Reference Study,⁷ which produced growth curves for children from birth to 5 years. Much of the bases of the protocols are therefore in the public domain. Kennedy and Villar are accused of having plagiarised the WHO Multicentre Study protocol in developing the INTERGROWTH-21st protocol and of obtaining rival funding while still involved with the WHO work.

McKendrick’s responses to us, on Nov 29, 2016, and Dec 13, 2016, were robust. It is clear from this response that the University of Oxford looked into these serious allegations at a high level, methodically dissected the claims, closely examined four pairs of protocols at different stages of development, engaged with the WHO Director-General, and retrieved supporting documentation before concluding that the allegations were unfounded. The Oxford researchers clearly stated the methodological foundations of INTERGROWTH-21st in their reports.

We were aware, however, that we had only heard the University’s version of events, and again pressed WHO for their inquiry report. This document was eventually shared with us in confidence on Jan 16, 2017, but we found it disappointingly insubstantial. We have therefore concluded that its far-reaching judgment

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