BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.15517
www.bjog.org

Review article

Falling perinatal mortality in twins in the UK: organisational success or chance?

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Accepted 12 October 2018. Published Online 27 November 2018.

A podcast to accompany this paper is available at https://soundcloud.com/bjog/author-interview-kilby

In June 2018, Mothers and Babies Reducing Risks through Audits and Confidential Enquiries across the UK (MBRRACE-UK) published a Perinatal Surveillance report of an audit between 2013–2016. This noted that the stillbirth rate for twins nearly halved between 2014–2016; whereas the stillbirth rate for singletons remained static. There was a statistically significant reduction in the rate of stillbirth in twins over this period from 11.07 (95% CI, 9.78–12.47) to 6.16 (95% CI, 5.20–7.24) per 1000 total births. This commentary discusses these observations, the effects of twin chorionicity, and the potential obstetric and neonatal interventions, as well as public health improvements, that may have influenced these findings.

Keywords Healthcare improvements, neonatal death, pregnancy, stillbirth, twins.

Please cite this paper as: Kilby MD, Gibson JL, Ville Y. Falling perinatal mortality in twins in the UK: organisational success or chance? BJOG 2018; https://doi.org/10.1111/1471-0528.15517.

Stillbirth and neonatal death are devastating perinatal outcomes, the causes of which are multifaceted, complex, and incompletely understood. Since 2013, Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) has been appointed by the Healthcare Quality Improvement Partnership to conduct the national programme of surveillance and investigation into the causes of maternal deaths, stillbirths, and infant deaths. The Perinatal Mortality Surveillance Report for Births between 2013–2016 was published in June 2018. One of the headline findings in this report was that the stillbirth rate for twins has nearly halved since 2014, whereas the stillbirth rate for singleton pregnancies remained static. There was a statistically significant reduction in the rate of stillbirth in twins over this period, from 11.07 (95% CI 9.78–12.47) to 6.16 (95% CI 5.20–7.24) per 1000 total births (Figure 1, blue histogram). In addition, there was a more modest fall in neonatal mortality for twin pregnancies from 7.81 (95% CI 6.73–9.01) to 5.34 (95% CI 4.47–6.36) per 1000 live births.[1] These data were validated against routine data collected for all UK countries. There were no methodological changes over the years studied. There was considerable stakeholder and media interest in these findings and professional reflection on these observations.[2]

The publication of the national statistics for perinatal loss is arguably one of the most important publications in obstetric, midwifery, and neonatal medicine. Data on twin loss rates are available in very few countries, and therefore publication of the UK data has international applicability and interest. The drive and ability to make improvements in perinatal care requires critical appraisal and assessment of these reported findings, along with an acknowledgement of any limitations of the report and the concurrent standard of national perinatal care. To these ends, this commentary aims to consider the possible reasons underlying this significant and indeed impressive presented fall in stillbirth and neonatal death rates in twin pregnancies. Could it, at least in part, be a consequence of chance, statistical variability, and data acquisition, or does it document the true success of developments in obstetric and neonatal care in the UK?

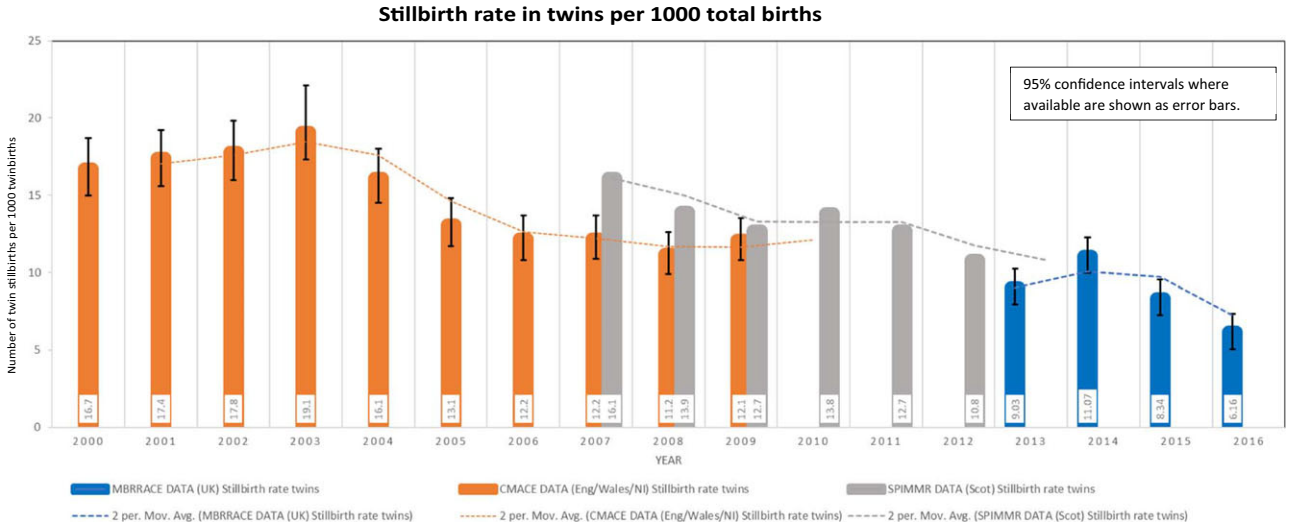

Figure 1. Stillbirth rate in twins (per 1000 total births) from 2000 to 2016. These data are from CMACE (orange), Scottish Perinatal Mortality data (grey, no confidence limits reported), and the MBRRACE-UK data (blue), published in 2018.[1]

It is good scientific practice and wise to question and remain cautious about the validity of relatively short-term trends in clinical outcomes. Further review of the MBRRACE-UK data for stillbirth and neonatal death through the total 4-year period suggests an improvement and fall in stillbirth rates in twin pregnancies, but these data are not as impressive as reviewing and focusing upon the last triennial reports from 2000 onwards. Indeed, there is variance across these data, with 2014 demonstrating a relatively high stillbirth rate and 2016 demonstrating a relatively low rate. Stillbirth (and indeed neonatal loss) rates may be better reported as a 'rolling average' (as previously reported for the Scottish data sets) as the MBRRACE-UK data set expands. Examination of a longer-term period by consideration of the Confidential Enquiry into Maternal and Child Health (CEMACH)/Centre for Maternal and Child Enquiries (CMACE) (2000–2009) and Scottish Perinatal Mortality (2007–2012) data sets alongside the current MBRRACE-UK data does demonstrate a steady trend in a reduction of the documented stillbirth rate in twins since 2003 (Figure 1).

It is widely acknowledged that twins are at higher risk of death in utero and neonatal death than singletons, because of increased rates of congenital malformations, preterm birth, and fetal growth restriction, as well as specific morbid complications of monochorionic twins.[3–6] The close fetal surveillance of twins is warranted.[7] Monochorionicity has a negative influence on gestational age-specific mortality, compared with dichorionic twins,[8,9] as a consequence of the complications arising from the conjoining of fetal circulations within a single shared placenta. These complications of twin-to-twin transfusion syndrome (TTTS), selective growth restriction (sGR), and twin anaemia polycythaemia sequence (TAPS) are associated with high risks of single or double fetal demise.[9,10] Although the death of any fetus is a tragedy, a single twin death in a monochorionic pregnancy is a particularly adverse event, as it may be associated with high rates of subsequent co-twin demise and a greater than 24% risk of pathologic neurologic sequelae in a co-twin survivor.[10] Monochorionicity is further associated with adverse neonatal outcomes, with an increased incidence of preterm birth, low birthweight, and more complicated morbidity, often resulting in a prolonged stay in the neonatal intensive care unit.[11,12]

The accuracy of stillbirth rates in monochorionic twins may be affected by a number of confounding factors. The morbid conditions associated with monochorionicity may be diagnosed before 24 weeks of gestation, and potentially associated with fetal loss at the threshold of viability, and may be variably classified as late fetal losses, stillbirths, or neonatal deaths depending upon the clinical judgement as to the timing of demise. Although MBRRACE-UK collects fetal loss rates between 22 and 24 weeks of gestation, only stillbirths (deaths at >24 weeks of gestation) and neonatal deaths are reported in the published document.[1] Thus, our ability to critique fetal loss rates for potential classification errors is presently limited. In addition, pregnancy losses (double) in twins under 22 weeks of gestation are not captured in our national surveillance data, and represent a 'hidden' mortality. A rise in 'hidden mortality' will have a positive effect to reduce stillbirth rates by potentially removing the most complicated monochorionic twin pregnancies from the surveyed population. With this consideration, it is certainly possible that increased obstetric surveillance of monochorionic twins has led to earlier identification, intervention by fetal therapy, and earlier fetal losses associated with pathologies such as TTTS and sGR.

Although the recently published official MBRRACE-UK report did not breakdown and report the twin data by chorionicity, these data are routinely collected. Owing to the importance of this missing information, we requested and were granted access to these data. In the 4-year period (2013–2016) there were a total of 817 stillbirths (deaths in utero at ≥24 weeks of gestation) complicating twin pregnancies. Of these, 420 stillbirths were classified as monochorionic (51.4%), 331 were classified as dichorionic (40.5%), and 66 had unknown chorionicity (8.4%). From 2013 (21 cases, 10.1%) through to 2016 (three cases, 2%) there was a significant reduction in the number of twin pregnancies unclassified by chorionicity, with monochorionic twins forming the largest group of twin stillbirths by 2014–2016. A similar finding was noted in the neonatal death data.

To allow the calculation of loss rates, we required denominator data: the number of all live and stillbirths. Although, the total denominator data from twins are known, subdivision on the basis of chorionicity was not possible from these national statistics.[1] To calculate stillbirth rates on the basis of chorionicity we therefore made the assumption that 20% of the twin pregnancies were monochorionic and 80% were dichorionic.[13,14] The crude data for stillbirth over the 4-year period (2013–2016) are shown in Figure 2, and the derived stillbirth rate (per 1000 total births) in twins by chorionicity compared with the singleton stillbirth rates is represented in Figure 3. There appears to be a reduction in the stillbirth rate in dichorionic twins between the beginning (2013) and the end (2016) of the MBRRACE-UK reported data set. The stillbirth rates in monochorionic twins are significantly higher than in dichorionic twins or singletons (up to five-fold increase), but also appear to show a reduction in rate over the studied period. The census data for the MBRRACE-UK 2018 data set have not been analysed for further clinical information on the twin pregnancies, and in particular there was no information extracted as to the proportion of monochorionic twins complicated by adverse events associated with placental vascular conjoining (i.e. TTTS, sGR, or TAPS), rates of fetal therapy, or the relative rates of preterm birth by chorionicity; however, this will form the basis of an MBRRACE-UK working group studying the 2017 data set (see below).

With the knowledge that there appears to have been a steady reduction in perinatal mortality of twin pregnancies, we are in a position to consider and speculate upon a number of potential key effectors. In 2005, the Royal College of Obstetricians and Gynaecologists (RCOG) recognised and evaluated international awareness that twin and triplet pregnancies had specific risks, with increased perinatal mortality and morbidity. An International Scientific Study Group was commissioned to bring experts from around the world to discuss evidence-based best practice.[15] The consensus statement from this meeting, built upon other international declarations, recognising the specific

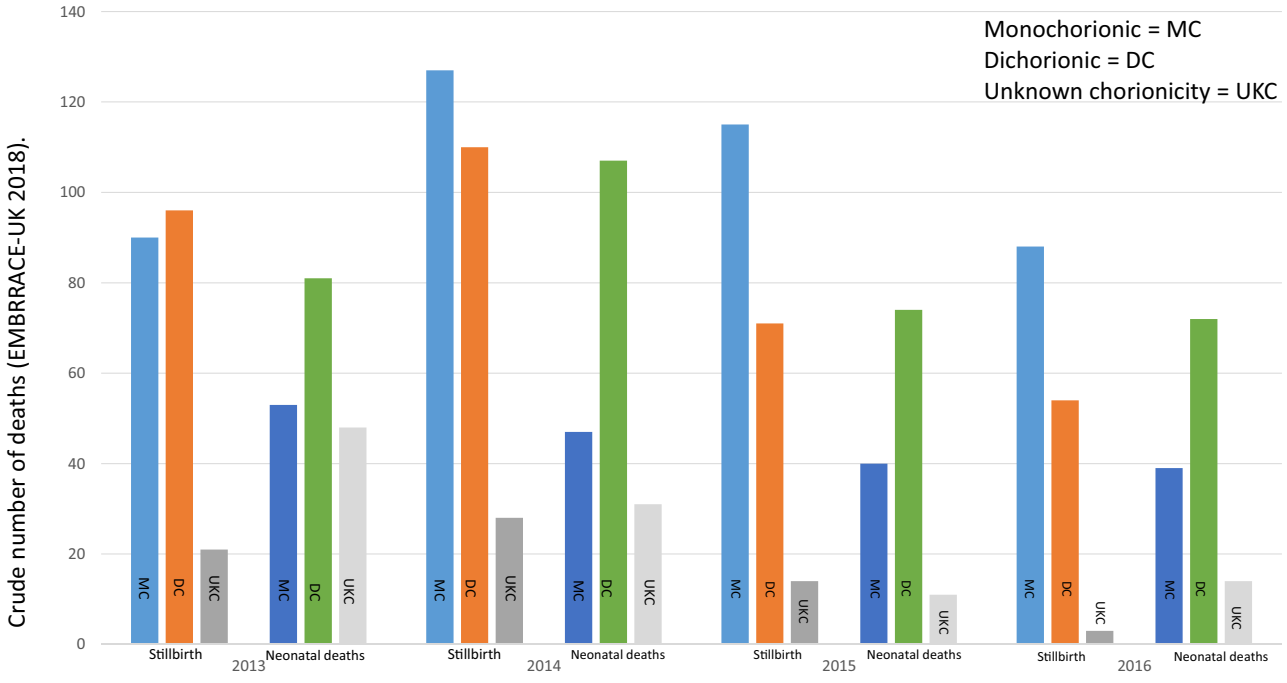

Figure 2. Raw data from the MBRRACE-UK report 2018,[1] demonstrating the total number of twin deaths (stillbirths and neonatal deaths) between 2013 and 2016 as classified by chorionicity (DC, dichorionic; MC, monochorionic; UKC, unknown chorionicity).

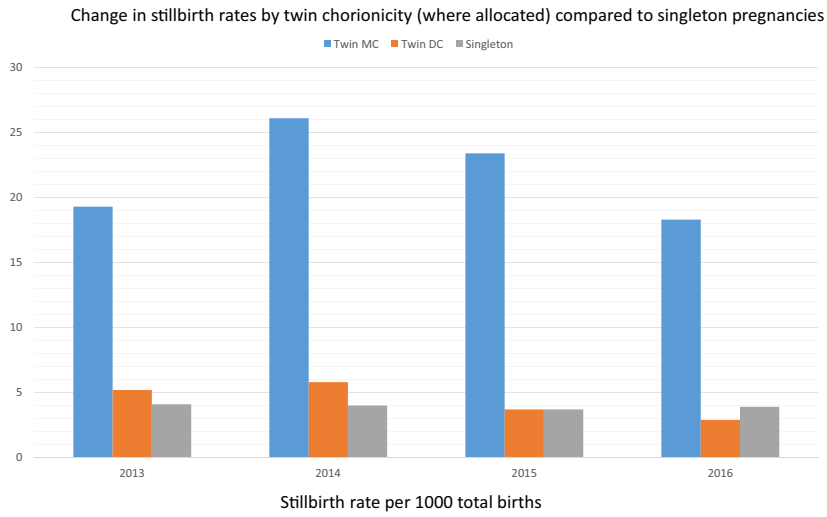

Figure 3. Change in twin stillbirth rates by chorionicity (where allocated), compared with singleton pregnancies.[1]

twin-related obstetric problems, compared with singleton pregnancy, and the need to stratify antenatal care based upon chorionicity.[16] In the UK, this led to the production of professional quality standards, with the RCOG publishing a Green-top Guideline on the management of monochorionic twin pregnancies (first published in 2008 and revised in 2016),[17,18] and with a National Institute for Health and Care (NICE) document outlining a template for antenatal care for twin and triplet pregnancies in 2011.[19,20] For the first time, these evidence-based documents outlined recommended clinical care and obstetric surveillance in twin and triplet pregnancies. For twins (as well as for rarer triplet pregnancies) there was a focus on the designation of clinical chorionicity based upon first-trimester ultrasound. This chorionicity-based programme of antenatal care is encapsulated in a guideline recommending a regimen of routine serial ultrasound examinations monitoring these pregnancies for chromosomal abnormalities, fetal structural anomalies, and fetal growth restriction. The recommended frequency of ultrasound scan examinations was higher (at 2-weekly intervals from 16 weeks of gestation) in monochorionic twins in order to monitor for TTTS and high rates of sGR.[19,20] In addition, it recommended that in order to minimise perinatal deaths in uncomplicated dichorionic twin pregnancies, delivery should be considered at 37 weeks of gestation; in monochorionic pregnancies delivery should be considered at 36 weeks of gestation. Perhaps though, the most novel recommendation of this guideline was that clinical care for women with twin and triplet pregnancies should be provided by 'a core team of named specialist obstetricians, specialist midwives and ultrasonographers, all of whom have experience and knowledge of managing twin and triplet pregnancies'.[21,22] This change placed the care of these high-risk pregnancies in the hands of the healthcare professionals best placed to implement adequate monitoring for maternal and fetal adverse disease processes, allowing the recognition of complications earlier so that timely treatment can be offered in appropriate specialist centres. Serial ultrasound scans have allowed for the better identification and understanding of management possibilities for twin pregnancies complicated by selective growth restriction, and for chorionicity-specific management differences in these potentially morbid pregnancies.[19,21]

It is likely that this organisational change is, at least in part, responsible for the observed reduction in perinatal and neonatal mortality reported between 2014 and 2016 (and perhaps from even earlier; Figure 1). From the publication of the RCOG consensus statement in 2006 and then the NICE guidelines in 2011, it would probably take at least 2 years for hospital trusts in the UK National Health Service (NHS) to engage with the recommendations by establishing multidisciplinary teams, multiple pregnancy services, and an infrastructure to deliver care. It should also be recognised that during this period, parent/patient education regarding the expected quality of antenatal care has improved, and this has been in no small part because of the active and educational work performed by the Twins and Multiple Births Association (TAMBA) and the Multiple Births Foundation (MBF).

In 2013, NICE published eight quality standards (NICEQS46) with the aim of improving the quality and consistency of clinical care for multiple pregnancies.[22] Recent data from TAMBA evaluating the uptake of these 'key standards' have indicated that there is still considerable variation in implementation by NHS healthcare providers across the UK.[23] To provide objectivity to this claim, the TAMBA Maternity Engagement Project enrolled the

participation of 30 maternity units across England to explore the range of uptake and adherence to the NICEQS46 standards during 2017. The report attempted to look at hospital units based upon the perinatal services that they provide and the number of total deliveries per annum. The King's Fund estimates that there are approximately 150 maternity service providers in the UK, so a sample of 30 units is relatively small (~20%) and therefore may have some representative selection bias; however, these data were analysed using nested case–control methodology to explore the outcomes against a relative comparator within each group, and with a 'control hospital' designated within each of the designated complexity groups. This interim audit demonstrated a significant correlation between complete adherence to the NICEQS46 standards (thus implementation of guidance outlined in CG129) and improved clinical outcomes.[24] Furthermore, in the 29 centres audited (one centre declined audit), across hospital units of various size, obstetric and neonatal expertise, and resourcing, there appeared to be a significant association between the implementation of specific elements of the eight quality standards in NICEQS46 and lower stillbirth, neonatal admissions, and neonatal deaths.[23,24] There is therefore some preliminary objective evidence that the NICE guidelines published in 2011, if implemented, may improve perinatal outcomes in twin pregnancies. Since 2011, the RCOG Green-top Guideline focusing specifically on the monitoring and management of monochorionic twins has been updated,[18] with recommendations that complex monochorionic twins be referred for management by Fetal Medicine Specialists. International recommendations on the use of ultrasound in the obstetric surveillance of twins has also been published.[21] It is highly likely that these documents have further increased the understanding of the sophisticated and unique challenges that patients with multiple pregnancies face.

Although the recent data from MBRRACE-UK relating to perinatal deaths in twin pregnancies is to be applauded, there is no room for complacency. The variation in uptake and implementation in hospital centres across UK providers requires the universal development of multidisciplinary teams and clinics, which will require adequate resourcing and professional engagement.

The risk of preterm birth is considerably higher in multiple pregnancy, occurring in at least 50% of twin pregnancies.[25] Recent epidemiological data from the Netherlands of 51 658 twin pregnancies indicated that the overall perinatal mortality rate was higher in twin pregnancies as compared with singletons. The authors postulate that this is caused by the high preterm birth rate, and that in the preterm period (<37 weeks of gestation) the antenatal rate of stillbirth (after 28 weeks of gestation) was lower than in singleton pregnancies, probably as a consequence of 'closer monitoring'.[26]

Although data indicate that the ultrasonographic measurement of cervical length between 18 and 24 weeks of gestation is a moderately good predictor of preterm birth in twins, the attenuation of this risk has been hampered by a lack of evidence-based interventions.[19,20] Data from an updated meta-analysis of individual patient data from several randomised controlled trials (RCTs) has demonstrated that vaginal progesterone administered to asymptomatic women with a twin gestation and a sonographically short cervix (<25 mm) in the mid-trimester reduces both the risk of preterm birth (from <30 to <35 weeks of gestation) and neonatal mortality.[27] In addition, continuing research into potential therapies to attenuate the risk of preterm birth, such as the use of the Arabin cervical pessary or targeted cervical cerclage, may play a future role in further reducing perinatal mortality in twins as a consequence of preterm birth.[28,29]

The timely identification of twins (particularly monochorionic twins) with selective growth restriction would allow assessment and the potential for management in utero.[30,31] Treatment strategies in the management of significant sGR in monochorionic twins (especially with abnormal fetoplacental Doppler assessment) are uncertain, however, and range from conservative/expectant management with early, premature delivery, through to the options of fetoscopic laser ablation of placental arteriovenous anastomoses or the selective termination of pregnancy. These choices are controversial and uncertain.[32] They will form the basis of a research call from the National Institute for Health Research (NIHR) in the UK for the synthesis of current evidence,[33] but there is some evidence that fetal therapy increases the risk overall of single twin demise (smaller twin).

The regular ultrasound monitoring of monochorionic twin pregnancies for adverse pathologies, such as TTTS, has led to earlier and timely referrals to centres with the expertise to manage these pregnancies by fetoscopic laser ablation.[18,34] The evaluation of screening in monochorionic twins to enhance detection may further improve this in the future.[35] Despite improvements in technique (such as the SOLOMON technique reducing the risk of post-operative twin anaemia polycythaemia sequence) and outcomes,[36] however, the risk of preterm prelabour rupture of membranes associated with the procedure increases the risk of miscarriage and preterm birth. The future pursuit of non-invasive techniques for treatment may further reduce miscarriage and perinatal loss associated with this disease.[37] It is also possible that the earlier detection and diagnosis of TTTS leads to more timely and appropriate treatment that, nonetheless, may be associated with single or indeed double twin demise before 24 weeks of gestation (the threshold gestation at which the MBRRACE audit started to record fetal demise). [1,38]

The recent MBRRACE-UK data from the UK indicating a reduction in perinatal and neonatal death in twins are welcome, and document a trend in reduced perinatal mortality associated with twins from the turn of this century. The UK has been innovative in recommending the establishment of twin multidisciplinary teams and clinics, along with several national clinical guidelines to aid the management of twin and triplet pregnancies and high-risk monochorionic pregnancies. The introduction and clinical uptake of these guidelines has almost certainly improved care, thereby reducing perinatal mortality rates in twins. The universal adoption of these guidelines, however, with greater parent/healthcare worker interaction, and the prioritisation of research in areas of morbidity and mortality in twin pregnancy will further reduce pregnancy loss rates in these high-risk pregnancies.[39]

A more comprehensive national assessment of the causes of perinatal mortality in twins by chorionicity is very important and would help to indicate the contribution of pathologies such as TTTS, TAPS, selective growth restriction, and extreme preterm birth to fetal demise. In August 2018, an MBRRACE-UK working group was formed to 'drill down' and study a cohort of twin pregnancy stillbirths (at >22 weeks of gestation) and neonatal deaths from a recently collected 2017 data set to examine the relative contributions of national healthcare delivery and underlying aetiology. This will report in late 2019.

Additionally, a UKOSS study has examined data and will shortly publish from the UK in which there was single twin demise in monochorionic twin pregnancies between 2016 and 2017.[40] There is a lack of robust data regarding the incidence of single twin demise, interventions offered, maternal, fetal, and neonatal outcomes, and any prognostic indicators. The knowledge gained from this study will enable recommendations for the management of monochorionic twin pregnancies following single twin demise, and will improve the counselling and management. These two initiatives alongside the next MBRRACE-UK perinatal surveillance report from 2017 to 2018 will, by 2019, allow us to more robustly examine trends in changing rates of twin stillbirth and early neonatal death in the UK, and understand the contributory and possibly preventable causes.

Disclosure of interests

MDK is a senior topic advisor for the NICE Guideline Development Group updating CG129, and is a founding member (from August 2018) of the MBRRACE-UK Working Group examining the effects of chorionicity on stillbirth and neonatal death in twins. He has also received a project grant from the Richard and Jack Wiseman Trust 2015–2019 (www.wisemantrust.co.uk) and a TAMBA/BMFMS grant to work with UKOSS on the study of single twin demise in monochorionic twin pregnancy. JLG is a member of the MBRRACE-UK Working Group and a member of the NICE Guideline Development Group updating CG129. YV has no conflicts of interest. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

MDK conceived the idea of the BJOG commentary in response to reviewing the MBRRACE-UK 2018 report. He wrote the original draft and then requested data on twin pregnancy chorionicity from MBRRACE-UK. He worked with these data and included them in the article. He responded to reviewers' comments and revised the commentary. JLG collated data from historical enquires into stillbirth rates in twin pregnancies to produce longitudinal data from 2000, presented in Figure 1. She worked with Professor Kilby to analyse the chorionicity data provided by MBRRACE-UK to allow stillbirth rates to be calculated per 1000 births for monochorionic and dichorionic twins. These valuable data are clearly presented graphically with reference to the rate in singleton pregnancy. She was involved in editing and re-writing sections of the article to aid the thoughtfulness and clarity of this commentary on the MBRRACE-UK publication, taking into account the reviewers' comments. She assisted in answering the reviewers' comments regarding the article, both within the document and in the written response. YV contributed to the writing and editing of the article. He made comments on the MBRRACE-UK 2018 report data and its context with regards to the present obstetric literature on the topic. He was involved in editing and re-writing sections of the article.

Acknowledgements

We would like to acknowledge the contribution and help of Professor Elisabeth Draper and Dr. Ian Gallimore Department of Health Sciences, University of Leicester for help in clarifying and obtaining addition data relating to the contribution of twin pregnancy chorionicity to the perinatal statistics within the MBRRACE-UK Report 2018. ■

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