Confidential Enquiry into Stillbirth and Neonatal Death in Twins: key messages for obstetricians and fetal medicine specialists

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Background

Despite continuing efforts to improve tailored antenatal care, identify pregnancies at increased risk of adverse perinatal outcome and implement heightened surveillance, twin pregnancies remain at increased risk of perinatal mortality and morbidity.[1] According to the most recent Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE) report, the stillbirth rate in the UK is falling in singleton pregnancies.[1] However, the risk of stillbirth in twin pregnancies remains twice that in singletons (Figure 1).[1-5]

On 14 January 2021, MBRRACE published for the first time its report on the Confidential Enquiry into Stillbirth and Neonatal Death in Twin Pregnancies.[6]

This enquiry follows a robust methodology, using a multidisciplinary panel of experts, to review the quality of care in a sample of pregnancies in which one or both twins died. The aim was to determine whether different care might have made a difference for the babies and/or the mother. The report reviewed the records of 50 twin pregnancies from 2017 and found that 'in around 1 in 2 baby deaths, the care was poor, and that if the care had been better it may have prevented the baby from dying'.[6] This evidences the need to address deficiencies in the care of twins where they occur. Moreover, the fact that in almost half of these cases no deficiency in care could be identified highlights the evidence gaps and the urgent need for high-quality research studies in twins. Concerted multidisciplinary initiative is now required to set up adequately powered studies to address the 10 most important research questions in multiple pregnancy (Figure S1).[7] Despite the fact that, compared to singletons, twin pregnancies are at increased risk of pre-eclampsia, fetal growth restriction and gestational diabetes, none of the randomized controlled trials published between 2012 and 2016 on these three conditions was restricted to women with multiple pregnancy.[8]

Key findings and recommendations related to preterm birth

Extreme preterm labor was the most frequent cause of perinatal loss in dichorionic twin pregnancies.[6] According to the report, 'almost two-thirds of deaths occurred before 28 weeks compared to just over 1 in 20 at term. In these pregnancies, both twins died in just under half of dichorionic pregnancies compared with almost three-quarters of monochorionic pregnancies'.[6] This finding highlights the importance of screening for and prevention of preterm birth in twin pregnancies. While acknowledging the fact that the screening performance for preterm birth in twins is lower than in singleton pregnancies, cervical-length

assessment at 20–24 weeks is the best available candidate and has been recommended as per the ISUOG guideline.[9] At 20–24 weeks' gestation, cervical length ≤20mm is the most accurate predictor of preterm birth before 32 and before 34 weeks' gestation in twin pregnancies (pooled sensitivities, specificities and positive and negative likelihood ratios were 39% and 29%, 96% and 97%, 10.1 and 9.0, and 0.64 and 0.74, respectively). Using a higher cut-off of 25 mm, the pooled positive likelihood ratio is 9.6 for the prediction of preterm birth before 28 weeks.[10,11] Some national organizations argue that screening is not justified in the absence of an effective intervention. However, interventions such as steroids and magnesium sulfate could potentially improve neonatal outcome when given in time. Unfortunately, nearly a third of eligible women did not receive these interventions[6], possibly as they remained unidentified until they presented in advanced extreme preterm labor.

Recently, in a multicenter, parallel group, open-label, randomized controlled trial of women with twin pregnancy and asymptomatic cervical dilation of 1–5 cm at 16^{+0} to 23^{+6} weeks, a combination of physical examination-indicated cerclage, indomethacin and antibiotics significantly reduced the risk of preterm birth.[12] Furthermore, this intervention resulted in a 50% reduction in preterm birth before 28 weeks of gestation (extreme preterm birth) and a 78% reduction in perinatal mortality.[12] Still, some would argue that this trial does not provide 'a screening and prevention' approach. However, recent evidence from a randomized, placebo-controlled, double-blind trial suggests that cervical-length assessment at 11–14 weeks' gestation, and administration of vaginal progesterone at a dose of 600 mg per day to those with a short cervix (<30mm), may reduce the risk of spontaneous preterm birth before 32 weeks.[13] However, this finding was a post-hoc analysis and universal treatment with vaginal progesterone did not reduce the incidence of spontaneous preterm birth in this trial. Nevertheless, a trial is urgently needed to investigate whether routine cervical-length assessment in the first trimester, combined with administration of vaginal progesterone to those with a short cervix, could prevent preterm birth in twin pregnancies. Reduction of preterm birth in twins has been identified as one of the top 10 research priorities in twins and multiples.[7]

Key findings and recommendations related to ultrasound monitoring and antenatal care

Areas of substandard care related to ultrasound monitoring included inconsistent labeling of twins, less frequent ultrasound scans than recommended, and failure of adequate growth assessment, increased surveillance, fetal Doppler assessment or referral to a tertiary fetal medicine centre when indicated. Moreover, delay in the diagnosis or referral of twin-to-twin

transfusion syndrome (TTTS) contributed to the perinatal loss of twins in this report.[6] The schedule for antenatal ultrasound monitoring in twin pregnancies has been recommended in the ISUOG twin guideline (Figures 2 and 3)[9] and broadly adopted in other guidelines.[14,15] Implementation of these guidelines was associated with a nearly 70% reduction in the stillbirth rate in twin pregnancies without a concomitant increase in neonatal death, admission to the neonatal unit or emergency Cesarean section.[16] Furthermore, a quality-improvement program working with 30 maternity units in the UK, the Twins Trust Maternity Engagement QI Project (T-MEP), demonstrated significant reductions in stillbirth, neonatal death, emergency Cesarean section and admission to the neonatal unit of twins over a 2-year period (https://twinstrust.org/healthcare-professionals/twins-trust-maternity-engagement-qi-project-t-mep.html).[17] The program aimed at improving the outcome of multiple pregnancies through improving the implementation of the National Institute for Health and Care Excellence (NICE) quality standards (Appendix S1).[18,19]

The stillbirth rate in the UK has been one of the highest in Europe, with little significant reduction in decades.[20] In 2015, a reduction in stillbirths became a top priority on the UK political and medical agenda, leading to the launch in November 2015 of a Government drive to halve the number of stillbirths and neonatal deaths in the UK by 2025. This was followed by the implementation of a number of national initiatives and targets to reduce stillbirths in the UK, such as the RCOG Each Baby Counts (https://www.rcog.org.uk/eachbabycounts) and NHS England Saving Babies' Lives Care Bundle (https://www.england.nhs.uk/wp-content/uploads/2019/03/Saving-Babies-Lives-Care-Bundle-Version-Two-Updated-Final-Version.pdf).[21,22] Together, these efforts were associated with a consistent reduction in stillbirths in the UK. It is now time to extend these efforts to include measures focused on one of the highest risk groups of pregnancies: twins and multiples.

Key to reducing the stillbirth rate is the identification of pregnancies at high risk of stillbirth and ensuring closer surveillance or delivery. However, currently recognized risk factors are extremely poor at predicting which twin pregnancies will result in stillbirth.[23,24] Therefore, until better screening tools are available, these high-risk pregnancies should be monitored closely, with early referral and timely intervention when deviation from normal is observed. Identifying those pregnancies destined for adverse perinatal outcome has many potential advantages, both clinical and financial and, most importantly, for the parents. Firstly, it would enable further stratification of care pathways for pregnant women, allowing antenatal surveillance and intervention to be focused on those at greatest risk, potentially reducing the incidence of stillbirth and other adverse outcomes. Secondly, pregnant women at high risk of adverse outcome would be ideally suited for recruitment to trials investigating promising preventative therapies, such as low-dose aspirin and early delivery. Thirdly, this model would

allow clinicians to reassure the majority of women pregnant with twins who are at low risk of adverse perinatal outcome, and possibly avoid unnecessary medical intervention or earlier delivery. Fourthly, it would be very valuable in better understanding the evolution of adverse perinatal outcomes, in particular stillbirth and extreme preterm birth. Identifying the most effective preventative interventions should help to promulgate best practice and reduce the stillbirth and extreme preterm birth rates.

Key findings and recommendations related to twin-to-twin transfusion

According to the recent MBRRACE Confidential Enquiry report, TTTS was the most common cause of pregnancy loss in monochorionic pregnancies.[6] The finding that TTTS went unrecognized in women presenting with classical maternal 'red-flag' symptoms (including sudden abdominal discomfort and swelling, abdominal pain, sudden breathlessness, inability to lie on her back, reduced fetal movements) and signs (rapidly increased abdominal girth, abdominal pain/tenderness on palpation, inability to feel fetal parts on abdominal palpation) highlights knowledge deficiency in monochorionicity-related complications. It remains to be seen whether this is an unintended consequence of the centralization of specialist services, whereby knowledge and skills are concentrated in the hands of fewer clinicians, while others become deskilled. However, this report also included examples of good care in complex pregnancies, including multidisciplinary input and preparation for birth in pregnancies complicated by discordant twin prognosis. Specialist services have been shown to be associated with improved outcome; what is needed is for these specialist services to liaise more closely with and educate other healthcare professionals in how to diagnose and facilitate the urgent initial management of complicated multiple pregnancy. The antenatal and perinatal care of these women requires far more than that provided by specialist services; close coordination and effective communication among the members of this multidisciplinary team are essential. Ultrasound training should be integral in obstetric training; the presence of polyhydramnios (Figure S2 and Videoclip S1) in a monochorionic twin pregnancy should trigger urgent referral for more detailed assessment by a fetal medicine specialist.

Key findings and recommendations related to aspirin prophylaxis

Current NICE guidance recommends prophylactic low-dose aspirin (75mg/day) for women with twin pregnancy at increased risk of pre-eclampsia according to the traditional risk factors (such as chronic hypertension, hypertensive disease during a previous pregnancy

and chronic kidney disease).[25] In a recent multicenter study in twin pregnancies, maternal risk factors alone had a detection rate (DR) of 31% for a 10% false-positive rate (FPR) for delivery with early-onset pre-eclampsia <32 weeks' gestation. For pre-eclampsia <37 weeks, the DR was 25% for a 10% FPR.[26] The combination of maternal risk factors, uterine artery Doppler, mean arterial pressure and maternal serum placental growth factor increased the DR to 86% for a 10% FPR for delivery with early-onset preeclampsia <32 weeks' gestation. For preeclampsia <37 weeks, the DR was 41% for a 10% FPR.[26] The evidence from the ASPRE trial on the effectiveness of low-dose aspirin (150mg/day) in the prevention of pre-eclampsia relates to singleton pregnancies only, as the trial excluded multiple pregnancies. Preliminary evidence suggests that, compared with 75mg/day, low-dose aspirin of 150mg/day is associated with a lower risk of hypertensive disorders in twin pregnancies with additional risk factors for pre-eclampsia.[27]

Key findings and recommendations related to care in labor

One of the recommendations in this report is to ensure prompt review by an obstetrician experienced in the management of multiple pregnancies, for all women upon attendance at a maternity triage unit, upon admission in labor and throughout labor.[6] Many would question the feasibility of this recommendation in view of current workforce demands, the lack of out-of-hours consultant presence on labor wards and limited availability of such expertise in multiple pregnancies. An alternative, perhaps more feasible strategy, might be to ensure enhanced training of all obstetric and midwifery team members on twin-specific complications that can present as an emergency, in particular the symptoms and signs of TTTS.

What is next?

Figure 4 lists the key recommendations from the Confidential Enquiry into Stillbirth and Neonatal Death in Twins relevant to obstetricians and fetal medicine specialists.

The findings of this confidential enquiry report demand a different approach to our clinical practice. It is no longer enough to simply produce guidelines based on the best quality evidence. Equally important is putting in place measures to ensure implementation of these guidelines, something that healthcare systems have struggled with for years. Despite the long-standing renown of NICE guidance, implementation has failed to match their quality. Apart from improving healthcare professionals' awareness of existing and new guidance,

ensuring adequate resources to facilitate timely and efficient implementation, despite the many competing demands, is equally important. Moreover, investment in relevant research studies is needed to address the identified evidence gaps, in particular those prioritized by our patients. Policy makers, commissioners and healthcare professionals need to ensure that the recommendations of this report are implemented in the near future.

Conclusions

The rates of stillbirth and neonatal death are still higher in twin than in singleton pregnancies, and more focused efforts are needed to redress this imbalance. Promoting best practice, updating protocols in line with evidence-based guidelines, education and staff training are essential measures likely to improve the outcome of these high-risk pregnancies. National efforts and quality-improvement initiatives, such as the UK T-MEP, provide support to clinicians in order to implement best practice.

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FIGURE LEGENDS

Figure 1. Stillbirth (a) and neonatal mortality (b) rates in UK, for births in 2014 to 2019, in singleton (blue) and twin (red) pregnancies.

Figure 2. Recommended frequency and content of ultrasound assessments for dichorionic twin pregnancy according to ISUOG guideline. DVP, deepest vertical pocket.

Figure 3. Recommended frequency and content of ultrasound assessments for monochorionic twin pregnancy according to ISUOG guideline. DVP, deepest vertical pocket; EFW, estimated fetal weight; MCA-PSV, middle cerebral artery peak systolic velocity; UA-PI, umbilical artery pulsatility index.

Figure 4. Key recommendations from the Confidential Enquiry into Stillbirth and Neonatal Death in Twins, which are relevant to obstetricians and fetal medicine specialists.

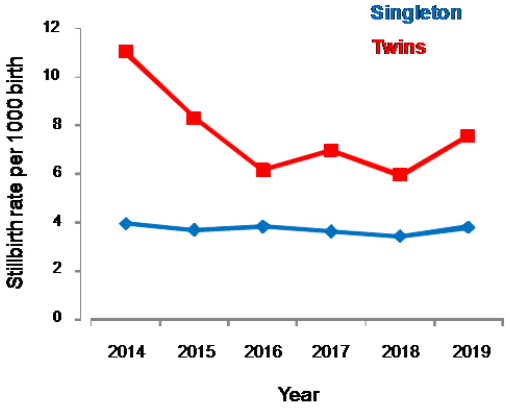

Figure 1

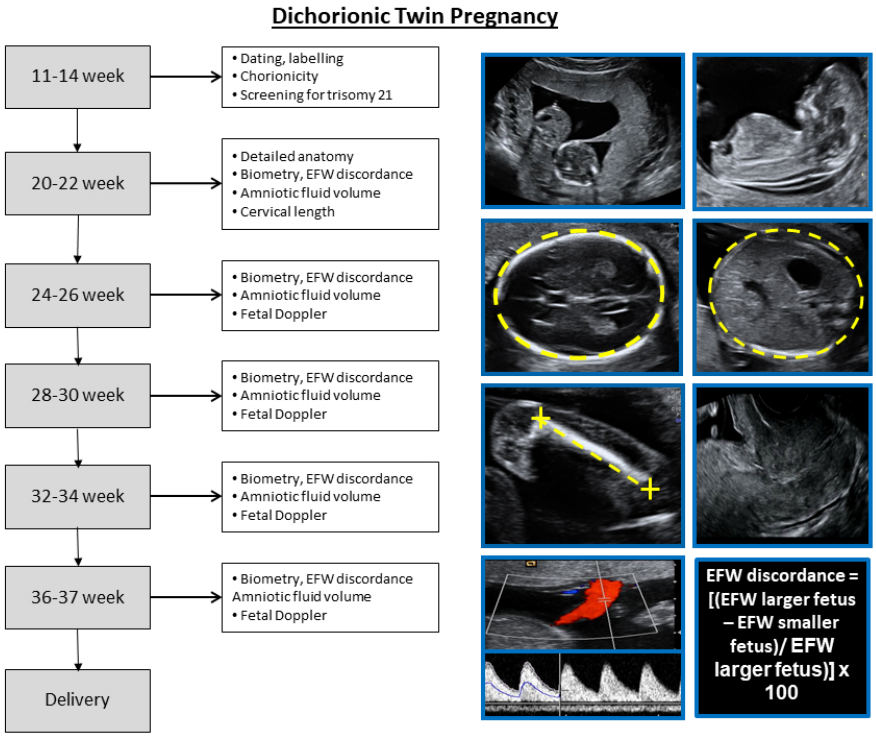

Figure 2

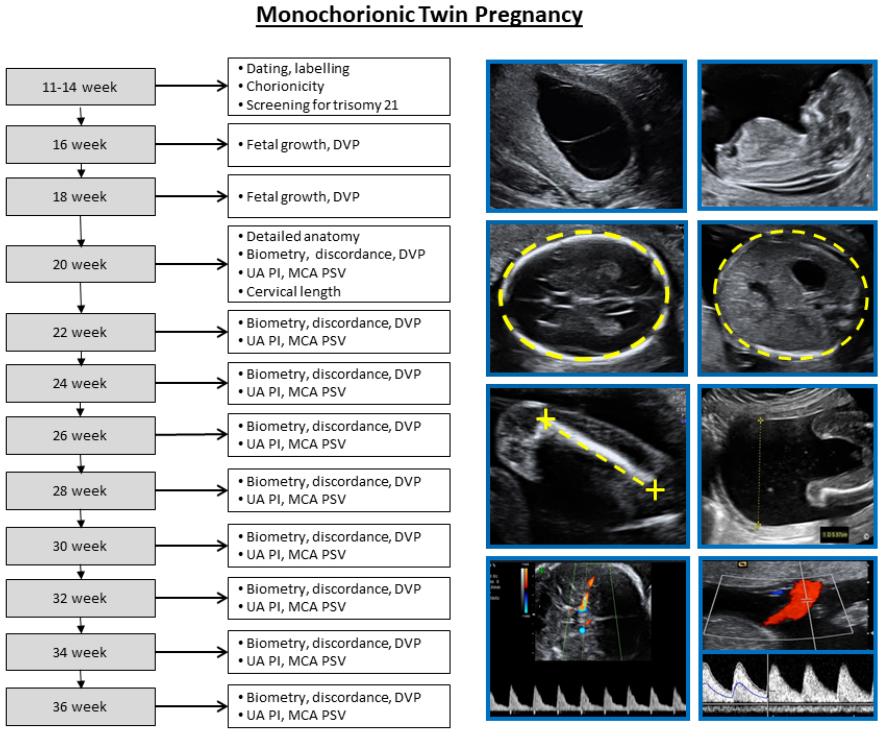

Figure 3

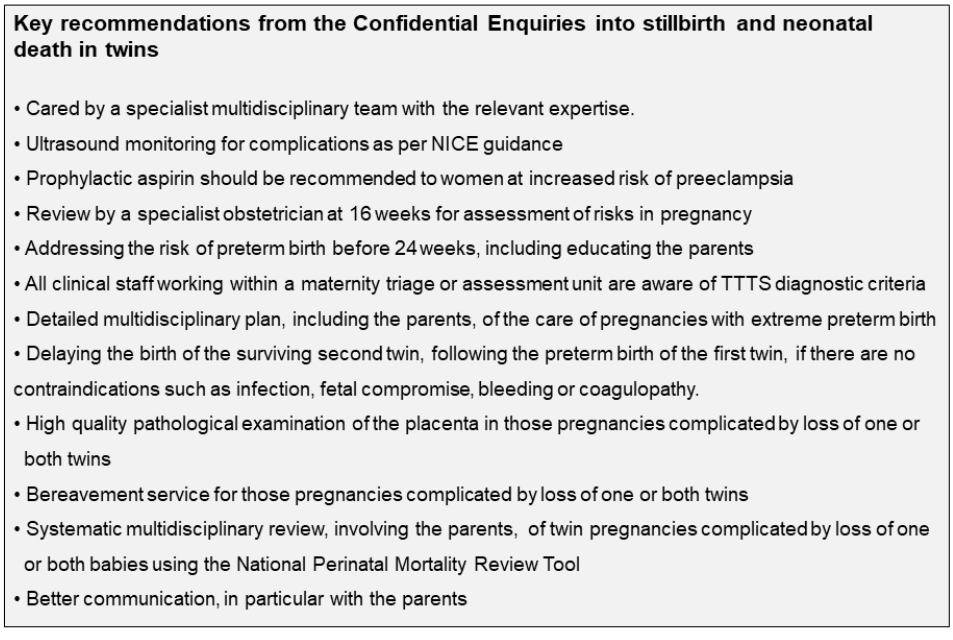

Figure 4