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Timing of Delivery for Twins with Growth Discordance and Growth Restriction: An Individual Participant Data Meta-analysis

Running title: Time of Delivery in Twins of Growth Disorders

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Credit statement:

Ashlee Koch: data curation, project administration, methodology, writing- original draft, reviewing and editing. Renee J. Burger: data curation, formal analysis, methodology, writing original draft, reviewing, and editing. R. Katie Morris: project administration, supervision, writing- reviewing and editing. Wessel Ganzevoort and Sanne J Gordijn: supervision, reviewing and editing. Ben W. Mol: conceptualization, supervision, reviewing and editing. Wentao Li: methodology, supervision, formal analysis, reviewing and editing. All other authors: collection and contribution of data; interpretation of data. All authors approved the final version of the manuscript.

Precis Growth disorders in twins are associated with higher absolute risks of stillbirth and neonatal death but no evidence was found that the optimal timing of delivery should be changed.

Abstract

Objective: The impact of growth discordance in twin pregnancies on the optimal time of delivery, with or without small for gestational age (SGA, birthweight <10th centile), is unknown. We aimed to elucidate this impact by evaluating the risks of stillbirth and neonatal death in women with different levels of growth discordance and in relation to SGA.

Data Sources: A search of MEDLINE, Embase, ClinicalTrials.gov and Ovid between 2015-2018 was performed of cohort studies reporting risks of stillbirth and neonatal death in twin pregnancies from 32 to 41 weeks. Studies from a previous meta-analysis using a similar search strategy (from inception to 2015) were combined. Women with monoamniotic twin pregnancies were excluded.

Methods of Study Selection: Overall, of 57 eligible studies, 20 cohort studies that contributed original data reporting on 7,474 dichorionic and 2,281 monochorionic twin pairs.

Tabulation, Integration and Results: An individual participant data meta-analysis was performed to calculate the risk of perinatal death (risk difference between prospective stillbirth and neonatal death) per gestational week. Analyses were stratified by chorionicity, levels of growth discordance and presence of SGA in one or both twins.

For both dichorionic and monochorionic twins, the absolute risks of stillbirth and neonatal death were higher when one or both twins were SGA and increased with greater levels of growth discordance. Regardless of level of growth discordance and birthweight, perinatal risk balanced between 36^{+0-6} and 37^{+0-6} weeks in both dichorionic and monochorionic twin pregnancies, with likely higher risk of stillbirth than neonatal death from 37^{+0-6} weeks onwards.

Conclusion: Growth discordance or SGA is associated with higher absolute risks of stillbirth and neonatal death. However, balancing these two risks, we did not find evidence supporting

that the optimal timing of delivery should be changed by the presence of growth disorders alone.

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Introduction

Twin-specific pregnancy complications and a higher proportion of obstetric complications mean that women with twin pregnancies are more likely to suffer stillbirth compared to singletons (1-12). Twins experience more neonatal morbidity and mortality, in part as a result of prematurity due to spontaneous or iatrogenic preterm delivery (3, 13). The timing of delivery for twins is a paramount decision balancing the risk of stillbirth with the neonatal mortality associated with earlier delivery (14).

A previous meta-analysis, in which the optimal timing of delivery for women with dichorionic and monochorionic diamniotic twins without growth restriction, was calculated at 37^{+0} and 36^{+0} weeks, respectively (15). However, the optimal timing of delivery for twins where the pregnancy is complicated by fetal growth disorders (growth discordance and/or growth restriction) is still unknown.

The probability of a twin pregnancy being affected by growth discordance greater than 20% is 7-15% (4, 5, 16). Growth discordance is associated with a higher risk of stillbirth compared to pregnancies with concordant growth (5, 17). As growth discordance increases, so does the likelihood that the smaller twin has growth restriction (18), which has been shown to be associated with stillbirth and perinatal morbidity (5). In cases of fetal growth discordance this finding might influence guidelines for recommended gestational age for delivery. We therefore aimed to evaluate the impact of growth disorders in twins on the optimal timing of delivery by performing a systematic review and individual participant data meta-analysis.

Methods

Sources

We performed a systematic review with an individual participant data meta-analysis in accordance with the Meta-analysis of Observational Studies in Epidemiology (19) (MOOSE) guidelines (Appendix 1). The review protocol was prospectively registered as PROSPERO CRD42018090866. All included studies had institutional review board approval and prospective studies had informed consent from participants. No separate ethics approval was necessary for this review.

A literature search strategy was formulated and a systematic search of Ovid, MEDLINE, Embase and ClinicalTrials.gov was performed. The search was limited to English language articles from December 2015-December 2018 and the results were added to studies previously identified in a separate systematic review which included studies of unselected twins from inception to December 2015 (15).

Search terms representing the participants (monochorionic OR dichorionic OR twin pregnancy OR multiple pregnancy) were combined with the outcome terms (stillbirth OR fetal or foetal or fetus or foetus AND death or demise or mortality AND with the mention of Growth restriction OR intrauterine growth restriction OR growth discordance). An additional search was performed with a list of neonatal outcomes (Neonatal death OR Neonatal morbidity OR Neonatal mortality OR Neonatal outcome OR Bronchopulmonary dysplasia OR Assisted ventilation OR Retinopathy of prematurity OR Hypoxic ischemic encephalopathy OR Neonatal sepsis OR Neonatal meningitis). (Appendix 2)

Study Selection

We included cohort studies nested in randomized controlled trials, prospective and retrospective observational studies of monochorionic and dichorionic twins, which reported on

stillbirth and neonatal death, all of which did not exclude growth restriction or growth discordance. Exclusion criteria were missing data on chorionicity, monoamnionicity, inability to exclude twin to twin transfusion syndrome, congenital anomalies, selective termination, or less than 25 participants. Small for gestational age (SGA) was defined as birthweight below the 10th centile for gestation using twin specific growth charts (20). Stillbirth was defined as the death of the fetus before birth, whereas perinatal loss included stillbirth and neonatal death within the first 7 days. Birthweight discordance was calculated as 100 × (larger birthweight–smaller birthweight)/larger birthweight.

A two-step approach was utilized for study selection (21). Firstly, the abstracts and titles of citations were assessed for eligibility followed by full text review of potentially relevant papers. If necessary, we contacted the authors of the original studies to confirm the eligibility criteria and to provide clarifications on the published data. Studies from the previous meta-analysis (15) were added to the updated search if they met the inclusion criteria.

Data access

The principal investigators of eligible studies were contacted to participate and were requested to provide individual participant data. At least five attempts were made to contact all authors named on a publication via email. Study contacts could either complete an Excel data sheet with definitions or send their data with a codebook of the definitions for variables. The data collected included gravidity, parity, chorionicity, fetal sex, uterine artery doppler parameters, deepest vertical pool of amniotic fluid prior to delivery, occurrence of stillbirth, onset of labour, indication for delivery, mode of delivery, gestational age at delivery, birthweight, neonatal death and neonatal morbidity data (including necrotizing enterocolitis (NEC), intra-ventricular haemorrhage (IVH), retinopathy of prematurity (ROP), respiratory distress syndrome (RDS), meningitis, and septicemia). Additional efforts were made to contact the original authors to

obtain data about gestational age at fetal demise (if applicable) wherever possible. Agreement approval to use the data was given by the authors of each included study. The data was deidentified format and password protected which was only accessible to certain investigators.

Quality assessment

Quality assessment was performed using the Newcastle-Ottawa Scale for assessing the quality of cohort studies in meta-analyses (NOS) (22) to determine the risk of bias of each individual study. The NOS assesses studies on three domains: selection, comparability, and outcome. Maximum score is 9 points.

Data cleaning

Datasets including information on all minimally required items (chorionicity, gestational age at delivery, perinatal death, and birthweight) were included in the analyses. The data from each individual study was checked for discrepancies, range, internal consistency, missing or extreme values and errors, and provided with consistent coding. When inconsistencies or unexpected missing data were identified, the study authors were contacted for clarification.

Evidence synthesis

The primary outcome was perinatal death per gestational week. We defined the risk of perinatal death as the risk difference between stillbirth and neonatal death of that week of gestation (between 32-41 weeks), which estimates the competing risk between stillbirth and neonatal death to reflect the benefit or harm for expectant management or immediate delivery in each week. A risk difference below zero indicates that the risk of neonatal death outweighs that of stillbirth if delivery occurred, and thus, expectant management is preferred. To the opposite, in the case of a positive risk difference, immediate delivery is desired. The gestational age at which the risk difference is equal to zero reflects the optimal timing of delivery. The secondary

outcome was the rate of a composite of neonatal morbidity including NEC, IVH, ROP, RDS or sepsis in one or both liveborn twins per gestational week.

We first computed the risks of stillbirth, neonatal death, and composite neonatal morbidity in twin pregnancies for each week of gestation per study. Analyses were performed stratified by chorionicity, birthweight (below and from the 10^{th} centile) and growth discordance (below 10%, 10-30% and greater than 30%). Similar to the method used in our previous meta-analysis on unselected twins, the prospective risk of stillbirth was calculated by dividing the number of stillbirths per week by the number of women at risk of stillbirth at the beginning of that week (15). Deliveries that occurred that week were accounted for by subtracting half of the number of women that delivered in that gestational week. If available, the estimated gestational age at fetal demise was used to calculate prospective stillbirth risks and estimate birthweight centile. For the risk of neonatal death and composite neonatal morbidity, the number of neonatal deaths or composite outcomes was divided by the number of neonates liveborn that week.

We then pooled the risk difference between stillbirth and neonatal death for each week from individual studies using fixed effects meta-analysis with the Mantel-Haenszel (MH) method. No continuity correction was used. We used this method because stillbirth and neonatal death are rare events (risks smaller than 1%) for most weeks of gestation and frequent observations of zero events were expected (23). For the composite neonatal morbidity outcome, as we expected heterogeneity of absolute risks between studies, we used a logistic-normal random-effects model for the estimation (24). In the event of non-convergence, we used a random-effects model with inverse-variance weights and exact confidence intervals.

Sensitivity analyses were performed using a moving average for growth discordance (0-10%, 0-20%, 10-30%, 20-40%, 30-50%) in both dichorionic and monochorionic twin pregnancies. A post hoc sensitivity analysis that only included cohorts entirely after 2004 was performed in

all twins to assess the impact of improved neonatal care over time. The analyses were performed using IBM SPSS Statistics 26 (25) and Stata 17.0 (26).

Results

Identification of studies

From 3762 articles identified through the search strategy and our previous meta-analysis, we included 20 unique studies on 9755 women with 7474 dichorionic (from 17 studies) and 2281 monochorionic twin gestation (from 13 studies) in our current analysis (Figure 1) (6-12, 27-43).

Characteristics and quality of included studies

Of the 17 studies on dichorionic twins, 15 provided data on stillbirth and neonatal mortality, and two on neonatal mortality only. For monochorionic twins, 12 studies provided data on stillbirth and neonatal mortality, and one on neonatal mortality only. In 1814 (19%) of the dichorionic and 699 (31%) of the monochorionic twins, one or both infants were SGA; in 1327 (18 %) dichorionic and 458 (20%) monochorionic twins, birthweight discordance was greater than 2 0%. There were no cases of major congenital anomalies in all twins or TTTS in monochorionic twins. The mean gestational age at delivery was 36.6 (1.7) for dichorionic and 36.0 (1.8) for monochorionic twin pregnancies. Additional characteristics of the population and study characteristics are provided in Appendix 3 - 5 .

The quality of the studies was in general satisfactory. Twelve out of the 20 studies were prospective, and of these 11 were nested within randomized trials. Most studies used consecutive or random sampling methods (18/20) and achieved adequate follow-up (>80%).

20 studies had low risk of bias for determining assessment of gestational age at delivery and chorionicity (Appendix 6).

Risk of stillbirth and neonatal mortality

Dichorionic twin pregnancies

In the population of dichorionic twins without taking SGA status or growth discordance into account (n=7,474), the prospective risk of stillbirth increased from 1.2/1000 (95% CI 0.6/1000 to 2.4/1000) at 34^{+0-6} to 6.0/1000 (95% CI 2.9/1000 to 12.4/1000) at 38^{+0-6}, while the risk of neonatal death decreased from 11.5/1000 (95% CI 5.8/1000 to 22.5/1000) at 34^{+0-6} to 2.1/1000 (95% CI 0.7/1000 to 6.1/1000) at 39^{+0-6} (Appendix 7). Perinatal risks are likely balanced between 36^{+0-6} and 37^{+0-6} (Table 1 & Figure 2).

In pregnancies where one or both twins were SGA (N=1,814), the absolute risk of stillbirth increased from 2.5/1000 (95% CI 1.0/1000 to 6.5/1000) to 11.8/1000 (4.0/1000 to 34.0/1000) from 34^{+0-6} to 38^{+0-6} , whereas the risk of neonatal mortality decreased from 17.2/1000 (95% CI 5.9/1000 to 49.5/1000) to 6.0/1000 (95% CI 1.7/1000 to 21.7/1000) (Appendix 7) . The perinatal risk was likely balanced at 37^{+0-6} (risk difference -5.1/1000, 95%CI -12.7/1000 to 2.4/1000, I^2=0%). From 38^{+0-6} the stillbirth risk was statistically comparable to the neonatal mortality risk (risk difference 4.5/1000, 95%CI -12.8 to 21.8, I^2=0%) . Similar findings with balanced perinatal risks at 37^{+0-6} were seen among twins with different levels of growth discordance (Table 1 & Figure 2).

In pregnancies in which both twins had birthweights appropriate for gestational age (birthweight ≥p10; N=5,654), the absolute risk of stillbirth ranged from 0.8/1000 (95% CI 0.3/1000 to 2.1/1000) to 4.4/1000 (1.7/1000 to 11.4/1000) between 34^{+0-6} and 38^{+0-6}. The risk of neonatal mortality was highest at 34^{+0-6} (9.6/1000, 95% CI 4.1/1000 to 22.3/1000) and lowest

at 38^{+0-6} (0.9/1000, 95% CI 0.2/1000 to 5.1/1000) (Appendix 7). T he perinatal risk was balanced between 36^{+0-6} (risk difference -0.9/1000, 95%CI -4.0/1000 to 2.1/1000, I^2=0%) and 37^{+0-6} (risk difference 0.3/1000, 95%CI -2.8/1000 to 3.4/1000, I^2=0%). From 38^{+0-6} the stillbirth risk seems to outweigh the neonatal mortality risk (risk difference 3.5/1000, 95%CI -1.7 to 8.7, I^2=0%), though results were not statistically significant. Similar findings with balanced perinatal risks between 36^{+0-6} and 37^{+0-6} were seen among twins with <10% (N=3,433) and 10-30% growth discordance (N=2,179; Table 1 & Figure 2).

Monochorionic twin pregnancies

In the population of monochorionic twins without taking SGA status or growth discordance into account (n=2,281), the prospective risk of stillbirth was 1.6/1000 (95% CI 0.6/1000 to 4.8/1000) at 34^{+0-6} and 7.1/1000 (95% CI 2.8/1000 to 18.1/1000) at 37^{+0-6}. The risk of neonatal death decreased from 15.9/1000 (95% CI 6.2/1000 to 40.1/1000) at 34^{+0-6} to 4.0/1000 (95% CI 1.1/1000 to 14.6/1000) at 37^{+0-6} (Appendix 8). Perinatal risks are likely balanced between 36^{+0-6} and 37^{+0-6}(Table 2 & Figure 3).

In pregnancies in which one or both twins were SGA (N=699), the absolute risk of stillbirth increased from 5.8/1000 (95% CI 2.0/1000 to 16.8/1000) to 12.4/1000 (3.4/1000 to 44.2/1000) from 34^{+0-6} to 37^{+0-6}, while the risk of neonatal mortality decreased from 10.8/1000 (95% CI 1.9/1000 to 58.4/1000) to 7.2/1000 (95% CI 1.3/1000 to 39.6/1000) (Appendix 8). The perinatal risk was balanced between 36^{+0-6} (risk difference -4.7/1000; 95%CI -19.2/1000 to 9.7/1000, I^2=0%) and 37^{+0-6} (risk difference 3.0/1000; 95%CI -15.9/1000 to 22.0/1000, I^2=0%). From 38^{+0-6} the stillbirth risk was statistically comparable to the neonatal mortality risk (risk difference 21.1/1000, 95%CI -18.1 to 60.2, I^2=0%) . In SGA twins with 10-30% growth discordance (N=363), a similar finding was observed, with balanced perinatal risks between

36^{+0-6} and 37^{+0-6} (Table 2 and Figure 3). For SGA twins with more than 30% growth discordance (N=173), stillbirth risk seemed to outweigh neonatal mortality risk at 36^{+0-6} weeks (risk difference 24.4/1000, 95%CI -17.0 to 65.8, I^2=0%), although this was not statistically significant; after 36^{+0-6} weeks data were insufficient to estimate perinatal risks.

In pregnancies where both twins were appropriate for gestational age (birthweight ≥p10; N=1,581), the prospective risk of stillbirth was 1.4/1000 (95% CI 0.4/1000 to 5.0/1000) at 33^{+0-6} and 5.0/1000 (95% CI 1.4/1000 to 18.0/1000) at 37^{+0-6}. The risk of neonatal death decreased from 18.9/1000 (95% CI 6.4/1000 to 54.0/1000) at 34^{+0-6} to 2.8/1000 (95% CI 0.5/1000 to 15.7/1000) at 37^{+0-6} (Appendix 8). The perinatal risk was balanced between 36^{+0-6} (risk difference -14.2/1000; 95%CI -26.5/1000 to -2.0/1000, I^2=0%) and $37+^{0-6}$ (risk difference 1.8/1000, 95%CI -7.2/1000 to 10.7/1000, I^2=0%). From 38^{+0-6} the stillbirth risk was statistically comparable to the neonatal mortality risk (risk difference 8.4/1000, 95%CI -8.0 to 24.8, I^2=0%) . Similar findings with balanced perinatal risks between 36^{+0-6} and 37^{+0-6} were seen among twins with <10% (N=1,052) and 10-30% growth discordance (N=513; Figure 3).

Sensitivity analyses in both dichorionic and monochorionic twin pregnancies using a moving average for growth discordance showed similar results as described above (Appendix 9). Only including cohorts entirely after 2004 resulted in similar findings as the main analysis (Appendix 10).

Neonatal morbidity

The risk of neonatal morbidity outcome in one or both twins decreased consistently with advancing gestational age up to 39^{+0-6} in dichorionic and 37^{+0-6} in monochorionic twin

pregnancies, after which no adverse events occurred. However, there was insufficient data after 37^{+0-6} for meaningful interpretation. Findings were similar in different levels of growth restriction and growth discordance (Appendix 11 & 12)

Discussion

In this study, we have demonstrated that growth discordance and SGA were associated with higher stillbirth and neonatal mortality risks, but they did not largely influence the optimal timing of birth. Perinatal risk balanced between 36^{+0-6} and 37^{+0-6} weeks in both dichorionic and monochorionic twin pregnancies and for different level of growth discordance and birthweight, which is largely in line with previous meta-analyses of twin pregnancies not complicated by growth disorders (15, 42). As expected, the risk of adverse neonatal morbidity outcome decreased consistently with advancing gestational age (6, 11).

This individual participant data meta-analysis allowed us to analyze different subgroups based on chorionicity, growth discordance and birthweight and report findings in clinically relevant weekly intervals. Using perinatal risk as an estimator of optimal timing of births considers both the number of stillbirths potentially avoided by delivery and the impact that delivery has on neonatal mortality. Wherever possible the gestational age at death was used for calculation of stillbirth rates and birthweight centile. Levels of growth discordance and birthweight centile were calculated from gestational age and birthweight, avoiding inter-study variability in calculations and cut-offs used for these parameters.

Despite our efforts to assemble all available data, our analyses were limited by the sample size, especially for monochorionic twins and some of the subgroups. In the case of single or zero event, the accuracy and precision of estimation could be affected. We applied meta-analysis

methods that are optimized for rare events to counteract this issue and the results are conservative for scenarios of single event. Second, our results were limited by policy of planned delivery beyond 37 and 38 weeks' gestation in most studies. Another limitation is that many of the included studies did not report on factors indicating pathology such as umbilical artery doppler measurements and placental pathology indicating placental insufficiency. Consequently, we were not able to distinguish those constitutionally small from those with actual growth disorders (44). Indication for delivery, mode of delivery and use of antenatal steroids were also not provided by many studies and could not be accounted for in our analyses. Knowledge of the mode of delivery can be relevant as preterm cesarean section is associated with increased risk of RDS, compared to vaginal delivery (36, 45). Many studies did not provide neonatal morbidity data, limiting the ability to analyze the risk of different neonatal morbidities separately and leading to an underestimation of the rate of the composite outcome for neonatal morbidity. Despite this limitation, we were able to analyze trends in neonatal morbidity. Long-term morbidity could also have weight in considering timing of delivery, but relevant data were mostly absent in studies.

In case of single intrauterine fetal death, clinical management varies largely, creating substantial variation in the time between fetal demise and delivery. The use of gestational age at delivery instead of at death in some studies could have resulted in an overestimation of the level of growth discordance as dead fetuses do not grow and even lose weight while gestational age increases (44), and could led to overestimation of stillbirth risk at higher gestations. This effect is most likely stronger in dichorionic twins as in monochorionic twins' delivery may be initiated in the case of single intrauterine fetal death. To counteract this bias, we were able to correct for gestational age at death in approximately 2/3rd of the stillbirths.

The analysis of the collated datasets was based on the use of birthweight, however the decision to deliver a fetus in practice, is based on estimated fetal weight from ultrasound. The percentage of birthweight predictions from ultrasound for twins within 10% and 15% accuracy is 49.7% and 68.5%, respectively; the accuracy declines for twin fetuses <2000g and at lower gestational ages(46). Twin birthweight charts were used which is known to have better predictive value for perinatal mortality(47), but uses a higher cut off for defining SGA compared to singleton growth charts. Using singleton growth charts would classify a greater proportion of twins with SGA, compared to using twin-specific charts(12, 48).

This study provides detail for the perinatal outcomes of twins per gestational week after 32 weeks, with further stratification by the degree of anticipated growth discordance or presence of SGA, which can guide counselling for parents about the prospective outcome of expectant management versus delivery. In the presence of growth discordance or growth restriction, increased monitoring for twins is desired because they have increased absolute risks of stillbirth and neonatal death. However, in the absence of other clinical indications for immediate intervention, the competing risks between stillbirth and neonatal death should be balanced to decide the optimal delivery time. The advice in current evidence for the optimal timing of delivery should not be changed by the presence of growth discordance or growth restriction alone. However, attention must be paid to individual maternal or additional fetal complications that may have arisen during the pregnancy.

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Figure legends

Figure 1. Meta-analyses Of Observational Studies in Epidemiology (MOOSE) flowchart for assessment of studies for eligibility. MCMA, monochorionic-monoamniotic; TRAP, twin reversed arterial perfusion; TTTS, twin-to-twin transfusion syndrome: IUGR, intrauterine growth restriction

Figure 2. Prospective risk of stillbirth from expectant management compared with risk of neonatal mortality from delivery at weekly intervals from 34 weeks of gestation in dichorionic twin pregnancies by birthweight centile and level of growth discordance. Statistically significant results are emboldened in Table 1.

Figure 3. Prospective risk of stillbirth from expectant management compared with risk of neonatal mortality from delivery at weekly intervals from 34 weeks of gestation in monochorionic twin pregnancies by birthweight centile and level of growth discordance. Statistically significant results are emboldened in Table 2.

Table 1 | Perinatal death in weekly intervals in dichorionic twin pregnancies from 32 weeks of gestation

	ALL LEVELS OF GROWTH DISCORDANCE			**<10% GROWTH DISCORDANCE**			**10-30% GROWTH DISCORDANCE**			**>30% GROWTH DISCORDANCE**		
Gestational age (weeks)	**N stillbirths / N ongoing pregnancies**	**N neonatal deaths / N women delivered†**	**Pooled risk difference* (per 1000 pregnancies) (95% CI)**	**N stillbirths / N ongoing pregnancies**	**N neonatal deaths / N women delivered†**	**Pooled risk difference* (per 1000 pregnancies) (95% CI)**	**N stillbirths / N ongoing pregnancies**	**N neonatal deaths / N women delivered†**	**Pooled risk difference* (per 1000 pregnancies) (95% CI)**	**N stillbirths / N ongoing pregnancies**	**N neonatal deaths / N women delivered†**	**Pooled risk difference* (per 1000 pregnancies) (95% CI)**
ALL BIRTHWEIGHTS												
32+0-6	4/7474	6/241	**-25.6 (-45.9 - -5.3)**	1/3832	1/103	-9.8 (-27.6 - 8.1)	0/3244	5/105	**-52.2 (-92.7 - -11.6)**	3/398	0/33	7.6 (-2.1 - 17.3)
33+0-6	5/7229	5/354	**-13.5 (-26 - -1.0)**	0/3728	1/174	-5.9 (-16.8 - 5.0)	1/3139	2/134	-14.1 (-33.3 - 5.1)	4/362	2/46	-29.2 (-91.0 - 32.7)
34+0-6	8/6871	8/695	**-8.9 (-16.6 - -1.2)**	1/3555	2/312	-6.3 (-15.3 - 2.6)	2/3004	4/319	-12.1 (-24.4 - 0.1)	5/312	2/64	8.3 (-32.4 - 49.0)
35+0-6	3/6169	10/971	**-9.6 (-15.9 - -3.3)**	0/3242	3/496	-5.8 (-12.3 - 0.7)	1/2683	5/421	**-11.2 (-21.4 - -1.0)**	2/244	2/54	-27.5 (-72.7 - 17.7)
36+0-6	5/5196	6/1362	-3.3 (-6.9 - 0.3)	4/2746	3/687	-3.1 (-8.4 - 2.3)	1/2261	2/607	-2.6 (-7.1 - 1.9)	0/189	1/68	-9.8 (-27.7 - 8.2)
37+0-6	6/3828	6/1937	-1.0 (-4.0 - 1.9)	1/2054	3/1027	-2.3 (-5.7 - 1.2)	5/1653	2/835	1.5 (-3.3 - 6.4)	0/121	1/75	-12.4 (-36.0 - 11.2)

38+0-6	7/1887	3/1449	3.4 (-2.1 - 8.9)	0/1026	0/797	INSUFFICIENT DATA	2/814	2/616	0.2 (-7.9 - 8.4)	3/47	1/36	77.9 (-42.0 - 197.8)
39+0-6	0/434	2/334	-6.1 (-14.4 - 2.3)	0/227	0/173	INSUFFICIENT DATA	0/196	2/152	-14.2 (-33.3 - 4.9)	0/11	0/9	INSUFFICIENT DATA
40+0-6	1/101	0/88	18.1 (-16.9 - 53.1)	0/54	0/47	INSUFFICIENT DATA	0/44	0/38	INSUFFICIENT DATA	0/3	0/3	INSUFFICIENT DATA
BIRTHWEIGHT <P10												
32+0-6	4/1814	4/68	**-66.7 (-124.8 - -8.5)**	1/396	1/7	-202.4 (-679.9 - 275.2)	0/1062	3/34	**-113.3 (-186.5 - -40.1)**	3/356	0/27	9.7 (-2.5 - 21.9)
33+0-6	5/1742	5/78	**-76.1 (-134.3 - -17.9)**	0/388	1/15	-124.2 (-488.7 - 240.2)	1/1028	2/27	-80.1 (-163.3 - 3.1)	4/326	2/36	-41.8 (-119.6 - 35.9)
34+0-6	4/1660	3/174	-8.7 (-26.3 - 8.9)	0/374	1/30	-35.5 (-167.9 - 97.0)	0/1000	1/86	-12.7 (-36.7 - 11.4)	4/286	1/58	26.0 (-2.4 - 54.4)
35+0-6	2/1483	6/233	**-24.4 (-44.3 - -4.6)**	0/344	1/35	-27.7 (-66.2 - 10.7)	0/914	3/145	-20.2 (-42.4 - 2.0)	2/225	2/53	-26.9 (-72.6 - 18.9)
36+0-6	1/1249	4/349	-10.1 (-20.7 - 0.5)	0/309	2/83	-22.4 (-51.6 - 6.8)	1/769	1/200	-3.7 (-13.4 - 6.1)	0/171	1/66	-10.4 (-29.3 - 8.6)
37+0-6	1/899	3/479	-5.1 (-12.7 - 2.4)	0/226	1/116	-7.6 (-20.5 - 5.3)	1/568	1/298	-1.5 (-8.9 - 5.9)	0/105	1/65	-14.8 (-42.8 - 13.2)
38+0-6	3/421	2/332	4.5 (-12.8 - 21.8)	0/110	0/92	INSUFFICIENT DATA	0/270	1/208	-5.0 (-14.3 - 4.4)	3/41	1/32	87.3 (-34.4 - 209.0)

39+0-6	0/89	0/76	INSUFFICIENT DATA	0/18	0/17	INSUFFICIENT DATA	0/62	0/52	INSUFFICIENT DATA	0/9	0/7	INSUFFICIENT DATA
40+0-6	0/14	0/14	INSUFFICIENT DATA	0/1	0/1	INSUFFICIENT DATA	0/9	0/10	INSUFFICIENT DATA	0/3	0/3	INSUFFICIENT DATA
BIRTHWEIGHT ≥P10												
32+0-6	0/5654	2/173	-11.8 (-27.6 - 4.0)	0/3433	0/96	INSUFFICIENT DATA	0/2179	2/71	-28.7 (-65.4 - 8.1)	INSUFFICIENT DATA		
33+0-6	0/5481	0/276	INSUFFICIENT DATA	0/3337	0/159	INSUFFICIENT DATA	0/2108	0/107	INSUFFICIENT DATA	INSUFFICIENT DATA		
34+0-6	4/5205	5/521	**-9.0 (-17.4 - -0.6)**	1/3178	1/282	-3.3 (-10.2 - 3.7)	2/2001	3/233	-11.8 (-26.1 - 2.5)	INSUFFICIENT DATA		
35+0-6	1/4680	4/738	-5.1 (-10.6 - 0.4)	0/2895	2/461	-4.5 (-10.7 - 1.6)	1/1766	2/276	-6.3 (-16.4 - 3.8)	INSUFFICIENT DATA		
36+0-6	4/3941	2/1013	-0.9 (-4.0 - 2.1)	4/2434	1/604	-0.1 (-4.0 - 3.9)	0/1489	1/407	-2.4 (-7.1 - 2.3)	INSUFFICIENT DATA		
37+0-6	5/2923	3/1458	0.3 (-2.8 - 3.4)	1/1825	2/911	-1.4 (-4.7 - 1.8)	4/1082	1/537	3.3 (-3.1 - 9.7)	INSUFFICIENT DATA		
38+0-6	4/1460	1/1117	3.5 (-1.7 - 8.7)	2/913	0/705	3.9 (-1.5 - 9.3)	2/541	1/408	3.2 (-7.9 - 14.2)	INSUFFICIENT DATA		
39+0-6	0/339	2/258	-7.8 (-18.4 - 2.9)	0/206	0/156	INSUFFICIENT DATA	0/131	2/100	-23.4 (-53.9 - 7.0)	INSUFFICIENT DATA		
40+0-6	1/81	0/74	23.5 (-21.7 to 68.7)	0/50	0/46	INSUFFICIENT DATA	1/31	0/28	64.3 (-58.5 to 187.1)	INSUFFICIENT DATA		
*Individual studies risk differences pooled by fixed effect model meta-analysis (see text); † number of women who delivered at least one liveborn twin. Boldface data are statistically significant.												

Table 2 | Perinatal death in weekly intervals in monochorionic twin pregnancies from 32 weeks of gestation

	All levels of growth discordance			**<10% growth discordance**			**10-30% growth discordance**			**>30% growth discordance**		
Gestational age (weeks)	**N stillbirths / N ongoing pregnancies**	**N neonatal deaths / N women delivered†**	**Pooled risk difference* (per 1000 pregnancies) (95% CI)**	**N stillbirths / N ongoing pregnancies**	**N neonatal deaths / N women delivered†**	**Pooled risk difference* (per 1000 pregnancies) (95% CI)**	**N stillbirths / N ongoing pregnancies**	**N neonatal deaths / N women delivered†**	**Pooled risk difference* (per 1000 pregnancies) (95% CI)**	**N stillbirths / N ongoing pregnancies**	**N neonatal deaths / N women delivered†**	**Pooled risk difference* (per 1000 pregnancies) (95% CI)**
ALL BIRTHWEIGHTS												
32+0-6	4/2281	4/144	-22.9 (-46.9 - 1.1)	1/1215	0/43	12.2 (-4.7 - 29.1)	3/877	3/57	-43.9 (-93 - 5.2)	0/189	1/44	-27.3 (-70.9 - 16.4)
33+0-6	2/2133	1/169	-4.7 (-14.0 - 5.3)	2/1171	0/66	1.6 (-0.6 - 3.9)	0/817	0/69	INSUFFICIENT DATA	0/145	1/34	-33.2 (-92.5 - 26.2)
34+0-6	3/1963	4/252	-11.0 (-25.8 - 3.8)	0/1103	2/109	-17.7 (-39.7 - 4.2)	2/749	1/103	-3.8 (-26.1 - 18.6)	1/111	1/40	-8.1 (-54.7 - 38.4)
35+0-6	2/1708	1/344	-1.2 (-7.0 - 4.5)	1/994	0/187	1.0 (-0.9 - 2.9)	0/644	0/127	INSUFFICIENT DATA	1/70	1/30	-4.3 (-75.1 - 66.5)
36+0-6	1/1362	6/549	**-11.6 (-21.6 - -1.7)**	0/806	4/316	**-14.5 (-28.3 - -0.6)**	0/517	2/216	-10.1 (-22.9 - 2.8)	1/39	0/17	20.2 (-15.2 - 55.7)
37+0-6	4/812	2/495	2.5 (-5.9 - 11.0)	1/490	1/301	-0.7 (-9.6 - 8.2)	3/301	1/181	6.3 (-11 - 23.5)	0/21	0/13	INSUFFICIENT DATA

38+0-6	2/314	0/258	11.0 (-4.0 - 26.0)	0/188	0/153	INSUFFICIENT DATA	2/118	0/100	31.9 (-10.1 - 73.9)	0/8	0/5	INSUFFICIENT DATA
39+0-6	0/55	0/41	INSUFFICIENT DATA	0/35	0/28	INSUFFICIENT DATA	0/17	0/12	INSUFFICIENT DATA	0/3	0/1	INSUFFICIENT DATA
40+0-6	0/12	1/13	INSUFFICIENT DATA	0/7	0/7	INSUFFICIENT DATA	0/5	0/4	INSUFFICIENT DATA	0/2	1/2	INSUFFICIENT DATA
BIRTHWEIGHT <P10												
32+0-6	0/699	4/70	**-60.7 (-112.1 - -9.3)**	0/163	0/3	INSUFFICIENT DATA	0/363	3/26	**-121.9 (-238.0 - -5.9)**	0/173	1/41	-30.1 (-78.3 - 18.1)
33+0-6	0/629	1/61	-15.8 (-45.2 - 13.6)	0/160	0/5	INSUFFICIENT DATA	0/337	0/25	INSUFFICIENT DATA	0/132	1/31	-36.4 (-101.6 - 28.8)
34+0-6	3/568	1/93	4.5 (-15.0 - 24.0)	0/155	0/13	INSUFFICIENT DATA	2/312	0/45	17.2 (-5.6 - 40.0)	1/101	1/35	-9.1 (-61.5 - 43.2)
35+0-6	1/472	1/91	-4.9 (-25.5 - 15.7)	0/142	0/19	INSUFFICIENT DATA	0/265	0/46	INSUFFICIENT DATA	1/65	1/26	-4.8 (-84.7 - 75.0)
36+0-6	1/380	1/148	-4.7 (-19.2 - 9.7)	0/123	0/47	INSUFFICIENT DATA	0/219	1/84	-12.7 (-35.4 - 10.0)	1/38	0/17	24.4 (-17.0 - 65.8)
37+0-6	2/231	1/139	3.0 (-15.9 - 22.0)	1/76	0/45	18.2 (-17.1 - 53.5)	1/135	1/82	-8.7 (-32.4 - 15.1)	0/20	0/12	INSUFFICIENT DATA
38+0-6	1/91	0/77	21.1 (-18.1 - 60.2)	0/30	0/25	INSUFFICIENT DATA	1/53	0/47	38.6 (-26.9 - 104.1)	0/8	0/5	INSUFFICIENT DATA

39+0-6	0/14	0/11	INSUFFICIENT DATA	0/5	0/5	INSUFFICIENT DATA	0/6	0/5	INSUFFICIENT DATA	0/3	0/1	INSUFFICIENT DATA
40+0-6	0/3	1/3	INSUFFICIENT DATA	0/0	0/0	INSUFFICIENT DATA	0/1	0/1	INSUFFICIENT DATA	0/2	1/2	INSUFFICIENT DATA
BIRTHWEIGHT ≥P10												
32+0-6	4/1581	0/74	9.7 (-3.5 - 22.9)	1/1052	0/40	13.1 (-5.1 - 31.3)	3/513	0/31	14.4 (-1.7 - 30.6)	INSUFFICIENT DATA		
33+0-6	2/1503	0/108	1.3 (-0.5 - 3.1)	2/1011	0/61	2.0 (-0.8 - 4.7)	0/479	0/44	INSUFFICIENT DATA	INSUFFICIENT DATA		
34+0-6	0/1394	3/159	-18.7 (-38.7 - 1.3)	0/948	2/96	-20.0 (-44.5 - 4.5)	0/436	1/58	-23.0 (-62.0 - 16.0)	INSUFFICIENT DATA		
35+0-6	1/1235	0/253	0.8 (-0.7 - 2.3)	1/852	0/168	1.2 (-1.1 - 3.4)	0/378	0/81	INSUFFICIENT DATA	INSUFFICIENT DATA		
36+0-6	0/981	5/401	**-14.2 (-26.5 - -2.0)**	0/683	4/269	**-16.9 (-33.0 - -0.7)**	0/297	1/132	-8.7 (-24.4 - 7.1)	INSUFFICIENT DATA		
37+0-6	2/580	1/356	1.8 (-7.2 - 10.7)	0/414	1/256	-4.2 (-12.3 - 4.0)	2/165	0/99	17.0 (-6.4 - 40.4)	INSUFFICIENT DATA		
38+0-6	1/222	0/181	8.4 (-8.0 - 24.8)	0/158	0/128	INSUFFICIENT DATA	1/64	0/53	31.6 (-29.4 - 92.6)	INSUFFICIENT DATA		
39+0-6	0/40	0/30	INSUFFICIENT DATA	0/30	0/23	INSUFFICIENT DATA	0/10	0/7	INSUFFICIENT DATA	INSUFFICIENT DATA		
40+0-6	0/10	0/10	INSUFFICIENT DATA	0/7	0/7	INSUFFICIENT DATA	0/3	0/3	INSUFFICIENT DATA	INSUFFICIENT DATA		

*Individual studies risk differences pooled by fixed effect model meta-analysis (see text); † number of women who delivered at least one liveborn twin. Boldface data are statistically significant.