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Falling perinatal and neonatal mortality in twins in the United Kingdom: organisational success or chance?

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Abstract:

In June 2018, MBRRACE-UK published a Perinatal Mortality Surveillance Report that outlined that the stillbirth rate for twins has nearly halved, since 2014, whilst 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. This commentary discusses these observations,

the effects of twin chorionicity and discusses the potential obstetric and neonatal interventions as well as public health improvements that may have influenced these finding.

KEY WORDS: Twins, stillbirth, neonatal death, pregnancy, healthcare improvements.

Stillbirth and neonatal death are devastating perinatal outcomes whose causes are multifaceted, complex and incompletely understood. Since 2013, 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 in 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, whilst 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, data acquisition or does it document a true success of developments in obstetric and neonatal care in the UK?

It is good scientific practice and wise to be questioning and 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 four year period suggests an improvement and fall in stillbirth rates in twin pregnancies but these data are not as impressive as by focusing upon the last triennia. Indeed, there is a variance in these data with 2014 demonstrating a relatively high stillbirth rate and 2016 a relatively low rate. Stillbirth (and indeed neonatal loss) rates may be better reported as a "rolling average" (as previously reporting in the Scottish datasets) as the MBRRACE-UK dataset expands. Examination of the more long-term period by examination of the CEMACH/CMACE (2000-2009) and Scottish Perinatal Mortality dataset (2007-2012) alongside the current MBRRACE-UK data does demonstrate a steady trend in reduction of documented stillbirth rate in twins since 2003 (Figure 1).

It is widely acknowledged that twins are at higher perinatal risk of in-utero and neonatal death than singletons, due to increased rates of congenital malformations, preterm birth and fetal growth restriction, as well as specific morbid complications of monochorionic twins[3,4,5,6]. Their close fetal surveillance of twins is warrented[7]. Monochorionicity has a negative influence on gestational age-specific mortality compared to dichorionic twins[8,9] as a consequence of the complications arising from the conjoining of the 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 also further associated with adverse neonatal outcomes, with an increased incidence of preterm birth, low birthweight, more complicated morbidity and often a prolonged stay in the neonatal intensive care unit[11,12].

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 collect fetal loss rates between 22-24 weeks, in the document published[1] only stillbirths (deaths >24 weeks) and neonatal deaths are reported. Thus our ability to critique the fetal loss rates for potential classification errors is presently limited. In addition, pregnancy losses (double) in twins under 22 weeks 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 report did not breakdown and report the twin data by chorionicity, these data are routinely collected. Due to its importance we requested and were granted access to these data. In the four years (2013-2016), there were a total of 817 stillbirths (in-utero deaths ≥24 weeks) complicating twin pregnancies. Of these, 420 stillbirths were classified as monochorionic (51.4%), 331 were classified as dichorionic (40.5%) and in 66, unknown chorionicity (8.4%). From 2013 (21 cases; 10.1%) through to 2016 (3 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 dominator data; the number of all live and stillbirths. Although, the total denominator data from twins is 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, 20% of the twin pregnancies were monochorionic and 80% were dichorionic[13,14]. The crude data for stillbirth over the four years 2013-2016 are shown in Figure 2 and the derived stillbirth rate (per 1000 total births) in twins by chorionicity compared to 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 EMBRRACE-UK reported dataset. The stillbirth rates in monochorionic twins is 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 EMBRRACE-UK 2018 dataset has not been analysed for further clinical information on the twin pregnancies and in particular there was no extracted information 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 a MBRRACE working group studying the 2017 dataset (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. A 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 twin-related obstetric problems compared to 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 'Green top' Guidance on the management of monochorionic twin pregnancies (first published in 2008 and revised in in 2016)[17,18] and then the 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 the rarer triplet pregnancy) there was a focus on the designation of clinical chorionicity based upon first trimester ultrasound. This chorionicity- based program 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) in monochorionic twins to monitor for twin to twin transfusion syndrome and high rates of sGR[19,20]. In addition, it recommended that to minimise perinatal deaths in uncomplicated dichorionic twin pregnancies, delivery should be considered at 37 weeks' gestation; in monochorionic pregnancies delivery should be considered at 36 weeks. 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 focused the care of these high-risk pregnancies in the hands of 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 better identification and understanding of management possibilities in twin pregnancies complicated by selective growth restriction and 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 – 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 two

years for hospital Trusts in the 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 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 pregnancy[22]. Recent data from TAMBA evaluating 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 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, across hospital units of various size, obstetric and neonatal expertise and resourcing, there appeared to be a significant association between 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 Guidelines focusing specifically on monitoring and management of monochorionic twins have 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 obstetric surveillance of twins has also been published[21]. It is highly likely that these documents have further increased understanding surrounding the sophisticated and unique challenges that patients with multiple pregnancy face.

Although the recent data from MBRRACE relating to perinatal deaths in twin pregnancies is to be applauded there is no room for compliancy. 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, occurring in at least 50% of twin pregnancies[25]. Recent epidemiological data from the Netherlands of 51,658 twin pregnancies has noted that overall perinatal mortality rate was higher in twin pregnancies as compared to singletons. The authors postulate that this is caused by high preterm birth rate and that in the preterm period (<37 weeks) the antenatal rate of stillbirth (after 28 weeks 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 18-24 weeks is a moderately good predictor of preterm birth in twins, 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 RCTs has demonstrated that vaginal progesterone administered to asymptomatic women with a twin gestation and a sonographically short cervix (<25mm) in the mid-trimester reduces both the risk of preterm birth (at < 30 to < 35 gestational weeks) and neonatal mortality[27]. In addition, ongoing research into potential therapies to attenuate the risk of preterm birth such as the use of the Arabin cervical pessary[28] or targeted cervical cerclage may play a future role in further reducing perinatal mortality in twins as a consequence of preterm birth[29].

The timely identification of twins (particularly monochorionic twins) with selective growth restriction would allow assessment and the potential for in-utero management[30,31]. However, treatment strategies in the management of significant sGR in monochorionic twins (especially with abnormal fetoplacental Doppler assessment) are uncertain and range from conservative/expectant management with early, premature delivery, through the options of fetoscopic laser ablation of placental arteriovenous anastomoses or selective termination of pregnancy. These choices are controversial and uncertain[32,]. They will form the basis of an evidence synthesis NIHR research call in the UK[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 gestation of referral 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]. However, despite improvement in technique (such as the SOLOMON technique reducing the risk of post-operative twin anaemia polycythaemia sequence) and outcomes[36], the risk of preterm, premature ruptured 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 earlier detection and diagnosis of TTTS[38] leads to more timely, appropriate treatment that nonetheless, may be associated with single or indeed double twin demise before 24 weeks gestation (the threshold gestation at which the MBRRACE audit started to record fetal demise[1]),

The recent MBRRACE data from the UK indicating a reduction in perinatal and neonatal death in twins is welcome, and documents a trend in reduced perinatal mortality associated with twin 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 of and uptake clinically of these guidelines has almost certainly improved care reducing perinatal mortality rates in twins. However, universal adoption of these guidelines, with greater parent/healthcare worker interaction and 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 would be very important and 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 Working Group was formed to 'drill down' and study a cohort of twin pregnancy stillbirths (>22 weeks) and neonatal deaths from a recently collected 2017 dataset 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 from the UK in which there was single twin demise in monochorionic twin pregnancies between 2016-2017[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 improve the counselling and management. These two initiatives alongside the next MBRRACE-UK perinatal surveillance report from 2017-2018 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 contributing and possibly preventable causes.

Declaration 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 interest forms are available to view online as supporting information.

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Contributions to Authorship: MDK conceive the idea of the BJOG commentary in response and reviewing the MBRRACE-UK 2018 report. He wrote the original draft and then requested data on twin pregnancy chorionicity from MBRRACE. He worked with these data and included them in the manuscript. 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 and I have presented this in Figure 1. She worked with Professor Kilby to analyse the chorionicity data provided by MBRRACE to allow stillbirth rates to be calculated per 1000 births for monochorionic and dichorionic twins. This valuable data is clearly presented graphically with reference to the rate in singleton pregnancy. She was involved in editing and re-writing sections of the paper 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 reviewer's comments regarding the commentary, both within the document and in the written response.

YV contributed to the writing and editing of the commentary. He made comments on the MBRACE-UK 2018 report data and its context to the present obstetric literature on the topic. He was was involved in editing and re-writing sections of the paper.

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Figure Legends

FIGURE 1.

Stillbirth rate in twins (per 1000 total births) from 2000-2016. These data are from CMACE (orange), Scottish Perinatal Mortality data (Grey [no confidence limits reported) and the EMBRRACE data (Blue), published in 2018[1]

Figure 2.

Crude figures from EMBRRACE-UK Report 2018[1]: demonstrating the total number of twin deaths (stillbirths and neonatal deaths) between 2013-2016 as classified by chorionicity (monochorionic=MC; dichorionic=DC or unknown chorionicity=UKC).

Figure 3.

Change in twin stillbirth rates by chorionicity (where allocated) compared to singleton pregnancies[1]

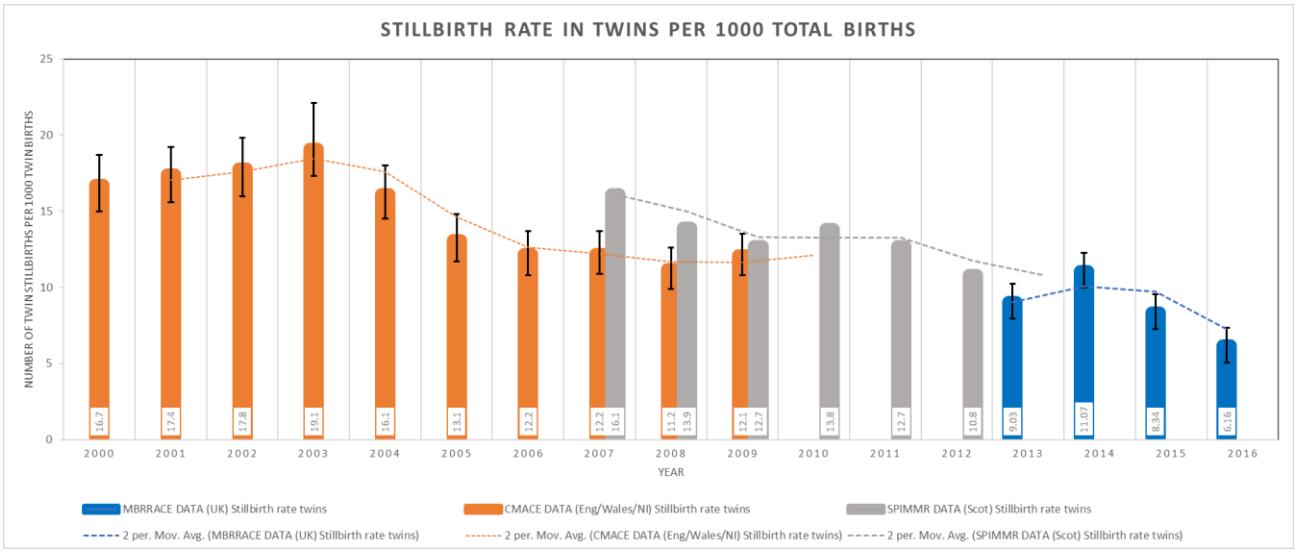

Figure 2

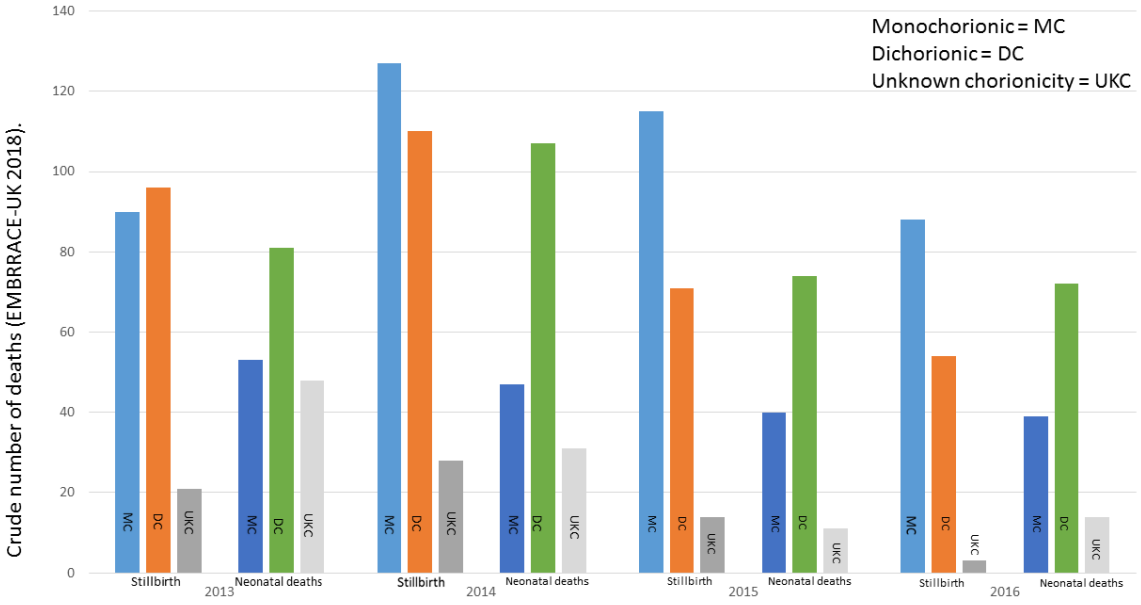

Figure 2. Change in stillbirth rates by twin chorionicity (where allocated) compared to singleton pregnancies