



Opinion

Key messages for obstetricians and fetal medicine specialists from the confidential enquiry into stillbirth and neonatal death in twins

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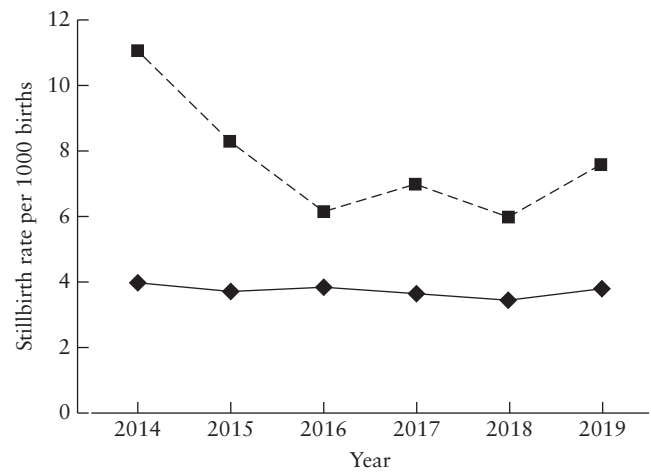


Figure 1 Stillbirth rate in the UK for births in 2014 to 2019, in singleton (—) and twin (---) pregnancies^{1–4,6}.

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 morbidity¹. According to the most recent MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK) report, the stillbirth rate in the UK is falling in singleton pregnancies¹. However, the risk of stillbirth in twin pregnancies remains twice that in singletons (Figure 1)^{1–6}.

On 14 January 2021, MBRRACE-UK published, for the first time, its report on the confidential enquiry into stillbirth and neonatal death in twin pregnancies⁶. The 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 improved quality of care could have changed the outcome of 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. A concerted multidisciplinary initiative is now required to design and conduct adequately powered

studies to address the 10 most important research questions in multiple pregnancy (Figure S1)⁷. Despite the fact that, compared with singleton pregnancies, 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 pregnancy⁸.

Key findings and recommendations related to preterm birth

In the MBRRACE-UK report, extremely preterm labor was noted as the most frequent cause of perinatal loss in dichorionic twin pregnancy⁶. According to the report, almost two-thirds of deaths occurred before 28 weeks, compared to just over 1 in 20 at term. Among cases of death in pregnancies with extremely preterm labor, both twins died in just under half of dichorionic pregnancies compared with almost three-quarters of monochorionic pregnancies⁶. This finding highlights the importance of screening for and prevention of preterm birth in twin pregnancy. While acknowledging the fact that the screening performance for preterm birth in twins is lower than that in singletons, cervical-length assessment at 20–24 weeks is the best available candidate and is recommended in the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)⁹. At 20–24 weeks’ gestation, cervical length ≤ 20 mm is the most accurate predictor of preterm birth < 32 and < 34 weeks’ gestation in twin pregnancy (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)¹⁰. Using a higher cut-off of 25 mm, the pooled positive likelihood ratio was 9.6 for the prediction of preterm birth before 28 weeks¹¹. 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 one-third of eligible women did not receive these interventions according to the MBRRACE-UK report⁶, possibly as they remained unidentified until they presented in advanced extremely 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 reduced significantly the risk of preterm birth¹². Furthermore, this intervention resulted in a 50% reduction in the rate of preterm birth before 28 weeks' gestation (extremely preterm birth) and a 78% reduction in the rate of perinatal mortality¹². Still, some would argue that this trial does not provide a 'screening-and-prevention' approach. 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 (< 30 mm) may reduce the risk of spontaneous preterm birth before 32 weeks¹³. However, this finding was based on *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 pregnancy. Reduction in the rate of preterm birth in twins has been identified as one of the top 10 research priorities in twins and multiples⁷.

Key findings and recommendations related to ultrasound monitoring and antenatal care

In the MBRRACE-UK report, areas of substandard care related to ultrasound monitoring included inconsistent labeling of twins, less frequent ultrasound scans than recommended and failure to perform adequate fetal growth or Doppler assessment, provide increased surveillance or refer the woman to a tertiary fetal medicine center when indicated. Moreover, delay in the diagnosis or referral of pregnancies with twin–twin transfusion syndrome (TTTS) contributed to the perinatal loss of twins⁶. A recommended schedule for antenatal ultrasound monitoring of twin pregnancy was proposed in the ISUOG twin pregnancy guideline (Figures S2 and S3)⁹ and has been broadly adopted in other guidelines^{14,15}.

Implementation of National Institute for Health and Care Excellence (NICE) guidelines was associated with a more than 70% reduction in stillbirth rate in twin pregnancies, without a concomitant increase in the rate of neonatal death, admission to the neonatal unit or emergency Cesarean section¹⁶. 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 the rates of stillbirth, neonatal death, emergency Cesarean section and admission to the neonatal unit of twins over a 2-year period¹⁷. The program aimed at improving the outcome of multiple pregnancies through promoting effective implementation of the NICE quality standards (Appendix S1)^{18,19}.

The stillbirth rate in the UK has in recent years been one of the highest in Europe, with little significant reduction in the rate over the past decades²⁰. In 2015, reducing 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 implementation of a number of national initiatives and targets to reduce stillbirths in the UK, such as the Royal College of Obstetricians and Gynaecologists' Each Baby Counts program and the NHS England Saving Babies' Lives Care Bundle^{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 groups of pregnancies at highest risk: twins and multiples.

The key to reducing the stillbirth rate is 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 clinically and financially as well as, 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, identification of high-risk pregnancies would be highly valuable in better understanding the evolution of adverse perinatal outcomes, in particular stillbirth and

extremely preterm birth. Determining the most effective preventative interventions should help to promulgate best practice and reduce the rates of stillbirth and extremely preterm birth.

Key findings and recommendations related to twin–twin transfusion

According to the recent MBRRACE-UK report, TTTS was the most common cause of pregnancy loss in monochorionic pregnancies⁶. 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 and reduced fetal movements) and signs (rapidly increased abdominal girth, abdominal pain/tenderness on palpation and 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, the 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; there is a need for these specialist services to liaise more closely with other healthcare professionals and to educate them 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 S4 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 (75 mg/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% at 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% at a 10% FPR²⁶. The combination of maternal risk factors, uterine artery Doppler, mean arterial pressure and maternal serum

placental growth factor increased the DR to 86% at a 10% FPR for delivery with early-onset pre-eclampsia < 32 weeks’ gestation. For pre-eclampsia < 37 weeks, the DR was 41% at a 10% FPR²⁶. The evidence from the ASPRE (Aspirin for Evidence-Based Preeclampsia Prevention) trial on the effectiveness of low-dose aspirin (150 mg/day) in the prevention of pre-eclampsia relates to singleton pregnancies only as the trial excluded multiple pregnancies. Preliminary evidence suggests that, compared with 75 mg/day, low-dose aspirin of 150 mg/day is associated with a lower risk of hypertensive disorders in twin pregnancies with additional risk factors for pre-eclampsia²⁷.

Key findings and recommendations related to care in labor

One of the recommendations in the MBRRACE-UK report is to ensure prompt review by an obstetrician experienced in the management of multiple pregnancy, for all women upon attendance at a maternity triage unit, upon admission during labor and throughout labor⁶. 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 the 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?

Box 1 lists the key recommendations from the confidential enquiry into stillbirth and neonatal death in twins that are relevant to obstetricians and fetal medicine specialists. The findings of the confidential enquiry report demand a different approach from our current 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 with which healthcare systems have struggled for years. Despite the long-standing renown of NICE guidance, implementation has failed to match their quality standards. Apart from improving healthcare professionals’ awareness of existing and new guidance, equally important is ensuring availability of adequate resources to facilitate timely and efficient implementation, despite the many competing demands. 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 the MBRRACE-UK report are implemented in the near future.

Box 1 Key recommendations from the confidential enquiry into stillbirth and neonatal death in twins⁶, which are relevant to obstetricians and fetal medicine specialists

- Care by a specialist multidisciplinary team with the relevant expertise
- Ultrasound monitoring for complications as per National Institute for Health and Care Excellence guidance
- Prophylactic aspirin recommended to women at increased risk of pre-eclampsia
- Review by a specialist obstetrician at 16 weeks for assessment of pregnancy risk
- Addressing the risk of preterm birth before 24 weeks, including educating the parents
- All clinical staff working within a maternity triage or assessment unit aware of twin–twin transfusion syndrome diagnostic criteria
- Detailed multidisciplinary plan, including the parents, of the care of pregnancies with extremely preterm birth
- Delaying the birth of the surviving second twin, following the preterm birth of the first twin, if there are no contraindications, such as infection, fetal compromise, bleeding or coagulopathy
- High-quality pathological examination of the placenta in those pregnancies complicated by loss of one or both twins
- Bereavement service for those pregnancies complicated by loss of one or both twins
- Systematic multidisciplinary review, involving the parents, of twin pregnancies complicated by loss of one or both babies using the National Perinatal Mortality Review Tool
- Better communication, in particular with the parents

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.

REFERENCES

1. Draper ES, Gallimore ID, Smith LK, Fenton AC, Kurinczuk JJ, Smith PW, Boby T, Manktelow BN; the MBRRACE-UK Collaboration. *MBRRACE-UK Perinatal Mortality Surveillance Report, UK Perinatal Deaths for Births from January to December 2018*. The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester: Leicester, 2020.
2. Office for National Statistics (ONS). Birth characteristics in England and Wales: 2019. <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthcharacteristicsinenglandandwales/2019>.
3. Draper ES, Gallimore ID, Smith LK, Kurinczuk JJ, Smith PW, Boby T, Fenton AC, Manktelow BN; the MBRRACE-UK Collaboration. *MBRRACE-UK Perinatal Mortality Surveillance Report, UK Perinatal Deaths for Births from January to December 2017*. The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester: Leicester, 2019.
4. Draper ES, Gallimore ID, Kurinczuk JJ, Smith PW, Boby T, Smith LK, Manktelow BN; the MBRRACE-UK Collaboration. *MBRRACE-UK Perinatal Mortality Surveillance Report, UK Perinatal Deaths for Births from January to December 2016*. The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester: Leicester, 2018.
5. Khalil A. Unprecedented fall in stillbirth and neonatal death in twins: lessons from the UK. *Ultrasound Obstet Gynecol* 2019; **53**: 153–157.
6. Draper ES, Gallimore ID, Kurinczuk JJ, Kenyon S; the MBRRACE-UK Collaboration. *MBRRACE-UK Perinatal Confidential Enquiry: Stillbirths and neonatal deaths in twin pregnancies*. The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester: Leicester, 2020.
7. Lam JR, Liu B, Bhate R, Fenwick N, Reed K, Duffy JMN, Khalil A; Global Twins and Multiples Priority Setting Partnership Collaborators. Research priorities for the future health of multiples and their families: The Global Twins and Multiples Priority Setting Partnership. *Ultrasound Obstet Gynecol* 2019; **54**: 715–721.
8. SMFM Research Committee; Grantz KL, Kawakita T, Lu YL, Newman R, Berghella V, Caughey A. SMFM Special Statement: State of the science on multifetal gestations: unique considerations and importance. *Am J Obstet Gynecol* 2019; **221**: B2–B12.
9. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, Kilby MD, Lewi L, Nicolaides KH, Oepkes D, Raine-Fenning N, Reed K, Salomon LJ, Sotiriadis A, Thilaganathan B, Ville Y. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. *Ultrasound Obstet Gynecol* 2016; **47**: 247–263.
10. Conde-Agudelo A, Romero R. Prediction of preterm birth in twin gestations using biophysical and biochemical tests. *Am J Obstet Gynecol* 2014; **211**: 583–595.
11. Conde-Agudelo A, Romero R, Hassan SS, Yeo L. Transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in twin pregnancies: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2010; **203**: 128.e1–12.
12. Roman A, Zork N, Haeri S, Schoen CN, Saccone G, Colihan S, Zelig C, Gimovsky AC, Seligman NS, Zullo F, Berghella V. Physical examination–indicated cerclage in twin pregnancy: a randomized controlled trial. *Am J Obstet Gynecol* 2020; **223**: 902.e1–11.
13. Rehal A, Benkó Z, De Paco Matallana C, Syngelaki A, Janga D, Cicero S, Akolekar R, Singh M, Chaveeva P, Burgos J, Molina FS, Savvidou M, De La Calle M, Persico N, Quezada Rojas MS, Sau A, Greco E, O’Gorman N, Plasencia W, Pereira S, Jani JC, Valino N, Del Mar Gil M, Maclagan K, Wright A, Wright D, Nicolaides KH. Early vaginal progesterone versus placebo in twin pregnancies for the prevention of spontaneous preterm birth: a randomized, double-blind trial. *Am J Obstet Gynecol* 2021; **224**: 86.e1–19.
14. Kilby, MD, Bricker, L; the Royal College of Obstetricians and Gynaecologists. Management of monochorionic twin pregnancy. *BJOG* 2016; **124**: e1–45.
15. National Institute for Health and Care Excellence. Twin and triplet pregnancy [NG137], 2019. <https://www.nice.org.uk/guidance/ng137>.
16. Khalil A, Giallongo E, Bhide A, Papageorgiou AT, Thilaganathan B. Reduction in twin stillbirth following implementation of NICE guidance. *Ultrasound Obstet Gynecol* 2020; **56**: 566–571.
17. Twins and Multiple Births Association. NICE works: the final report. Twins and Multiple Births Association Maternity Engagement Project Final Report, 2019. <https://twintrust.org/uploads/assets/afcc44b3-776e-4341-8a16e9bd990c3425/NICE-works-final-report.pdf>.
18. Twins Trust Maternity Engagement QI Project (T-MEP). <https://twintrust.org/healthcare-professionals/twins-trust-maternity-engagement-qi-project-t-mep.html>.
19. National Institute for Health and Care Excellence. Multiple pregnancy: twin and triplet pregnancies [QS46], 2013. <https://www.nice.org.uk/guidance/qs46>.
20. Flenady V, Koopmans L, Middleton P, Frøen JF, Smith GC, Gibbons K, Coory M, Gordon A, Ellwood D, McIntyre HD, Fretts R, Ezzati M. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 2011; **377**: 1331–1340.
21. Royal College of Obstetricians and Gynaecologists. Each Baby Counts. <https://www.rcog.org.uk/eachbabycounts>.
22. NHS. Saving Babies’ Lives Version Two. A care bundle for reducing perinatal mortality <https://www.england.nhs.uk/wp-content/uploads/2019/03/Saving-Babies-Lives-Care-Bundle-Version-Two-Updated-Final-Version.pdf>.

23. Cimpoa B, Syngelaki A, Litwinska E, Muzaferovic A, Nicolaides KH. Increased nuchal translucency at 11–13 weeks' gestation and outcome in twin pregnancy. *Ultrasound Obstet Gynecol* 2020; 55: 318–325.
24. Mackie FL, Hall MJ, Morris RK, Kilby MD. Early prognostic factors of outcomes in monochorionic twin pregnancy: systematic review and meta-analysis. *Am J Obstet Gynecol* 2018; 219: 436–446.
25. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management [NG133], 2019. <https://www.nice.org.uk/guidance/ng133>.
26. Benkó Z, Wright A, Rehal A, Cimpoa B, Syngelaki A, Delgado JL, Tsokaki T, De Alvarado M, Vojtassakova D, Malligiannis Ntalianis K, Chaveeva P, Del Campo A, De Ganzo T, Resta C, Atanasova V, Accurti V, Villalain C, Aguilera J, Dojcinovska D, O'Gorman N, Plasencia W, Zingler E, Dutemeyer V, Alvar B, Casanova MC, Nicolaides KH. Prediction of pre-eclampsia in twin pregnancies by maternal factors and biomarkers at 11–13 weeks' gestation: data from the EVENTS trial. *Ultrasound Obstet Gynecol* 2021; 57: 257–265.
27. Kalafat E, Shirazi A, Thilaganathan B, Khalil A. The role of aspirin in prevention of preeclampsia in twin pregnancies: does the dose matter? *Am J Obstet Gynecol* 2020; 223: 457–458.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:


 **Figure S1** Top 10 most important research questions related to twins and multiples⁷.

Figure S2 Recommended frequency and content of ultrasound assessments for dichorionic twin pregnancy, according to International Society of Ultrasound in Obstetrics and Gynecology guidelines⁹. EFW, estimated fetal weight.

Figure S3 Recommended frequency and content of ultrasound assessments for monochorionic twin pregnancy, according to International Society of Ultrasound in Obstetrics and Gynecology guidelines⁹. DVP, deepest vertical pocket; EFW, estimated fetal weight; MCA-PSV, middle cerebral artery peak systolic velocity; UA-PI, umbilical artery pulsatility index.

Figure S4 Ultrasound images of a monochorionic diamniotic twin pregnancy complicated by twin–twin transfusion syndrome.

Appendix S1 The National Institute for Health and Care Excellence (NICE) Quality Standards for multiple pregnancy¹⁹

 **Videoclip S1** Ultrasound imaging of a monochorionic diamniotic twin pregnancy complicated by twin–twin transfusion syndrome.