2. Invited Commentary by Dr Sieglinde Mullers; The contribution of Twin Pregnancy to Perinatal Mortality

Introduction

The decades spanning the 1980's to 2000's witnessed an exponential increase in twin and higher-order multiple births worldwide.[1] According to the economic and social research institute (ESRI) and the Euro-Peristat perinatal data, the twinning rate in Ireland for 2015 was 18.7 per 1,000 maternities, representing an increase of 22.1% over the preceding decade.[2,3] As of 2015, our multiple pregnancy birth rate was higher than the U.K. and the fifth highest in Europe[2] (Figure 2.1). Furthermore, our rates of triplet and higher order multiple births are the second highest in the E.U. (0.5 per 1,000 maternities) after Cyprus with 0.9 per 1,000 maternities.[3]

Owing to more stringent use of assisted reproductive techniques (ART), epidemiological data now indicate a declining multiple birth rate in the U.K. and USA, however this is not the current experience in Ireland.[4] While there has been a significant decline in total births per annum in Ireland since 2012, the rate of twin and higher-order multiple births has not significantly changed. In 2019 there were 59,084 infants born, including a total of 2,096 twins (1,048 twin-pairs), such that the rate of multiple pregnancy births in 2019 was 1.8% (17.7 per 1,000 maternities) of all births. This has been fairly constant since 2012 (Figure 2.2). Consequently, the ongoing clinical workload generated from the high-risk nature of these pregnancies is undoubtedly felt on-the-ground in maternity and neonatal intensive care (NICU) units all over the country. Thus, multiple pregnancy remains an important issue in the provision of obstetric and neonatal services.

Population based studies indicate a declining perinatal mortality (PNM) rate in multiple pregnancy.[5-7] Despite these promising contemporary data, multiple pregnancy continues to disproportionately contribute to perinatal morbidity and mortality, with the risk of stillbirth (SB) and early neonatal death (NND) in twins being twice and three times that of singletons respectively.[5-8] Furthermore, the increased rate of preterm delivery in multiple pregnancy confers a four-fold increased risk of developing cerebral palsy compared to singleton pregnancy.[9,10]

In January 2021, MBRRACE-UK published its inaugural report on the Confidential Enquiry into Stillbirth and Neonatal Death in Twin Pregnancies in the U.K.[11] The report was conducted by 11 separate multidisciplinary panels who comprehensively reviewed the quality of care in the case of 50 pregnancies with 80 twin deaths. The findings indicated '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'.[11]

Recognising the contribution of multiple pregnancy to overall PNM, together with the relatively high twin-birth rate in Ireland, this invited commentary focuses on twin perinatal mortality in 2019 in relation to trends over the last eight years (2012-2019). Together with the NPEC audit, the inclusion of a more detailed review of twin perinatal mortality represents a concerted effort to address and reduce perinatal mortality in this high-risk group.

Figure 2.1 shows the rates of twin, triplet and higher-order births, expressed as numbers of women with twin, triplet or higher-order births per 1,000 women giving birth to one or more fetuses (adapted from Euro-Peristat 2015, 2018).[3] In 2015, Ireland had the fifth and second highest rate of twins and higher-order multiple births in the E.U. (18.7/1000 and 0.5/1,000 maternities, respectively).

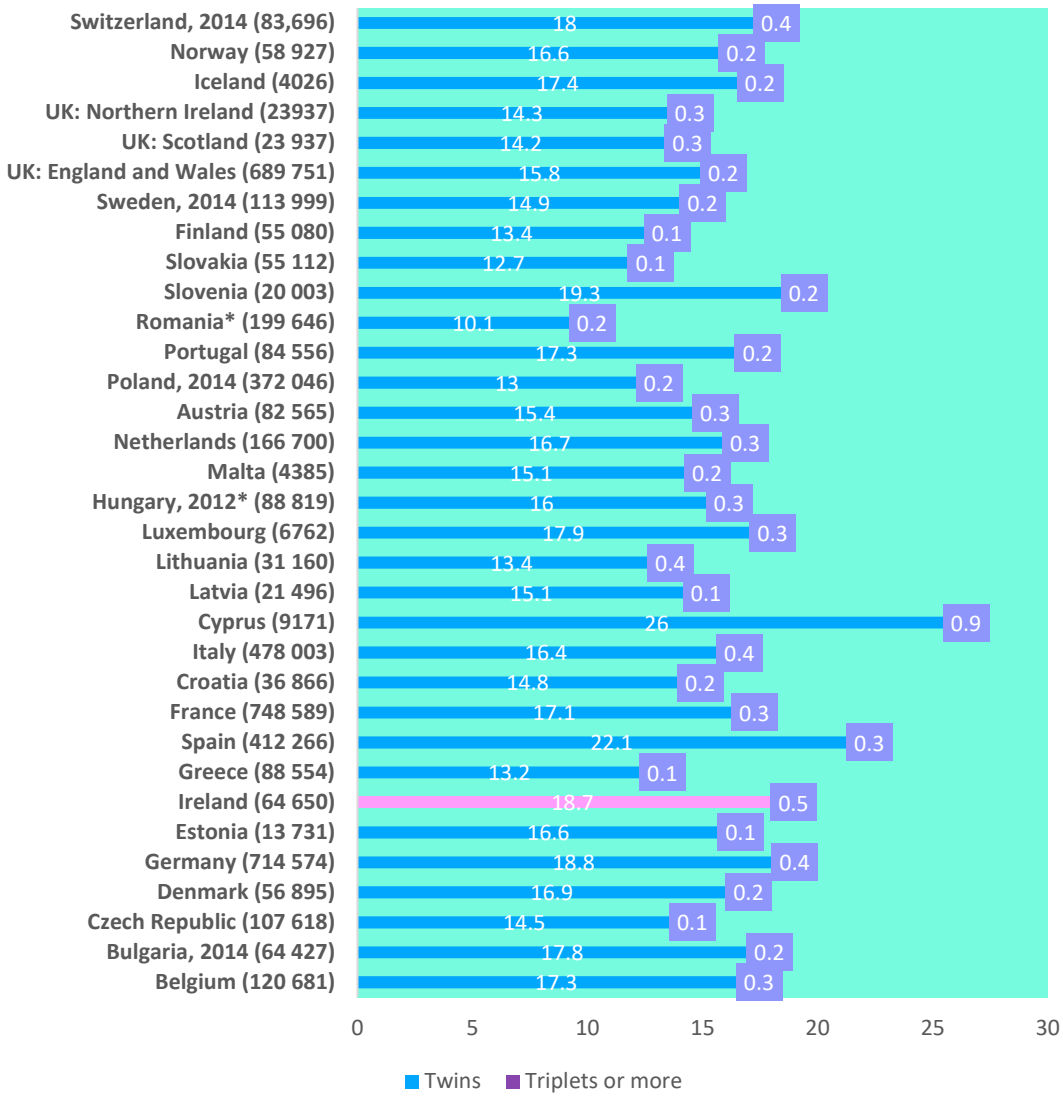


Figure 2.1 Multiple birth rates per 1,000 women with live births or stillbirths by number of fetuses in 2015 (adapted from Euro-Peristat 2015, 2018)

Figure 2.2 is derived from HIPE data, and shows a declining overall birth rate in Ireland in the years 2012-2019. It must be noted that although the overall birth rate has declined during this period, no significant reduction in twin or high-order multiple births was shown. Data for twins and other multiples represent individual births.

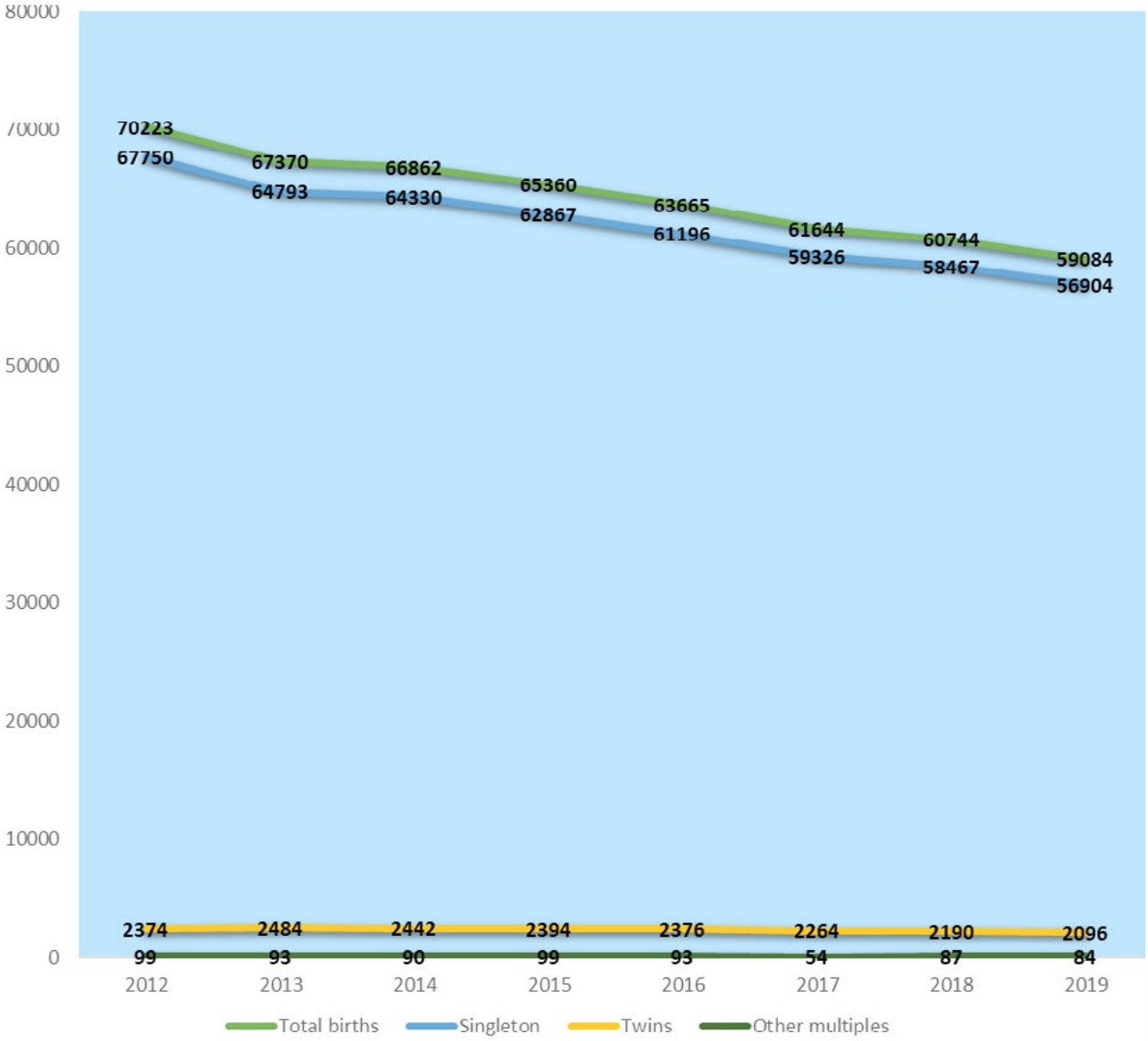


Figure 2.2 Births by plurality in 2012-2019 (HIPE data)

Perinatal Mortality in twins

Perinatal mortality in multiple pregnancy for the purpose of this report is recorded for individual deaths in twins. This is based on perinatal deaths (stillbirth (SB) and early neonatal deaths (NND) in twins with a birthweight ≥500g or gestational age at delivery ≥24 weeks). Cases of intrauterine death diagnosed before 24 gestational weeks with a birthweight <500g are not considered to have reached a gestational age of 24 weeks or more and thus are not included as stillbirths. For the purpose of this report, data will be presented as combined PNM or separately as SB or NND associated with twin pregnancy.

In 2019 there were a total of 360 perinatal deaths, of which 35 (9.7%) involved multiple pregnancies (Table 2.1). This included 30 cases involving twins and five involving triplets. Regarding the 30 twin deaths in 2019, there are five cases where both twins died (three cases involved dichorionic (DC) twins and two cases involved monochorionic diamniotic twins (MCDA). Regarding twins, there was one case of congenital anomaly associated with SB and five cases associated with NND, thus the corrected perinatal mortality rate for twins in 2019 was 5.7 per 1000 twin births.

Table 2.1: Perinatal deaths from singleton, twin, triplet and other multiple births, 2012-2019

	2012 (N)	2013 (N)	2014 (N)	2015 (N)	2016 (N)	2017 (N)	2018 (N)	2019 (N)
Singleton	396	411	420	390	341	303	282	325
Twin	43	41	43	60	31	40	38	30
Triplet	1	3	1	3	1	3	4	5
Other Multiple	0	0	0	0	1	0	0	0
Total	**440**	**455**	**464**	**453**	**374**	**346**	**324**	**360**

*Perinatal deaths in twins and higher-order multiples refers to individual deaths.

Comparison of perinatal mortality rate in twins, 2012-2019

Overall, compared with singleton pregnancies, there was a threefold increased risk of perinatal deaths among twins from the period spanning 2012-2019 (risk ratio=3.04, 95% CI 2.71-3.41) (Table 2.2). This relative risk was 2.79 in 2012-14 and was 3.16 in 2017-19. This is comparable to international perinatal mortality figures for twins.[12-14]

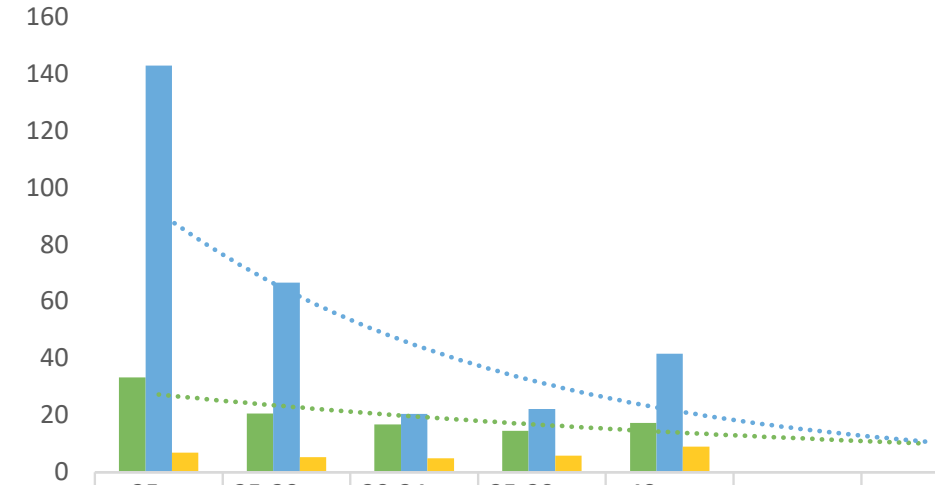
Table 2.2: Perinatal mortality rate by plurality and grouped by specified triennia (2012-2019)

	Births		Perinatal deaths		Perinatal mortality rate per 1,000 births	
Triennium	**Singletons**	**Twins**	**Singletons**	**Twins**	**Singletons**	**Twins**
2012-14	196873	7300	1227	127	6.23	17.40
2013-15	191990	7320	1221	144	6.36	19.67
2014-16	188393	7212	1151	134	6.11	18.58
2015-17	183389	7034	1034	131	5.64	18.62
2016-18	178989	6830	927	109	5.18	15.96
2017-19	174697	6550	911	108	5.21	16.49

The PNM in twins varied significantly by maternal age, with the greatest relative risk observed for twins of mothers aged < 25 years (Figure 2.3). The relative risk for PNM in twins compared with singletons *decreased* with *increasing* maternal age, being nearly five times higher in the <25 year old (RR 4.86, 95% CI 3.4-6.94), four times higher in 25-29 year-olds (RR 3.90 , 95% CI 2.92-5.22), 3.4 times higher risk for twins of 30-34 year-olds (RR 3.39, 95% CI 2.77-4.16), 2.5 times higher risk for twins of 35-39 year-olds (RR 2.48, 95% CI 2-3.06), and approximately twice the risk among twins of mothers aged at least 40 years (RR 1.94, 95% CI 2.71-3.41). All risk ratios were based on pooled information from 2012-2019 and were noted to be highly statistically significant (p <0.001).

The lower rate of PNM in older mothers expecting twin and high-order multiple pregnancies may be reflective of the increased prenatal surveillance, judicious use of aspirin, and lower thresholds for delivery that are likely afforded to this group, owing to the higher anticipated risk profile. Increasing maternal age has been associated with less perinatal mortality in twins compared to singletons.[15] One of the key findings from the MBRRACE-UK report on twin mortality centered around the recommendation of prophylactic aspirin for women with multiple pregnancy, reporting that in only half of eligible women was there documentation of aspirin being prescribed.[11] Current NICE guidance recommends low-dose aspirin for women with multiple pregnancy and with additional risk factors for the development of preeclampsia.[16] Thus, being a first time mother with a multiple pregnancy already constitutes two moderate risk factors, and therefore these women should be prescribed aspirin. Preliminary evidence appears to support the higher dose of 150mg per day for preeclampsia prevention in multiple pregnancies.[17]

The relatively high rate of PNM in twins and higher-order multiple pregnancies in our younger mothers requires further comprehensive review. Of note, where documented, fertility treatment featured in 23.3% of perinatal twin deaths, which is comparable with published data.[18]



	<25 yrs	25-29 yrs	30-34 yrs	35-39 yrs	40+ yrs		
Perinatal mortality rate Twins	33.33	20.66	16.76	14.56	17.39		
Perinatal mortality rate Other mutiples	142.86	66.67	20.58	22.22	41.67		
Perinatal mortality rate Singletons	6.86	5.29	4.94	5.88	8.98		

Figure 2.3 Perinatal mortality rate by plurality and maternal age (2012-2019)

The relative risk for PNM in twins compared with singletons *decreased* with *increasing* maternal age, with a four times higher risk for twin PNM in 25-29 year-olds, 3.4 times higher risk for twins of 30-34 year-olds, 2.5 times higher risk for twins of 35-39 year-olds and approximately twice the risk among twins of mothers aged at least 40 years.

Causes of perinatal mortality in twins

Regarding twin perinatal mortality in 2019, of the 30 perinatal deaths there were 12 cases of SB and 18 cases of early NND. The main causes of SB and early NND in twins spanning 2012-2019 are outlined in Tables 2.3 and 2.4 respectively. Major congenital anomaly is broken down by specific cause/system for all perinatal deaths spanning 2012-2019 in Figure 2.4

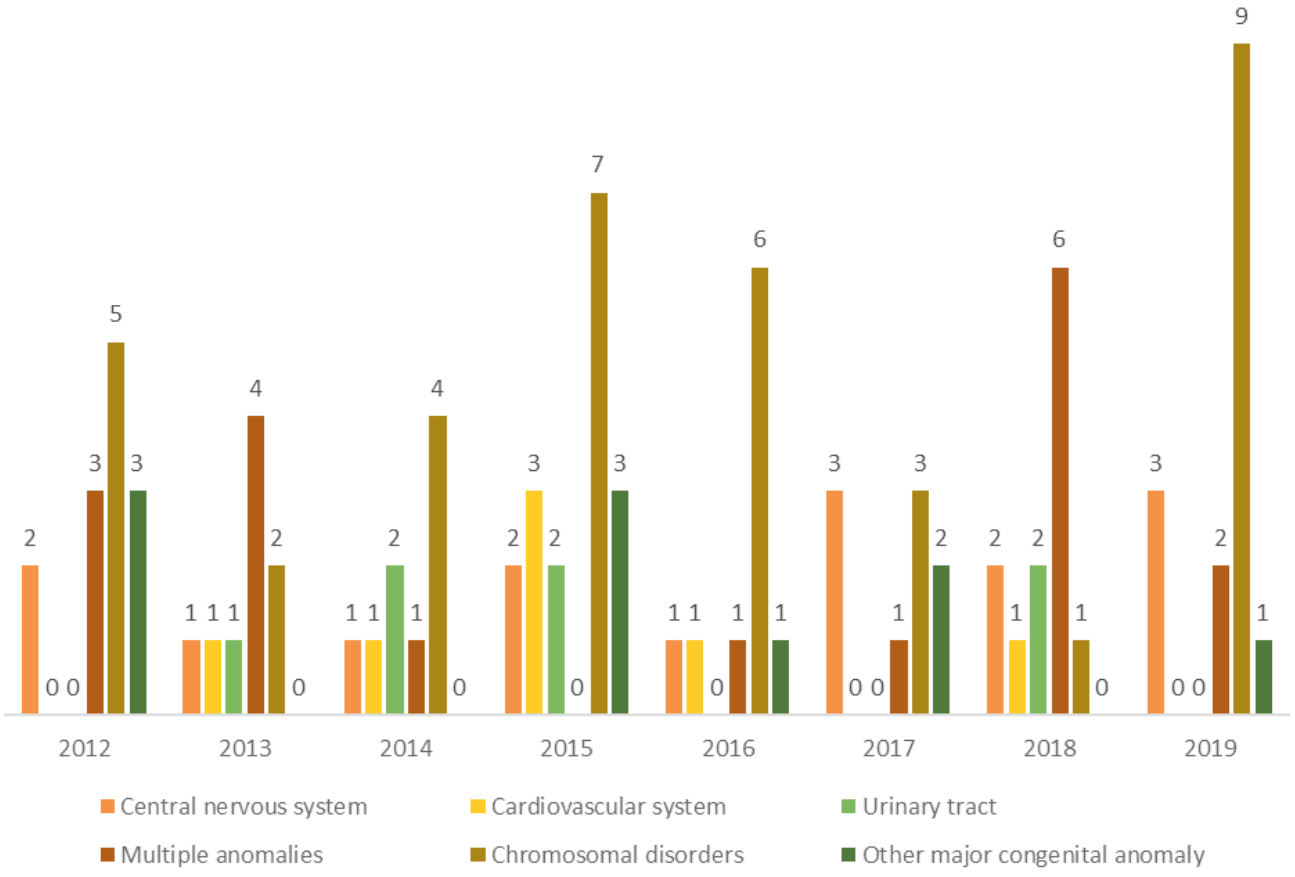


Figure 2.4 Major congenital anomaly as the main cause of perinatal mortality (stillbirths and early neonatal death combined) in 32 twins, 2012-2019

Stillbirth in twins

Regarding cause of stillbirths (SB) in twins in 2019 (n=12), a significant number of cases were due to specific placental causes (n=12, 58%). These included maternal vascular malperfusion (n=3), fetal vascular malperfusion (n=2), cord pathology (n=1), other (n=1). This highlights the necessity for dedicated perinatal pathologists in the investigation of perinatal twin mortality. In two cases the cause of stillbirth was noted to be due to specific fetal conditions (namely twin-twin transfusion syndrome, TTTS). There was one case each of congenital anomaly (gastrointestinal disease), infection (chorioamnionitis) and one case were unexplained. The breakdown of infection as a cause of SB in twins, 2012-2019 is highlighted in Figure 2.2.

Of note in 2019, maternal disorders including hypertensive disorders, antepartum or intrapartum haemorrhage, mechanical factors, other obstetric factors or IUGR did *not* account for any of the stillbirths associated with twins. The increasing use of aspirin for preeclampsia prevention in multiple pregnancy may partly explain the lack of association of maternal hypertensive conditions in perinatal death in twins.

There were a total of eight intrapartum stillbirths in twins spanning 2012-2019. This included five cases with spontaneous onset of labour at < 24 weeks gestation with associated chorioamnionitis, and one case each of maternal sepsis and PPROM (< 24 weeks and >500g), induction of labour at 35 weeks for TTTS, and spontaneous onset of labour

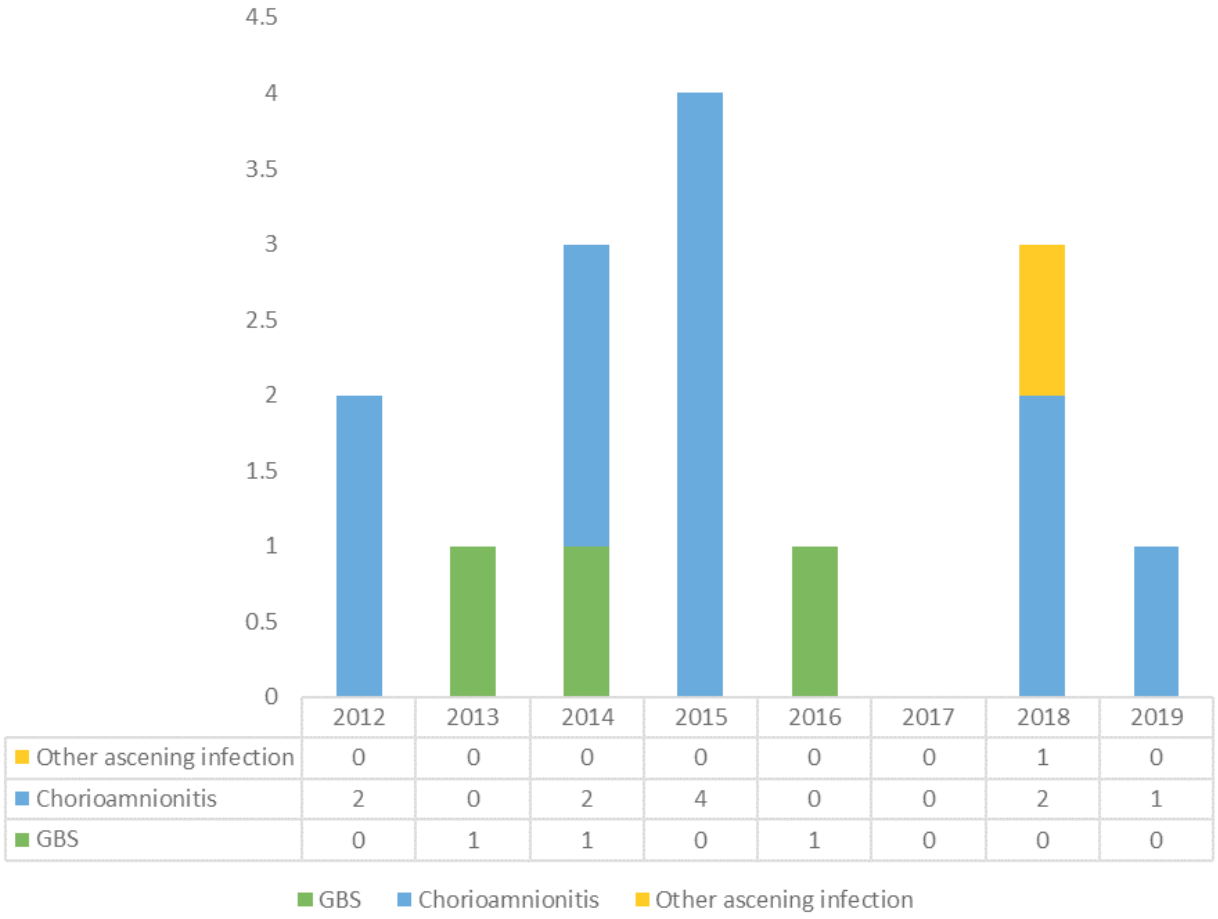
at 25 weeks noted to have TTTS. A key recommendation from the recent MBRRACE-UK report necessitates senior obstetric input for all women with multiple pregnancy presenting to maternity units, and throughout labour and delivery.[11] Further, individual case review may identify deficiencies, if any, in intrapartum care in cases of twin intrapartum SB.

Over the time period 2012-2019 of 29 stillborn babies whose main cause of death was noted to be TTTS, only four cases make a reference to laser ablation having been performed in the pregnancy. However, laser ablation is not a specific data collection point, therefore data are incompletely captured in the NPEC audit. TTTS-associated perinatal mortality will be discussed further in this commentary.

Table 2.3 Main cause of death in stillborn twins, 2012-2019

Main cause of death, stillborn twins	2012 (N)	2013 (N)	2014 (N)	2015 (N)	2016 (N)	2017 (N)	2018 (N)	2019 (N)	2012-2019 (N)
Major Congenital Anomaly	6	1	3	9	7	2	3	1	32
Antepartum or intrapartum haemorrhage (abruption)	0	1	2	0	0	0	0	0	3
Mechanical	0	1	0	0	2	0	2	0	5
Other cord entanglement or knot	0	1	0	0	2	0	0	0	3
Uterine rupture before labour	0	0	0	0	0	0	2	0	2
Maternal disorder (obstetric cholestasis)	0	0	0	0	0	0	1	0	1
Infection	2	1	3	4	1	0	3	1	15
Specific fetal conditions*	2	4	7	10	1	4	0	2	30
Twin-twin transfusion (TTTS)	2	4	6	10	1	4	0	2	29
IUGR	1	0	0	3	0	0	0	0	4
IUGR Suspected antenatally	0	0	0	3	0	0	0	0	3
IUGR Observed at post mortem	1	0	0	0	0	0	0	0	1
Associated Obstetric factors	2	0	0	0	0	1	1	0	4
Prolonged rupture of membranes >24 hrs	0	0	0	0	0	1	0	0	1
Other obstetric factors	0	0	0	0	0	0	1	0	1
Spontaneous premature labour	2	0	0	0	0	0	0	0	2
Unexplained	2	3	4	3	1	4	2	1	20
No Antecedent or Associated Obstetric Factors	1	1	3	1	0	2	1	1	10
Unexplained but with some reported Antecedent or Associated Obstetric Factors	1	1	1	1	1	2	1	0	8
Little or nothing known about the case	0	1	0	0	0	0	0	0	1
Pending results of post-mortem or other investigations	0	0	0	1	0	0	0	0	1
Specific placental conditions	6	5	4	4	3	8	2	7*	39
Total	**21**	**16**	**23**	**33**	**15**	**19**	**14**	**12**	**153**

Note: Twin births refer to individual babies born following a twin delivery. *Specific fetal conditions as a cause of stillbirth in twins refers almost exclusively to cases of Twin-twin transfusion (TTTS).



	2012	2013	2014	2015	2016	2017	2018	2019
Other ascening infection	0	0	0	0	0	0	1	0
Chorioamnionitis	2	0	2	4	0	0	2	1
GBS	0	1	1	0	1	0	0	0

Figure 2.5. Infection as the main cause of stillbirth in 15 twins in 2012-2019

Note: Infection broken down by specific cause in twin stillbirths, 2012-2019 (refer to table 2.3).

Neonatal death in twins

Regarding early neonatal death (NND) in twins in 2019, the majority (n= 10 of 18, 55.5%) were due to respiratory disorders, followed by major congenital anomalies (n=5, consisting of 3 cases each of CNS malformation and 2 cases with multiple anomalies), neurological disorders (n=2, includes IVH and PVL), and there was one NND due to specific fetal causes. There were no cases of necrotising enterocolitis (NEC) or infection as a cause of NND in twins in 2019. The breakdown of causes of NND in twins is illustrated in Table 2.4. The contribution of gestational age at delivery to twin early neonatal mortality will be further discussed.

Table 2.4 Main cause of early neonatal twin deaths, 2012-2019

Main cause of death neonatal twin birth*	2012 (N)	2013 (N)	2014 (N)	2015 (N)	2016 (N)	2017 (N)	2018 (N)	2019 (N)	2012-2019 (N)
Major Congenital Anomaly	7	8	6	8	3	7	10	5	54
Central nervous system	1	1	1	1	0	2	1	3	10
Other major congenital anomaly	1	0	0	1	0	2	0	0	4
Cardiovascular system	0	0	1	2	1	0	1	0	5
Urinary tract	0	1	1	2	0	0	2	0	6
Musculo-skeletal system	0	0	0	0	0	0	1	0	1
Multiple anomalies	3	4	1	0	0	0	5	2	15
Chromosomal disorders	2	2	2	2	2	3	0	0	13
Previable	1	0	0	0	0	0	0	0	1
Pre-viable (<22 weeks)	1	0	0	0	0	0	0	0	1
Respiratory Disorders	12	16	11	14	12	12	7	10	94
Severe pulmonary immaturity	6	9	9	13	7	7	6	9	66
Surfactant deficiency lung disease	4	7	1	0	2	1	1	0	16
Pulmonary hypoplasia	0	0	1	1	2	3	0	1	8
Other respiratory disorder	2	0	0	0	1	1	0	0	4
Gastro Intestinal Disease	0	0	0	0	1	0	0	0	1
Necrotising enterocolitis	0	0	0	0	1	0	0	0	1
Neurological Disorder	2	1	0	1	0	2	3	2	11
Hypoxic ischaemic encephalopathy	0	1	0	0	0	1	0	0	2
Intraventricular/periventricular haemorrhage	2	0	0	1	0	1	3	2	9
Infection	0	0	3	1	0	0	1	0	5
Sepsis	0	0	3	0	0	0	1	0	4
Pneumonia	0	0	0	1	0	0	0	0	1
Other Specific Causes	0	0	0	0	0	0	0	1	1
Other specific cause	0	0	0	0	0	0	0	1	1
Sudden Unexpected Death	0	0	0	0	0	0	1	0	1
SIDS	0	0	0	0	0	0	1	0	1
Unexplained	0	0	0	3	0	0	2	0	5
Pending results of post mortem or other investigations	0	0	0	3	0	0	2	0	5
Total	**22**	**25**	**20**	**27**	**16**	**21**	**24**	**18**	**173**

Twin births refers to individual babies born following a twin delivery.

Factors associated with perinatal mortality in multiple pregnancy

Chorionicity

In 2019, of the 30 perinatal deaths in twins (Table 2.5), over seventy percent were DCDA twins (n=22 of 30, 73.3%), with eight deaths in MCDA twins (n=8 of 30, 26.7%). Information regarding national baseline chorionicity, integral to a discussion on the contribution of chorionicity to twin PNM, is regrettably not currently available through HIPE data collection. However, given DCDA twins are more commonly encountered, the relatively higher contribution of DCDA twins to total twin perinatal mortality is proportional. The breakdown of perinatal deaths in twins by chorionicity, 2012-2019 is shown in Table 2.5. Notably, compared to 2012, there has been a reduction in PNM in MCDA twins in 2019, with the highest contribution to twin PNM in 2014 (n=20 of 39, 51.3%) and the lowest in 2016 (n=5 of 30, 16.7%). It is worth noting there are incomplete data regarding chorionicity for 18 of the 326 perinatal deaths in twins in 2012-2019.

Table 2.5 Perinatal deaths (stillbirths and early neonatal deaths) from twin births, 2012-2019

Chorionicity	2012 (N)	2013 (N)	2014 (N)	2015 (N)	2016 (N)	2017 (N)	2018 (N)	2019 (N)	2012-2019 (N)
DCDA	26	19	19	33	25	29	25	22	198
MCDA	16	16	20	23	5	8	13	8	109
MCMA	0	1	0	0	0	0	0	0	1
Total	**42**	**36**	**39**	**56**	**30**	**37**	**38**	**30**	**308**

Note: Data unknown/missing for 18 of the 326 deaths in 2012-2019. Twin births refers to individual babies born following a twin delivery. Dichorionic diamniotic (DCDA), Monochorionic diamniotic (MCDA) and Monochromic Monoamniotic (MCDA).

Outcome in twins is largely driven by chorionicity, with monochorionicity contributing significantly to perinatal mortality at all gestations.[19-23] Complications specific to the shared monochorionic placenta include selective intrauterine growth restriction (SIUGR), twin-twin transfusion syndrome (TTTS), twin-anaemia polycythaemia syndrome (TAPS), and the situation of single twin demise with the significant risk of death (12%) or neuro-morbidity in the surviving twin (25%).[24] According to the recent MBRRACE-UK report, mortality in twins was significantly influenced by chorionicity.[11] Of the 50 individual twin deaths, both babies died in all three of the reviewed monoamniotic (MA) twins, in 15 of 22 cases of MCDA pairs, and in 12 of 25 dichorionic (DC) twins.

Early determination of chorionicity, with emphasis on identifying the less common monochorionic pairs, and adherence to internationally recommended ultrasound monitoring of twins (monthly for DC twins and 2-weekly from 16 weeks in MCDA twins) is critical in minimising the perinatal disease burden in twins.[19-21] According to the recent MBRRACE-UK report, frequency of ultrasound surveillance failed to follow guidance for monochorionic pregnancies with a total of 20% of eligible women not undergoing the recommended sonographic surveillance in twins.[11] Although assignment of chorionicity was high at 98% compliance, there were additional areas within ultrasound surveillance that fell beneath the standard of care, for example incorrect labelling of twins, lack of reporting of percentage intertwin growth discordance, and failing to act on abnormal ultrasound findings in twins or referral for specialist input. These are auditable outcomes in twin pregnancies for all obstetric units. Furthermore, in a concerted effort to minimise late perinatal mortality in twins, contemporary recommendations regarding the timing of delivery in uncomplicated DC twins (consider by 37 weeks' gestation) and MCDA twins (consider by 36 weeks' gestation) are to be balanced against the risk of neonatal morbidity.[25]

While MA twins represent one of the highest risk groups, as per the MBRRACE-UK report,[11] there were no cases of perinatal deaths associated with MA twins in Ireland over the last five years, with only one case in 2013. These data reinforce the national effort in compliance with guidance regarding heightened prenatal surveillance and timing of delivery of MA twins under the specialised care for high-risk multiple pregnancy.[19-21,25]

Gestational age at delivery

In 2019, the majority of cases of twin early neonatal deaths delivered at < 28 weeks (12/18, 66.6%, comprising 6 cases delivering < 24 weeks and 6 at 24-27 weeks (Table 2.6a, Figure 2.6). Similarly, according to the recent MBRRACE-UK, almost two-thirds of twin deaths delivered before 28 weeks.[11] There appears to be decreasing numbers of deaths in very preterm twins delivering between 24-27 weeks (11/22, 50% in 2012 versus 6/18, 33% of cases in 2019). The highest reported number of early neonatal deaths in twins <24 weeks was reported in 2015 (eight cases of a total of 27 twin NND). Table 2.6a details the gestational age at delivery broken down by stillbirths and early neonatal deaths from twin births, 2012-2019.

Gestational age at delivery in relation to chorionicity is highlighted in Table 2.6b.

Table 2.6a Gestational age at delivery in stillbirths and early neonatal deaths from twin births, 2012-2019

	2012 (N)		2013 (N)		2014 (N)		2015 (N)		2016 (N)		2017 (N)		2018 (N)		2019 (N)		2012-2019 (N)	
Gestational age at delivery	**SB**	**END**	**SB**	**END**	**SB**	**END**	**SB**	**END**	**SB**	**END**	**SB**	**END**	**SB**	**END**	**SB**	**END**	**SB**	**END**
<24	4	4	0	7	4	7	3	8	1	6	2	5	3	6	1	6	18	49
24-27	0	11	5	9	8	8	3	6	1	7	1	5	6	6	5	6	29	58
28-31	4	1	3	1	1	1	1	4	2	0	5	5	0	4	1	4	17	20
32-36	11	5	7	4	8	2	21	8	7	3	8	5	3	6	4	2	69	35
37 +	2	1	1	4	2	2	5	1	4	0	3	1	2	2	1	0	20	11
Total	**21**	**22**	**16**	**25**	**23**	**20**	**33**	**27**	**15**	**16**	**19**	**21**	**14**	**24**	**12**	**18**	**153**	**173**

Twin births refers to individual babies born following a twin delivery.

Table Table 2.6b Gestational age and chorionicity associated with perinatal death in twins, 2012-2019

Gestational age at delivery	**Stillbirths 2012-2019 N=144* of 153**			**Early neonatal deaths 2012-2019 N=164* of 173**		
Chorionicity	**DCDA (N)**	**MCDA (N)**	**MCMA (N)**	**DCDA (N)**	**MCDA (N)**	**MCMA (N)**
<24	10	8	0	33	11	0
24-27	10	17	1	36	22	0
28-31	9	8	0	12	8	0
32-36	40	24	0	26	5	0
37 +	13	4	0	9	2	0
Total	**82**	**61**	**1**	**116**	**48**	**0**

Note: *Data unknown/missing for 9 stillbirths and 9 early neonatal deaths in 2012-2019. Dichorionic diamniotic (DCDA), Monochorionic diamniotic (MCDA) and Monochromic Monoamniotic (MCDA).

Figure 2.6. Gestational age at delivery in early neonatal twin deaths, 2012-2019.

Though numbers are small, there appears to be decreasing numbers of deaths in very preterm twins delivering between 24-27 weeks.

According to MBRRACE-UK, in the case of four of 19 pregnancies following preterm vaginal birth of the first twin, the second twin was augmented, and birth expedited without clear clinical indication.[11] Furthermore, the report found that neither antenatal corticosteroids nor magnesium sulphate were considered and/or offered in nearly a third of eligible pregnancies. Following spontaneous birth of a first twin at less than 24 weeks' gestation, consideration should be given to delaying the birth of the surviving second twin, provided there are no contraindications such as infection, fetal compromise, bleeding or coagulopathy. Echoing MBRRACE-UK, the importance of early involvement of senior obstetric and midwifery staff when faced with rare complications of twins, and particularly those presenting at the threshold of viability, is highlighted.

Screening and prevention of preterm delivery in twins remains an important obstetric and neonatal agenda. A cervical length of <or= 25mm at 20-24 weeks' gestation has been found to be associated with an increased risk of preterm birth before 28 weeks' gestation.[26] However, screening by means of cervical length assessment in twins underperforms that of singleton pregnancies, although a single cervical length performed at 20-24 weeks appears to be a potential candidate and is endorsed by International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG).[27] However, there is a lack of international consensus on the topic; those against screening cite a lack of effective treatment to prevent preterm delivery in twins mitigating the successful implementation of a screening program. However, some would argue that corticosteroids and magnesium sulphate are effective and impactful forms of treatment when administered in a timely manner to those at risk of preterm delivery, and therefore any means of identifying these patients may be important.[8] New evidence supports a role for physical examination-indicated cerclage, combined with indomethacin and antibiotics in women with twin pregnancies and asymptomatic cervical dilation before 24 weeks of gestation, being associated with a 50% reduction in early preterm birth < 28 weeks' gestation and an 8% decrease in perinatal mortality.[28] Further study on interventions to prevent twin-related preterm birth, and their applicability to our population are required.

IUGR and growth discordance in multiple pregnancy

Referring to Table 2.3 outlining the main causes of SB in twins, IUGR was not found to be the main cause of death in any twin SB in 2019. For the time period spanning 2012-2019, IUGR was the main cause of SB in a total of only 4 cases of 153 twin stillbirths.

A diagnosis of growth discordance is frequently encountered in twins, with discordance in fetal growth affecting 20% of twin pregnancies and approximately a third of all triplet pregnancies.[29,30] Severely growth discordant MCDA twins (≥25%) are more likely to be delivered before 30 weeks' gestation and have a longer neonatal intensive care stay (> 10 days) than their DCDA counterparts.[31-33] Overall, the reported incidence of intrauterine fetal death (IUFD) in the growth restricted twin is reported between 14-40%.[33-37] Data on chorionicity and/or a diagnosis of growth restriction was available for 300 of the 326 perinatal twin deaths in 2012-2019. Although not the main cause of death, a diagnosis of growth restriction (either suspected antenatally or observed at delivery or post-mortem) was made in 23.3% (45/193) of DC twin deaths and 20.6% (22/107) MCDA twin deaths (Table 2.7). Further individual chart review will clarify timing of diagnosis, the degree of intertwin growth discordance, and the contribution of IUGR to single IUFD in these cases.

Table 2.7 Growth restriction associated with perinatal death in twins by chorionicity, 2012-2019

		DCDA	MCDA	MCMA	Total
Growth restriction	Suspected antenatally	39	18	0	57
	Observed at delivery or post-mortem	6	4	0	10
	No diagnosis	148	85	1	233
Total		**193**	**107**	**1**	**300**

Note: Data unknown/missing for 26 of 326 cases in 2012-2019. Data represented in this table include cases where perinatal deaths in twins had an associated diagnosis of IUGR, though not the main cause of death. Dichorionic diamniotic (DCDA), Monochorionic diamniotic (MCDA) and Monochromic Monoamniotic (MCDA).

The prospective multicentre ESPRiT study conducted in Ireland with completed perinatal outcome on 1,001 twin-pairs established that the threshold for significant birth weight discordance, i.e. that which is associated with an increase in composite perinatal morbidity, is 18% for both DC and MCDA twins.[29] Overall, the absolute risk of adverse perinatal outcome was found to be higher in MCDA versus DC twins at every level of discordance.[29] Cases of significant IUGR and inter-twin growth discordance presenting at previable gestations represent high risk cases mandating specialist input from fetal medicine and neonatology as part of multi-disciplinary team (MDT) care. The importance of MDT care and documentation of discussions and decisions in twin care is a key recommendation from MBRRACE-UK.[11]

Twin-twin transfusion Syndrome

Twin-twin transfusion syndrome (TTTS) complicates between 5-15% of MC twin pregnancies.[37-39] Without treatment with fetoscopic laser ablation of the communicating placental vessels responsible for the disease in severe cases, the condition is associated with 90% perinatal mortality.[37] Since 2006, the Irish National Fetal Laser Programme, consisting of fetal surgical teams at the National Maternity Hospital and the Rotunda Hospital, Dublin, have jointly collaborated for the management of TTTS. Cases of suspected or confirmed TTTS from all 19 maternity units in the country are typically reviewed within 24-48 hours in either site.

In 2019, a total of 11 cases of severe TTTS requiring intervention were managed by the Irish National Fetal Laser Programme. Amongst these 11 pregnancies, 7 (64%) resulted in survival of both fetuses, and 4 (36%) resulted in survival of one fetus. This included two sets of triplets with a monochorionic pair. The overall survival was 20 of 24 fetuses (83%). As of 2019, the group have completed 186 cases of laser surgery for severe TTTS, with at least one survivor occurring in 84% of cases (157/186). These results are comparable with survival outcome data from the major international centres providing fetal intervention in twins.[39] Importantly, audit data from the national laser group indicate improving survival rates over time in cases of TTTS that have undergone intervention.[40]

Perinatal mortality associated with TTTS for the purpose of this report is reported for monochorionic twin perinatal deaths. It is worth mentioning the totality of the burden of outcome in TTTS is not described in this report, as data regarding total fetal loss in TTTS are not captured in these perinatal mortality figures. TTTS was found to be the main cause of death in two cases of a total of eight MCDA twin deaths in 2019. In 2018 there were no perinatal deaths due to TTTS. Over the timeframe from 2012-2019, TTTS was noted to be the main cause of death in a total of 29/106 (27%) of MCDA twin deaths (Table 2.3). This is comparable with international outcome data on survival in TTTS.[39]

As outlined in the recent MBRRACE-UK report, TTTS is the most common cause of perinatal loss in MC twins.[11] Furthermore, it highlighted the under-recognition of women presenting with 'red flag' symptoms and signs of TTTS, and it was felt that this may be related to a general knowledge deficiency in monochorionic-related complications. It was noted that the gap in the care of some women with TTTS-associated perinatal mortality may be a consequence of centralisation of specialist services. It would be the collective experience in Ireland that cases of severe TTTS are generally recognised and referred for specialist input in a timely manner. The hub and spoke Irish maternity model, in addition to the collaboration of the Irish National Fetal Laser Programme with all 19 units in the country, alongside the provision of sonographers trained in the recognition of early signs of TTTS, contribute to a high standard of twin care in this country.

The total numbers of cases and deaths associated with TTTS each year are notably small, and overall survival outcome is improving. There are multiple factors associated with the observed improving overall outcome in MCDA twins with TTTS, namely the roll-out of first trimester dating ultrasounds in all obstetric units, clear guidance on timing of assignment of chorionicity, such that TTTS is identified earlier, clear TTTS referral pathways to the Irish National Fetal Laser Programme and increasing collaborative operator experience over time.

Post-mortem in twin perinatal deaths

The proportion of stillbirths and early neonatal deaths of twins pregnancies undergoing post-mortem examination over the timeframe 2012-2019 are detailed in Table 2.8. Post-mortem examinations are performed in twice as many cases of twin stillbirths without congenital anomaly (55/116, 47%) compared with cases of twin neonatal deaths without congenital anomaly (29/110, 26%)

Table 2.8 Uptake and offer of autopsy in stillbirth and early neonatal twin deaths with and without a major congenital anomaly, 2012-2019

Autopsy	Stillbirth (N=146* of 153)		Neonatal death (N=159* of 173)	
Pooled data 2012-2019	Cause of death: major congenital anomaly		Cause of death: major congenital anomaly	
	Yes (n=30) N	No (n=116) N	Yes (n=49) N	No (n=110) N
Performed	10	55	20	29
Offered	17	51	24	72
Not offered	3	10	5	9
Total	**30**	**116**	**49**	**110**

*Data on whether autopsy was performed and/or offered was incomplete for seven cases of stillbirth and 14 cases of early neonatal deaths.

Summary of the key findings

- In Ireland we have among the highest twin and higher-order multiple pregnancy birth rates in Europe. This is despite a steady year-on decline in the overall birth rate.
- Multiple pregnancy contributes significantly to perinatal mortality, with overall PNM three times that of singletons (2012-2019).
- Increasing maternal age is protective against perinatal mortality in twins, with mothers aged <25 years having twice the rate of twin deaths compared to women aged over 40 years.
- Regarding causes of perinatal mortality in twins in 2019, placental factors were found to be the main cause of stillbirth in 7/12 cases, with the main cause of NND being due to respiratory disorders (10/18).
- Since 2012, there has been a reduction in PNM associated with MCDA twins and there have not been any cases of perinatal deaths associated with MA twins in Ireland over the last five years.
- Over the time period 2012-2019, two thirds of the cases of early neonatal deaths in twins were associated with very preterm deliveries <28 weeks' gestation.
- TTTS was noted to be the main cause of PNM in a total of 29/106 (27%) of MC twins over the time period 2012-2019. Increasing survivor outcome is being reported for cases undergoing fetosocpic laser ablation for TTTS.

Key recommendations

In light of the findings of this report and that of the recent MBRRACE-UK report on twin perinatal mortality, the following focuses on current key recommendations to limit perinatal morbidity and mortality through the identification of early complications. The goal of antenatal surveillance and optimum timing of delivery in multiple pregnancies is aimed at reducing the risk of in-utero demise, balanced against minimising perinatal morbidity. Recommendations on the comprehensive management pathways of multiple pregnancy is out of the scope of this commentary and is readily available through established guidelines.

Recommendation for the NPEC audit

- Expansion of NPEC audits to include more detailed information regarding perinatal mortality in twins and higher-order multiple pregnancies. This report has highlighted a high rate of PNM in our youngest mothers delivering twins. Additional information pertaining to fetal characteristics in twins (for example capturing timelines in relation to gestational age of occurrence of a single intrauterine fetal demise) are important in understanding impact on survival in the other twin. For cases of TTTS-associated perinatal mortality, documenting within NPEC if fetal intervention occurred is encouraged.

- Consideration to the establishment of a National Working Group in relation to Perinatal Mortality in Multiple Pregnancy. On the foot of the inaugural MBRRACE-UK enquiry into stillbirth and early neonatal death in twins, and in an effort to address perinatal mortality in twins, it would be prudent to establish an Irish group of specialists to investigate, on a rolling basis, twin and higher-order multiple deaths through a confidential individual chart review.

- Auditing of all fetal loss in relation to TTTS <24 weeks as a means of identifying factors leading to the under-recognition of TTTS.

Recommendations for clinical care that should assist a reduction in twin mortality

- Continued emphasis on additional resources, recruitment and retention of highly trained obstetric sonographers to continue to deliver the mandated highly specialised multiple pregnancy services across all 19 maternity units.

- Hospital-based antenatal care delivered by a specialised group of obstetricians, midwives, sonographers, and neonatologists.

- Commencement of aspirin by 16 weeks' gestation in multiple pregnancies with additional risk factors for the development of preeclampsia.

- Adherence to national standards in relation to timing of assignment of chorionicity of twins, adherence to the schedule of twin-specific sonographic assessments, and ensuring referral to fetal medicine specialists in the event of specified twin complications:

- Indications for referral for specialist fetal medicine input in a tertiary unit:
  - TTTS (suspected or confirmed)
  - IUGR (EFW of one or both twins <10th percentile, and/or intertwin growth discordance of >18%)
  - Structural anomalies
  - Single intrauterine fetal demise
  - Monoamniotic twins
  - Higher-order multi-fetal gestations

- Adherence to guidance regarding optimal timing of delivery in twin pregnancies to include:
  - Delivery of uncomplicated MCDA twins from 36 weeks' gestation and no later than 37 weeks' gestation (accepting a residual risk of 1.5% of late IUFD in twins)
  - Delivery for uncomplicated DCDA twins, consider at 37 weeks' gestation, no later than 38 weeks' gestation.

- Addressing the risk of preterm birth in multiple pregnancy

- Placental examination by dedicated perinatal pathologists remains an essential part of the investigation of any twin mortality.

- Continued investment in bereavement care.

Recommendations for education to enhance care that should assist a reduction in twin mortality

- Widespread education in relation to the identification of twin-specific complications for all clinical staff responsible for the care of women with multiple pregnancy.

- Education of all clinical staff regarding peri-viable counselling in twin gestations with clear guidance regarding escalation of care and early MDT involvement in cases at risk of extreme premature delivery.

References

1. Monden C, Pison G, Smits J. Twin peaks: more twinning in humans than ever before. Human Reproduction, Vol.00, No.0, pp. 1–8, 2021

2. ESRI Perinatal Statistics Report 2016, Health Research and Information Division, December2016 http://www.hpo.ie/latest_hipe_nprs_reports/NPRS_2016/Perinatal_Statistics_Report_2016.pdf

3. Euro-Peristat Project. European Perinatal Health Report. Core indicators of the health and care of pregnant women and babies in Europe in 2015. November 2018. www.europeristat.com

4. Khalil, A. The rate of twin births is declining. Ultrasound Obstet Gynecol. 2021 Feb 25. https://doi.org/10.1002/uog.23620

5. Kilby MD, Gibson JL, Ville Y. Falling perinatal mortality in twins in the UK: organisational success or chance? BJOG: An International Journal of Obstetrics and Gynaecology 2019, 126(3), 341-347. Available online at: https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.15517.

6. Draper E S, Gallimore I D, Smith L K, Kurinczuk J J, Smith P W, Boby T, Fenton A C, Manktelow B N, on behalf of 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. Available online at: https://www.npeu.ox.ac.uk/mbrrace-uk/reports/perinatal-mortality-surveillance.

7. Khalil A. Unprecedented fall in stillbirth and neonatal death in twins: lessons from the UK. Ultrasound Obstet Gynecol 2019; 53: 153–157

8. Khalil A, Reed K. Confidential Enquiry into Stillbirth and Neonatal Death in Twins: key messages for obstetricians and fetal medicine specialists. doi: 10.1002/uog.23594

9. Donovan EF, Ehrenkranz RA, Shankaran S, Stevenson DK, Wright LL, Younes N et al. Outcomes of very low birth weight twins cared for in the National Institute of Child Health and Human Development Neonatal Research Network's intensive care units. Am J Obstet Gynecol 1998;179:742-749

10. Rettwitz-Volk W, Tran TM, Veldman A. Cerebral morbidity in preterm twins. J Matern Fetal Neonatal Med 2003; 13:218-23

11. MBRRACE-UK 2019. 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.

12. Rizwan N, Abbasi RM, Mughal R. Maternal morbidity and perinatal outcome with twin pregnancy. J Ayub Med Coll Abbottabad. 2010;22(2):105–7.

13. Vogel JP, Torloni MR, Seuc A, Betrán AP, Widmer M, Souza JP, et al. Maternal and perinatal outcomes of twin pregnancy in 23 low- and middle-income countries. PLoS One. 2013;8(8):e70549.

14. Werder E, Mendola P, Männistö, O'Loughlin J, Laughon SK. Effect of maternal chronic disease on obstetric complications in twin pregnancies in a United States cohort. Fertil Steril 2013; 100(1): 142–149.

15. Lisonkova S, Sheps S B, Janssen PA, Lee SK, Dahlgren L. Effect of older maternal age on birth outcomes in twin pregnancies: a population-based study. Journal of Perinatology 2011;31:85-91

16. Hypertension in pregnancy: diagnosis and management. NICE Clinical Guidelines, No. 133, 25 June 2019

17. 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.

18. Anbazhagan, A. Hunter H, Breathnach FM, McAuliffe FM, Geary MP, Daly S, et al. Comparison of outcomes of twins conceived spontaneously and by artificial therapy. J Matern Fetal Neonatal Med, Vol 27 (5) , 2015

19. Monochorionic twin pregnancy, management (RCOG Green-top Guideline No. 51, Nov 2016)

20. Multifetal Gestations: Twin, triplet and high-order multifetal pregnancies. ACOG Practice Bulletin no 144, May 2014.

21. Breathnach FM, Malone FD. Fetal growth disorders in twin gestation. Semin Perinatol 2012; 36(3):175-81.

22. Lewi L, Jani J, Blickstein I, Huber A, Gucciardo L, Van Mieghem T, Doné E, Boes A-S, Hecher K, Gratacós E, Lewi P, Deprest J. The outcome of monochorionic diamniotic twin gestations in

the era of invasive fetal therapy: a prospective cohort study. American Journal of Obstetrics and Gynecology 2008, 199(5), 514.e511-514.e518. Available online at: http://www.sciencedirect.com/science/article/pii/S0002937808003451.

23. Lee YM, Wylie BJ, Simpson LL, D'Alton ME. Twin chorionicity and the risk of stillbirth. Obstet Gynecol 111:301-8, 2008.

24. Hillman S, Morris R, Kilby M. Co-twin prognosis after single fetal death: a systematic review and metaanalysis. Obstetrics and Gynecology 2011, 118(4), 928-940.

25. Cheong-See F, Schuit E, Arroyo-Manzano D. Prospective risk of stillbirth and neonatal complications in twin pregnancies: systematic review and meta-analysis. British Medical Journal 2016, 354. Available online at: https://www.bmj.com/content/354/bmj.i4353.

26. 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.

27. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, et al. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. Ultrasound Obstet Gynecol 2016; 47:247-263.

28. Roman A, Zork N, Haeri S, Schoen CN, Saccone G, Colihan S , et al. Physical examination-indicated cerclage in twin pregnancy: a randomized controlled trial. Am J Obstet Gynecol. 2021 Dec;223(6):902.e1-902.e11

29. Breathnach FM, McAuliffe FM, Geary M, Daly S, Higgins JR, Dornan J, Morrison JJ, Burke G, Higgins S, Dicker P, Manning F, Mahony R, Malone FD. Definition of intertwin birth weight discordance. Obstet Gynecol 2011;118(1):94-103.

30. Blickstein I, Kalish RB. Birthweight discordance in multiple pregnancy. Twin Res 6(6):526–531, 2003.

31. Hsieh TT, Chang TC, Chiu TH et al. Growth discordancy, birthweight and neonatal adverse events in third trimester twin gestations. Gynecol Obstet Invest 1994;38:36-40

32. Cohen SB, Elizur SE, Goldenberg M, Beinder M, Novikov I, Mashiach S, et al. Outcome of twin pregnancies with extreme weight discordancy. Am J perinatal 2001;18:427-32

33. Gratacos E, Lewi L, Munoz B, et al. A classification system for selective intrauterine growth restriction in monochorionic twins with selective intrauterine growth restriction and intermittent absent or reversed end-diastolic umbilical artery flow. Ultrasound Obstet Gynecol 30:28-34, 2007.

34. Ishil K, Murakoshi T, Takahashi Y, Shino T, Matasushita M, Naruse H, et al. Perinatal outcome of monochorionic twins with selective intrauterine growth restriction and different types of umbilical artery Doppler under expectant management. Fetal Diagn Ther 26(3):157-61, 2009.

35. Engineer N, Fisk N. Multiple pregnancy, in Rodeck, CH, Whittle MJ (eds): Fetal medicine: Basic Science and Clinical Practice, London, UK. Churchill Livingstone, 2009.

36. Kilie M, Aygun C, Kaynar-Tuncel E, Kucukoduk S. Does birth wright discordance in preterm twins affect neonatal outcome? J Perinatol 2006;26:268-72.

37. Lewi L, Jani J, Blickstein I et al. The outcome of monochorionic diamniotic twin gestations in the era of invasive fetal therapy: a prospective cohort study. Am J Obstet Gynecol 199:514.e1-8, 2008

38. Lopriore E, van Wezel-Meijler G, Middeldorp JM, Sueters M, Vandenbussche FP, Walther FJ. Neurodevelopmental outcome after laser therapy for twin-twin transfusion syndrome. Am J Obstet Gynecol 196(1):e20, 2007, author reply e20-21.

39. Akkermans J, Peeters SHP, Klumper FJ, Lopriore E, Middeldorp JM. Twenty-five years of fetoscopic laser coagulation in twin-twin transfusion syndrome: a systematic review. Fetal Diagn Ther 38:241-253, 2015.

40. Müllers SM, McAuliffe FM, Kent E, Carroll S, Mone F, Breslin N, Dalrymple J, Mulcahy C, O'Donoghue K, Martin A, Malone FD. Outcome following selective fetoscopic laser ablation for twin to twin transfusion syndrome: an 8 year national collaborative experience. Eur J Obstet Gynecol Reprod Biol 191:125-129, 2015.