Cause of intrauterine and neonatal Death in Twin Pregnancies (CoDiT)

Gulati, Nidhi; Mackie, Fiona; Cox, Phillip; Marton, Tamas; Heazell, Alexander; Morris, R. Katie; Kilby, Mark

DOI:
10.1111/1471-0528.16291

Document Version
Peer reviewed version

Citation for published version (Harvard):
Gulati, N, Mackie, F, Cox, P, Marton, T, Heazell, A, Morris, RK & Kilby, M 2020, 'Cause of intrauterine and neonatal Death in Twin Pregnancies (CoDiT): development of a novel classification system', *BJOG: An International Journal of Obstetrics & Gynaecology*. https://doi.org/10.1111/1471-0528.16291

Cause of intrauterine and neonatal Death in Twin Pregnancies (CoDiT): development of a novel classification system

Nidhi Gulati[1,2], Fiona L Mackie[1,2], Phillip Cox[3], Tamas Marton[3], Alexander E P Heazell[4,5], R Katie Morris[2,6], Mark D Kilby[1,2]

[1]Institute of Metabolism & Systems Research, College of Medical & Dental Sciences, University of Birmingham, Birmingham, B15 2TT

[2]Fetal Medicine Centre, Birmingham Women's & Children's Foundation Trust, Birmingham, B15 2TG.

[3]Cellular Pathology Department, Birmingham Women's Hospital, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK

[4]Maternal and Fetal Health Research Centre, University of Manchester, Manchester, UK.

[5]St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK.

[6]Institute of Applied Health Research, College of Medical & Dental Sciences, University of Birmingham, Birmingham, B15 2TT.

Corresponding Author: Dr Nidhi Gulati. Institute of Metabolism and Systems Research, College of Medical & Dental Sciences, University of Birmingham, Birmingham, B15 2TT. **nidhigulati@nhs.net**

Running Head: Classifying Cause of Death in Twins: CoDiT

ABSTRACT

Objective: Twin pregnancies have a significantly higher perinatal mortality than singleton pregnancies and current classification systems for perinatal death lack twin-specific categories, potentially leading to loss of important information regarding cause of death. We introduce and test a classification system designed to assign a cause of death in twin pregnancies (CoDiT).

Design: Retrospective cross-sectional study.

Setting: Tertiary maternity unit in England with a perinatal pathology service.

Population: Twin pregnancies in the West Midlands affected by fetal or neonatal demise of one or both twins between 1st January 2005 and 31st December 2016 in which post-mortem examination was undertaken.

Methods: A multidisciplinary panel designed CoDiT by adapting the most appropriate elements of singleton classification systems. The system was tested by assigning cause of death in 265 fetal and neonatal deaths from 144 twin pregnancies. Cause of death was validated by another obstetrician blinded to the original classification.

Main Outcome Measures: Inter-rater, intra-rater, inter-disciplinary agreement and cause of death.

Results: Cohen's Kappa demonstrated "strong" (>0.8) inter-rater, intra-rater and inter-disciplinary agreement (95% CI 0.70-0.91). The commonest cause of death irrespective of chorionicity was the placenta; twin-to-twin transfusion syndrome (TTTS) was the commonest placental cause in monochorionic twins and acute chorioamnionitis in dichorionic twins.

Conclusions: This novel classification system records causes of death in twin pregnancies from post-mortem reports with high inter-user agreement. We highlight differences in aetiology of death between monochorionic and dichorionic twins.

Keywords: Twins; Multiple Pregnancy; Cause of death; Classification system; Stillbirth; Perinatal Death; Monochorionic; Dichorionic.

Twitter: New classification system for #twin cause of death 'CoDiT' shows high rater agreement

MANUSCRIPT

Introduction

Multiple pregnancies occur in 1.6% of pregnancies in England and Wales; the commonest are twin pregnancies (98%)(1). Compared with singletons, monochorionic twins have a thirteen-fold increased risk of stillbirth, and dichorionic twins a five-fold increased risk(2-4). Twin pregnancies account for almost 6% of all stillbirths, 18% of neonatal deaths (NND) and 20% of preterm births (many of which occur <28 weeks' gestation)(5,6). Complex anastomoses connecting fetal circulations in monochorionic placentas leads to highly morbid conditions unique to these pregnancies, such as twin-to-twin transfusion syndrome (TTTS). Twin-specific risks of dichorionic pregnancies include prematurity, selective growth restriction and co-twin interventions. Whilst pathological causes of death in twin pregnancies are well established, a classification system specifically for twins does not exist.

Classification systems standardise recording of aetiology of mortality, inform public healthcare policies, clinical care, research, and facilitate comparison of global rates(7). Existing classification systems include limited acknowledgement of the complexity of multiple pregnancies. In Codac (Cause of Death and Associated Conditions), multiple pregnancies are classified as an associated perinatal cause of death, and TTTS is the only twin-specific cause cited in ReCoDe (Relevant Condition at Death)(7,8).

A 2016 systematic review identified 81 classification systems created, modified and/or used between 2009 and 2014; not including the World Health Organisation (WHO) International Classification of Diseases 10th revision classification for perinatal deaths (ICD-PM)(9-11). A Delphi consensus identified the 17 most important characteristics required for a global classification system of perinatal deaths, including: [1] a sufficiently comprehensive list of categories to minimise the proportion of deaths classified as "other", [2] accommodates stillbirths and NND, and [3] shows high inter- and intra-rater reliability(12). Assessment of existing classification systems against the 17 characteristics found that

82% of systems aligned with fewer than 5 of these characteristics. The most aligned to these aims were Codac (9/17) and Tulip (7/17)(10). Despite overall poor performance, development of a globally effective system would benefit from referring to the most aligned systems(13).

To address the need to record causes of mortality in twin pregnancies, we developed and validated a classification system to report causes of fetal or NND in twin pregnancies that aimed to meet as many of the characteristics of the Delphi study as possible.

Methods

Developing the classification system

A multidisciplinary panel of four obstetricians and two perinatal pathologists created a classification system for twin pregnancies by adapting and combining the two systems which scored highest against the Delphi consensus criteria: Codac and Tulip(7,12,14). As Tulip resonates with the aim of our system to identify underlying aetiologies, the main categories of Tulip – congenital abnormality, placenta, prematurity, infection, other and unknown – feature in our system; named CoDiT (Cause of Death in Twins) (Appendix S1). Codac, unlike Tulip, recognises umbilical cord events as a main category for cause of death. As cord accidents are a specific risk for monochorionic monoamniotic (MCMA) pregnancies, umbilical cord is a main category in CoDiT.

Each of the seven main categories has subcategories drawn from singleton classification systems, with additional twin-specific subcategories. Conjoined twins and twin-reversed arterial perfusion (TRAP) were added to congenital abnormalities, with distinction between the pump and acardiac twin. TTTS is a subcategory in placental causes of death, with distinction between chronic and acute, intrapartum or antenatal variants (the latter with or without neurological damage) and treated and untreated TTTS. Combining pathological and clinical entities recognises the multi-dimensional causes of perinatal mortality in twins and acknowledges that there may be inherent differences between diagnosing TTTS antenatally and post-mortem. The “unknown” category has two subcategories allowing distinction

between cases in which cause of death is unknown despite thorough post-mortem investigation or unknown because important information was missing to determine the cause of death.

CoDiT is prefaced with a section to record the mother's demographics, medical and obstetric history, whether demise was of one or both twins, gestation at death, age at death if a NND, and gestation at delivery. Recording mode of death enables distinction between "how" and "why" the death occurred. For example, if a pregnancy was terminated for a lethal congenital abnormality, the classification system should reflect that the fetus(es) would have had a high chance of mortality because of the underlying anomaly irrespective of prenatal intervention.

Once agreement within the panel was achieved on the final classification system, it was used to classify causes of death from post-mortem reports. It was determined *á priori* that the reliability of CoDiT would be determined by the level of inter-rater, inter-disciplinary and intra-rater agreement.

Testing CoDiT

Post-mortems conducted at a West Midlands tertiary unit between 1st January 2005 and 31st December 2016 on fetuses and neonates from twin pregnancies were identified from a pre-existing database of all post-mortems conducted at the unit (Figure 1). All post-mortems had written parental consent and were performed by perinatal pathologists. Project development had no funding, patient involvement, or core outcome set and was registered as a service evaluation project by the unit's clinical governance team. Each pregnancy was anonymised by assigning a case number then the letter "A" for twin 1, or "B" for twin 2. Each post-mortem report begins with a clinical summary provided by the referring hospital, from which all demographic and clinical data was obtained, including gestation at death and delivery (or age at death if NND). A summary of the main findings and a detailed description of macroscopic external and internal organ examination findings is provided, followed by a description of the placenta including chorionicity, vascular territories and findings from injection studies. An injection study was conducted if TTTS was suspected or there was significant weight discordance between twins. Injection studies were not possible if the placenta was too small or damaged.

Individual organ and placental histology and microbiological and genetic testing results are then described. All post-mortem reports of fetuses and neonates in this cohort were examined and a cause of death assigned independently by an obstetrician and perinatal pathologist. Whilst CoDiT enables users to capture all post-mortem findings, users understood to select a single cause of death. Subsequent panel consensus was drawn to allow data analysis. One-third of cases were randomly selected for independent classification by an external obstetrician, who had the same information and case numbers as other raters, and re-classification by the initial obstetrician after a 2-year interval. Cohen's Kappa was used to separately calculate inter-rater agreement between the external and initial obstetrician, intra-rater agreement and inter-disciplinary agreement, using a hand-programmed matrix in Microsoft Excel. Qualitative interpretation of Kappa values was as follows: <0.4, minimal; 0.4-0.59, weak; 0.6-0.79, moderate; 0.8-0.9, strong; and >0.9, almost perfect(15).

Results

General Findings

Between 1st January 2005 and 31st December 2016, 265 fetal and neonatal post-mortems from 144 twin pregnancies were performed, referred from 14 hospitals throughout the West Midlands. Table 1 summarises maternal demographic and descriptive data. Forty-six percent of deaths occurred in monochorionic twins (122/265 post-mortems). Chorionicity was undesignated at post-mortem in 18% (47/265) as the placenta was either not submitted or unsuitable (too fragmented or incorrectly fixed) for examination. Most demises were in-utero (miscarriages and stillbirths); 7% were NND (18/265), of which 61% (11/18) were dichorionic pregnancies. Most deaths, irrespective of chorionicity, were double-twin deaths (246/265; 93%); a greater proportion of single twin deaths occurred in dichorionic compared with monochorionic pregnancies (8% vs. 5%). Mean gestation at death was 19-20 weeks (range 8-37 weeks). Most deaths were spontaneous (219/265; 83%); selective reduction and death within a week of medical intervention solely affected monochorionic pregnancies (9% of monochorionic deaths (11/122).

Irrespective of chorionicity, the most commonly assigned main category was "placental" (117/265) (Figure 2), followed by "unknown" (65/265), of which 80% (52/65) were unknown "despite thorough post-mortem investigation". The remaining 20% (13/65) were subcategorised as unknown due to "important information missing", most commonly referring to the placenta not being submitted.

Inter-rater, intra-rater and inter-disciplinary agreement

The Kappa coefficient for the main cause of death was "strong" for all measured combinations of agreement; inter-rater 0.80 (95% CI 0.70-0.91), intra-rater 0.80 (95% CI 0.71-0.90) and an inter-disciplinary agreement 0.81 (95% CI 0.75-0.87). This indicates that the main cause of death can be reproducibly categorised by different users. However, agreement was "minimal" and "weak" when all 51 subcategories were considered, with a Kappa co-efficient of 0.39 (95% CI 0.27-0.51) for inter-rater, 0.33 (95% CI 0.22-0.43) for intra-rater, and 0.4 (95% CI 0.34-0.47) for inter-disciplinary agreement. This may be influenced by the large number of subcategories. Nevertheless percentage agreement in

main- and subcategories for all combinations was high; 86% (70/81) inter-rater main- and 83% (67/81) subcategory agreement, 86% (80/93) intra-rater main- and 76% (71/93) subcategory agreement and 86% (228/265) inter-disciplinary main- and 82% (216/265) subcategory agreement. The commonest subcategory disagreement was acute chorioamnionitis versus ascending infection, representing 29% (4/14) of inter-rater, 18% (4/22) of intra-rater and 16% (8/49) of inter-disciplinary disagreement. Although user guidance states that ascending infection should only be assigned when there is proven birth canal colonisation, users argued that acute chorioamnionitis often derives from ascending infection.

Cause of death by chorionicity

Figure 3 summarises cause of death by chorionicity and amnionicity. Chi-squared testing demonstrated that cause of death was significantly different between monochorionic and dichorionic twins ($p<0.01$). Significantly more monochorionic twins died of congenital abnormalities ($p<0.05$) or umbilical cord events ($p<0.05$) than dichorionic twins and significantly more dichorionic twins died of infection than monochorionic twins ($p<0.001$).

Dichorionic twins

Placental causes represented 47% (45/96) of deaths in dichorionic pregnancies, with acute chorioamnionitis being the commonest subcategory (40/45; 89%). An "unknown" cause of death was the second commonest classification (19/96; 20%), all "despite thorough investigation", except one, classified as unknown due to important information missing because parental consent was for a limited post-mortem.

Prematurity, the third commonest cause (10/96; 10%), was secondary to preterm prelabour rupture of membranes (PPROM) in 6/10 cases, spontaneous preterm labour in 3/10, and complications of prematurity in one 22-day old neonate, born at 31 weeks' gestation. The 8 deaths due to infection (8/96; 8%) were double twin deaths from 4 pregnancies, 3 of which were ascending infections and 1 transplacental infection. Congenital abnormalities affected 8 fetuses, of which 2 were co-twins

affected by lethal urogenital anomalies. All but one of the dichorionic pregnancies affected by congenital abnormalities resulted in death of the co-twin within two weeks of death of the abnormal twin. The 5 deaths categorised as "other" were from 3 dichorionic pregnancies; 2 sets of twins that died secondary to maternal diseases, and a NND at 17 minutes of age at 25 weeks gestation due to fetal trauma at birth.

Monochorionic twins

Placental causes of death were most common in monochorionic twins (53/122; 43%); TTTS was the commonest subcategory (36/53; 68%). In total, 51 deaths were categorised as TTTS but in 15/51 (29%), the placenta was not submitted or too fragmented to confirm chorionicity, and TTTS was diagnosed from supporting information using the clinical history and ultrasound findings provided by the referring hospital and examining the fetuses. Most TTTS deaths were chronic and untreated (40/51; 78%). Only 20 of the 36 cases of TTTS with a placenta sent to pathology underwent injection studies, representing 39% (20/51) of the total number of fetuses categorised as TTTS. Of the 4 fetal deaths secondary to chronic treated TTTS, one set of twins died at 27+2 weeks' gestation following amnioreduction, 1 fetus died spontaneously more than 7 days after fetoscopic laser ablation (FLA), with survival of its co-twin, and the other died within 4 days of FLA with subsequent death of its co-twin due to acute TTTS. In 47% (24/51) of TTTS cases, clinical information from the referring hospital provided no information about possible evidence of TTTS antenatally and as such TTTS was diagnosed solely based on post-mortem findings. For 13 of these 24 cases diagnosed with TTTS solely at post-mortem, the diagnosis was made without a suitable placenta to examine and was based on features noted on fetal examination such as body or organ weight discordance. Of the 20 cases in which injection studies were performed, TTTS was diagnosed solely from injection studies in 20% (n=4).

An "unknown" cause of death was the second commonest category (29/122; 24%), all of which were categorised as such "despite thorough investigation". A third of these "unknown" cases underwent injection studies (10/29; 34%), all demonstrating a balanced circulation.

The third commonest cause was congenital abnormalities, representing 23% of monochorionic twin deaths (28/122), of which TRAP (acardiac and pump) was the commonest abnormality (13/28; 46%). There were 28 MCMA pregnancies, representing 23% of the monochorionic pregnancies in this cohort with a gestational age at death ranging from 8 to 28 weeks' gestation. The commonest cause of death in MCMA twins was congenital abnormalities (11/28), of which almost two-thirds were twin-specific (7/11) (i.e. TRAP or conjoined twins). All deaths due to umbilical cord events (4/122; 3%) occurred in MCMA pregnancies.

Cause of death by double and single-twin demise

In monochorionic pregnancies, 95% were double twin deaths (116/122), with 44% (51/116) classified as placental, 24% (28/116) due to congenital abnormalities, 22% (25/116) as unknown, and the remaining due umbilical cord events (n=4), prematurity (n=3) and "other" (n=5). In TTTS, 98% of deaths were double twin deaths (50/51). In dichorionic pregnancies, 92% of deaths were double twin deaths (88/96), with 50% (44/88) classified as placental and 15% (13/88) as unknown. All deaths due to prematurity, infection, "other" causes and congenital abnormalities in dichorionic twins were double twin deaths.

Of the 19 single twin deaths, 58% had an unknown cause of death (11/19), all of which were spontaneous fetal losses with a mean gestational age at death of 23 weeks (range 12-20^{+3} weeks' gestation). Four of these single twin deaths with an unknown cause were from monochorionic pregnancies, six from dichorionic pregnancies and one did not have a placenta submitted to confirm chorionicity.

Gestation at death and delivery

Table 2 outlines the causes of death by gestational age and chorionicity. The most common gestation for death irrespective of chorionicity was before 24 weeks' gestation (129/218; 59%), representing 60% of deaths in monochorionic (73/122) and 58% of deaths in dichorionic twins (56/96). In both

chorionicities, the most common cause of death before 24 weeks was placental, affecting 41% of monochorionic twins (30/73) that died before 24 weeks and 43% of dichorionic twins (24/56).

Gestation at death and delivery was specified in 59% of cases, of which 11% delivered more than 4 weeks after death (n=17). In most of these, cause of death was unknown (65%; n=11) and 76% were <24 weeks' gestation (13/17). Of the 4 deaths >24 weeks' gestation that delivered more than 4 weeks after death, three were single intrauterine deaths in dichorionic pregnancies, delivered with the surviving co-twin between 34+0 and 40+2 weeks, and one was a monochorionic twin that died at 24 weeks' gestation with termination of the co-twin at 32 weeks, when both twins were delivered together.

Discussion

Main Findings

CoDiT is a classification system designed specifically for twin pregnancies using post-mortem reports as the primary source of information. Initial testing demonstrates high inter- and intra-rater reliability for main cause of death. The commonest cause of death overall was placental conditions, with acute chorioamnionitis the commonest subcategory in dichorionic twins, and TTTS in monochorionic twins. Most deaths were double demises and irrespective of chorionicity, most occurred before 24 weeks' gestation. Delivery more than 4 weeks after death was associated with increased likelihood of the cause of death being unknown.

Strengths and Limitations

As parents had to consent to post-mortem examination, this introduces a potential source of case selection bias. As such, our cohort may include disproportionately fewer terminated pregnancies due to a known abnormality, single deaths with prolonged in utero retention or a higher number of spontaneous deaths without an obvious antenatal cause. Pre-existing classification systems rely on clinical information, yet post-mortems provide new information to change the diagnosis in 9-11%, and additional information in 22-76%(16-21). However, pathological causes of twin demise remain

unknown in 25%. Post-mortem reports are not standardised and depend upon availability of local expertise in perinatal pathology and the quality of clinical information received. A standardised approach to submitting clinical information, post-mortem procedure, reporting and criteria for conducting injection studies may improve the accuracy of assigning cause of death.

In the 2017 UK Perinatal Mortality Surveillance Report only 50% of parents of stillborn babies and 28% of parents affected by NND consented to post-mortem(22). Restricting CoDiT to cases in which post-mortem was undertaken limits its general usability.

CoDiT already aligns with six of the essential characteristics in the Delphi study (accommodates fetal death, stillbirths and NND; distinguishes between NND and stillbirth; has a small number of main categories; shows strong inter- and intra- rater agreement; allows associated factors such as placental descriptions to be recorded and distinguished from the cause of death; requires the single most important factor to be recorded)(12). CoDiT requires external validation to meet other characteristics (ease of use; clear guidelines; produces easily understood data; has a sufficiently comprehensive list of categories to minimise the proportion of deaths classified as "unknown")(12). An important characteristic we were unable to assess was the ability of CoDiT to distinguish between antepartum and intrapartum deaths, as our cohort contained no intrapartum deaths(12). As a higher proportion of twin pregnancies are delivered electively by Caesarean section, a lack of intrapartum deaths may reflect the reduced number of women who labour with twin pregnancies.

The proportion of cases classified as unknown (25%) is comparable to Codac but higher than Tulip (11%), which captured late fetal losses, stillbirths, NNDs and infant deaths, and ReCoDe (15%), which only applies to stillbirths(8,14). CoDiT was designed to be used across all gestations including first trimester. In our cohort, 20% (54/265) of fetuses were <16 weeks' gestation. Determining cause of death from early gestation fetal post-mortems can be extremely difficult. However, we have shown the value of incorporating these early gestations, as the commonest cause of death <24 weeks' in our cohort was placental (54/129; 42%).

The high number of placental causes of deaths in this cohort highlights the importance of submitting the placenta for histopathological examination in twin deaths. In our view it should be a mandatory component of postnatal investigation(23). It is crucial that obstetricians provide high quality clinical information to inform a post-mortem. Ultrasound designation of chorionicity in the first trimester has high sensitivity and specificity(24). Such data are vital to inform the pathologist when no placenta is submitted. A systematic review concluded that placental examination was useful to determine cause of stillbirth in 60% of studies(25). Placental examination is associated with a significant reduction in "unexplained" deaths in singleton pregnancies (OR 0.17; 95% CI 0.04-0.70) and is more cost-effective than post-mortem of the baby or cytogenetics(26,27). For twins, placental examination confirms chorionicity and amnionicity and in monochorionic twins, injection studies determine whether inter-twin transfusional processes contributed to demise(28). Lopriore et al. suggest that injection studies should be performed on all monochorionic placentas, irrespective of birth outcome, to evaluate the effect of any FLA and to understand the pathophysiology of disorders affecting monochorionic pregnancies, potentially uncovering patterns associated with fetal demise(29-32).

Interpretation

CoDiT is the first classification system designed specifically for perinatal deaths in twin pregnancies. One study concluded that no existing classification system was suitable to classify causes of death in twin pregnancies as they did not reflect the diversity of diagnoses in twins; at best, they identified twin pregnancies as subcategories under "other conditions"(33). Another study identified that a major risk factor for double fetal deaths in twins was monochorionicity, which is reflected in the higher proportion of double monochorionic twin deaths compared to dichorionic deaths in our cohort(34). Using Codac to assign cause of death in twins and singletons found a higher prevalence of twin pregnancies in cases with a placental and unknown cause of death, aligning with the overall top two causes in our cohort(35). A large retrospective cohort analysis comparing the risks and causes of stillbirths in singletons and twins using ReCoDe, found that stillbirths were mainly due to TTTS in

monochorionic twins, as in our cohort, but unlike our cohort, congenital anomalies were the biggest cause of death in dichorionic twins and singletons(4).

Future work

The guidelines require modification to clarify how users should distinguish infection from acute chorioamnionitis. Adding a subcategory to distinguish between deaths due to prematurity from PPROM with or without evidence of infection may be useful. Furthermore, comparative studies to evaluate the performance of CoDIT against other classification systems in twin pregnancies will determine whether the system employed affects the classification of cause of death and the frequency of unexplained deaths.

CoDiT has undergone testing in one tertiary UK hospital with a dedicated perinatal pathology service, by a small panel, with limited external validation. To determine its suitability as a global classification system, CoDiT requires large-scale validation using external cohorts and panels.

Conclusion

We introduce the first classification system specifically designed for twin pregnancies. Whilst external validation and modifications are required, preliminary testing demonstrates that CoDiT has the potential to be a powerful tool in furthering our understanding of deaths in twin pregnancies and a catalyst to improve management.

Disclosure of Interests: FLM is a BJOG editor. The remaining authors have no disclosures.

Contribution to Authorship: NG, FLM, RKM, PC, MDK co-designed the classification system. NG, FLM, PC, TM tested the classification system by assigning cause of death to cases in the cohort to assess inter-disciplinary agreement. AEH independently assigned cause of death to a subset of cases to assess inter-rater agreement. NG reclassified a subset of cases to determine intra-rater agreement. All authors contributed to the write-up and approval of the final manuscript.

Ethical Approval: The project was registered as a service evaluation project by the unit's clinical governance team in 2017.

Funding: none

References

1. Birth characteristics in England and Wales: 2017 Annual live births by sex, ethnicity and month, maternities by place of birth and with multiple births, and stillbirths by age of parents and calendar quarter. Office of National Statistics.

2. Peter C, Wenzlaff P, Kruempelmann J, Alzen G, Bueltmann E, Gruessner SE. Perinatal morbidity and early neonatal mortality in twin pregnancies. Open J Obstet Gynecol 2013;3:78-89doi:10.4236/ojog.2013.31017.

3. Ortibus E, Lopriore E, Deprest J, Vandenbussche FP, Walther FJ, Diemert A et al. The pregnancy and long-term neurodevelopmental outcome of monochorionic diamniotic twin gestations: a multicenter prospective cohort study from the first trimester onward. Am J Obstet Gynecol 2009;200:494.e1-8. doi:10.1016/j.ajog.2009.01.048.

4. Russo FM, Pozzi E, Pelizzoni F, Todyrenchuk L, Bernasconi DP, Cozzolino S et al. Stillbirths in singletons, dichorionic and monochorionic twins: a comparison of risks and causes. Eur J Obstet Gynecol Reprod Biol 2013;170:131-6. doi:10.1016/j.ejogrb.2013.06.014.

5. Blondel B, Macfarlane A, Gissler M, Breart G, Zeitlin J; PERISTAT Study Group. Preterm birth and multiple pregnancy in European countries participating in the PERISTAT project. BJOG 2006; 113: 528–535.

6. Khalil A. Unprecedented fall in stillbirth and neonatal death in twins: lessons from the UK. Ultrasound Obstet Gynecol. 2019 53(2):153-157.

7. Frøen JF, Pinar H, Flenady V, Bahrin S, Charles A, Chauke L et al. Causes of death and associated conditions (Codac) – a utilitarian approach to the classification of perinatal deaths. BMC Pregnancy and Childbirth 2009;9:22

8. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. BMJ 2005; 331

9. Leisher SH, Teoh Z , Reinebrant H, Allanson E, Blencowe H, Erwich JJ et al. Seeking order amidst chaos: a systematic review of classification systems for causes of stillbirth and neonatal death, 2009-2014. BMC Pregnancy and Childbirth. 2016;295

10. Leisher SH, Teoh Z , Reinebrant H, Allanson E, Blencowe H, Erwich JJ et al. Classification systems for causes of stillbirth and neonatal death, 2009-2014: an assessment of alignment with characteristics for an effective global system. BMC Pregnancy and Childbirth. 2016;16:269

11. The WHO application of ICD-10 to deaths during the perinatal period: ICD-PM

12. Wojciezek AM, Reinebrant H, Leisher SH, Allanson E, Coory M, Erwich JJ et al. Characteristics of a global classification system for perinatal deaths: a Delphi consensus study. BMC Pregnancy and Childbirth 2016;16:223.

13. Gordijn SJ, Korteweg FJ, Erwich JJHM, Holm JP, van Diem MT, Bergman KA et al. A multilayered approach for the analysis of perinatal mortality using different classification systems. Eur J Obstet Gynecol Reprod Biol. 2009;144(2):99–104.

14. Korteweg FJ, Gordijn SJ, Timmer A, Erwich JJ, Bergman KA, Bouman K et al. The Tulip classification of perinatal mortality: introduction and multidisciplinary inter-rater agreement. BJOG 2006;393-401.

15. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012; 22(3): 276-282.

16. Faye-Peterson OM, Guinn DA, Wenstrom KD. Value of perinatal autopsy. Obstet Gynecol. 1999;94:915-20.

17. Kock KF, Vestergaard V, Hardt-Madsen M, Garne E. Declining autopsy rates in stillbirths and infant deaths: results from Funen County, Denmark, 1986-96. J Matern Fetal Neonatal Med. 2003;13:403-7.

18. Cartlidge PH Dawson AT, Stewart JH, Vujanic GM. Value and quality of perinatal and infant post-mortem examinations: cohort analysis of 400 consecutive deaths. BMJ 1995;310:155-8.

19. Cernach MC, Patricio FR, Galera MF, Moron AF, Brunoni D. Evaluation of a protocol for postmortem examinations of stillbirths and neonatal deaths with congenital abnormalities. Pediatr Dev Pathol. 2004;7:335-41.

20. Saller Jr DN Lesser KB, Harrel U, Rogers BB, Oyer CE. The clinical utility of the perinatal autopsy. JAMA. 1995;273:663-5.

21. Gordijin SJ, Erwich JJ, Khong TY. Value of the perinatal autopsy critique. Pediatr Dev Pathol. 2002;5: 480-8.

22. Draper ES, Gallimore ID, Smith LK, Kurinczuk JJ, Smith PW, Boby T et al, on behalf of the MBRRACE-UK Collaboration. MBRRACE-UK Perinatal Mortality Surveillance Report, UK Perinatal Deaths for Births from January to December 2017. Leicester: The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester. 2019.

23. Evans C, Cox P. Tissue pathway for histopathological examination of the placenta. The Royal College of Pathologists 2019.

24. Dias T, Arcangeli T, Bhide A, Napolitano R, Mahsud-Dornan S, Thilaganathan B. First-trimester ultrasound determination of chorionicity in twin pregnancy. Ultrasound Obstet Gynecol. 2011;38: 530-532.

25. Ptacek I Sebire NJ, Man JA, Brownbill P, Heazell AE. Systematic review of placental pathology reported in association with stillbirth. Placenta. 2014;35:552-62.

26. Heazell AE, Martindale EA. Can post-mortem examination of the placenta help determine the cause of stillbirth? J Obstet Gynaecol. 2009;29: 225-8.

27. Heazell AEP, Byrd LM, Cockerill R, Whitworth MK. Investigations following stillbirth – which tests are most valuable? Arch Dis Child Fetal Neonatal Ed. 2011;96:Fa135.

28. Fitzgerald B. Histopathological examination of the placenta in twin pregnancies. APMIS 2018; 126: 626–637.

29. Lopriore E, Slaghekke F, Middeldorp JM, Klumper FJ, van Lith JM, Walther FJ et al. Accurate and simple evaluation of vascular anastomoses in monochorionic placenta using colored dye. J Vis Exp. 2011 Sep 5;(55):e3208.

30. Lopriore E, Middeldorp JM, Sueters M, Vandenbussche FP, Walther FJ. Twin-to-twin transfusion syndrome: from placental anastomoses to long-term neurodevelopmental outcome. Curr. Pediatr. Rev. 2005; 1:191-203.

31. Lopriore E, Sueters M, Middeldorp JM, Vandenbussche FP, Walther FJ. Haemoglobin differences at birth in monochorionic twins without chronic twin-to-twin transfusion syndrome. Prenat. Diagn. 2005; 25: 844-850.

32. Papathanasiou D, Witlox R, Oepkes D, Walther FJ, Bloemenkamp KW, Lopriore E. Monochorionic twins with ruptured vasa previa: double trouble! Fetal Diagn. Ther; 2010: 28, 48-50.

33. Skeie A, Frøen JF, Vege A, Stray-Pedersen B. Cause and risk of stillbirth in twin pregnancies: a retrospective audit. Acta Obstet Gynecol Scand. 2003; 82: 1010-1016.

34. Rydhstroem H. Pregnancy with stillbirth of both twins. BJOG 1996; 103:25-32.

35. Helgadóttir LB, Turowski G, Skjeldestad FE, Jacobsen AF, Sandset PM, Roald B et al. Classification of stillbirths and risk factors by cause of death – a case-control study. Acta Obstet Gynecol Scand. 2013; 92:325-333.

Table 1. Demographic information of all post-mortem reports from twin pregnancies between Jan 2005-Dec 2016 at a West Midlands Tertiary Hospital. The chorionicity of 47 cases was unknown and so the total does not reflect the sum of monochorionic and dichorionic deaths.

	Monochorionic	Dichorionic	Total
No. pregnancies	66	78	144
Mean maternal age	29.1 (95% CI 27.4-30.7)	30.2 (95% CI 28.2 -32.1)	29.6 (95% CI 28.5-30.7)
Mean maternal BMI	27.7 (95% CI 25.6-29.8)	26.3 (95% CI 24.4-28.3)	26.7 (95% CI 25.4-28.1)
% Nuliparity	31/66 (47%)	32/78 (41%)	73/144 (51%)
Total perinatal deaths	122	96	265 (unknown chorionicity in 47)
No. fetal deaths	117/122 (96%)	85/96 (89%)	247/265 (93%)
No. NNDs	5/122 (4%)	11/96 (11%)	18/265 (7%)
No. Single deaths	6/122 (5%)	8/96 (8%)	19/265 (7%)
No. Double deaths	116/122 (95%)	88/96 (92%)	246/265 (93%)
Mean gestation at death (weeks)	19.6 (95% CI 18.3-20.8)	19.7 (95% CI 18.5-21.0)	19.6 (95% CI 18.8 - 20.5)
No. spontaneous deaths	95/122 (78%)	85/96 (89%)	219/265 (83%)
No. terminations of whole pregnancy	9/66 (14%)	6/78 (8%)	17/144 (6%)
No. selective reductions	4/122 (3%)	0	4/265 (2%)
No. deaths within 7 days of medical intervention	7/122 (6%)	0	9/265 (3%)

Table 2. Distribution of gestational age at death by cause and chorionicity with numbers and percentage within each group.

	<24 weeks gestation		**>24 weeks gestation**		**Neonatal death**		**Unknown gestation at death**	
Cause of Death	**MC n (%)**	**DC n (%)**	**MC n (%)**	**DC n (%)**	**MC n (%)**	**DC n (%)**	**MC n (%)**	**DC n (%)**
Congenital Abnormality	23 (32%)	5 (9%)	1 (5%)	1 (11%)	1 (20%)	1 (9%)	3 (13%)	2 (10%)
Placental	**30 (41%)**	**24 (43%)**	**9 (43%)**	**4 (44%)**	**2 (40%)**	**4 (36%)**	12 (52%)	13 (65%)
Umbilical cord	3 (4%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Prematurity	0 (0%)	4 (7%)	0 (0%)	0 (0%)	1 (20%)	5 (45%)	2 (9%)	1 (5%)
Infection	0 (0%)	8 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	4 (5%)	2 (4%)	1 (5%)	2 (22%)	0 (0%)	1 (9%)	0 (0%)	0 (0%)
Unknown	13 (18%)	13 (23%)	9 (43%)	2 (22%)	1 (20%)	0 (0%)	6 (26%)	4 (20%)
Total	**73**	**56**	**21**	**9**	**5**	**11**	**23**	**20**