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Systematic Review

Timing of Delivery for Twins With Growth Discordance and Growth Restriction

An Individual Participant Data Meta-analysis

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OBJECTIVE: First, to evaluate the risks of stillbirth and neonatal death by gestational age in twin pregnancies with different levels of growth discordance and in relation to small for gestational age (SGA), and on this basis to establish optimal gestational ages for delivery. Second, to compare these optimal gestational ages with previously established optimal delivery timing for twin pregnancies not complicated by fetal growth restriction, which, in a previous individual patient meta-analysis, was calculated at 37 0/7 weeks of gestation for dichorionic pregnancies and 36 0/7 weeks for monochorionic pregnancies.

DATA SOURCES: A search of MEDLINE, EMBASE, ClinicalTrials.gov, and Ovid between 2015 and 2018 was performed of cohort studies reporting risks of stillbirth and neonatal death in twin pregnancies from 32 to 41 weeks of gestation. 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: We performed an individual participant data meta-analysis 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 birth weight, perinatal risk balanced between 36 0/7–6/7 and 37 0/7–6/7 weeks of gestation in both dichorionic and monochorionic twin pregnancies, with likely higher risk of stillbirth than neonatal death from 37 0/7–6/7 weeks onward.

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

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Twin-specific pregnancy complications and a higher proportion of obstetric complications mean that women with twin pregnancies are more likely to suffer stillbirth compared with those with singleton pregnancies.[1–11] Twins experience more neonatal morbidity and mortality, in part, as a result of prematurity due to spontaneous or iatrogenic preterm delivery.[3,12] The

timing of delivery for twins must balance the risk of stillbirth and neonatal mortality.[13]

In a previous meta-analysis, the optimal timing of delivery for women with dichorionic and monochorionic diamniotic twins without growth restriction was calculated at 37 0/7 and 36 0/7 weeks of gestation, respectively.[14] However, the optimal timing of delivery for twins when the pregnancy is complicated by fetal growth disorders (growth discordance, growth restriction, or both) is still unknown.

We therefore aimed to evaluate whether fetal growth disorders in twin pregnancies should influence delivery timing by performing a systematic review and individual participant data meta-analysis.

SOURCES

We performed a systematic review with an individual participant data meta-analysis in accordance with MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines.[15] 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

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was limited to English-language articles from December 2015 to December 2018, and the results were added to studies previously identified in a separate systematic review that included studies of unselected twins from inception to December 2015.[14]

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 1, available online at http://links.lww.com/AOG/C689).

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, none of which excluded growth restriction or growth discordance. Exclusion criteria were missing data on chorionicity, monoamnionicity, inability to exclude twin–twin transfusion syndrome, congenital anomalies, selective termination, or fewer than 25

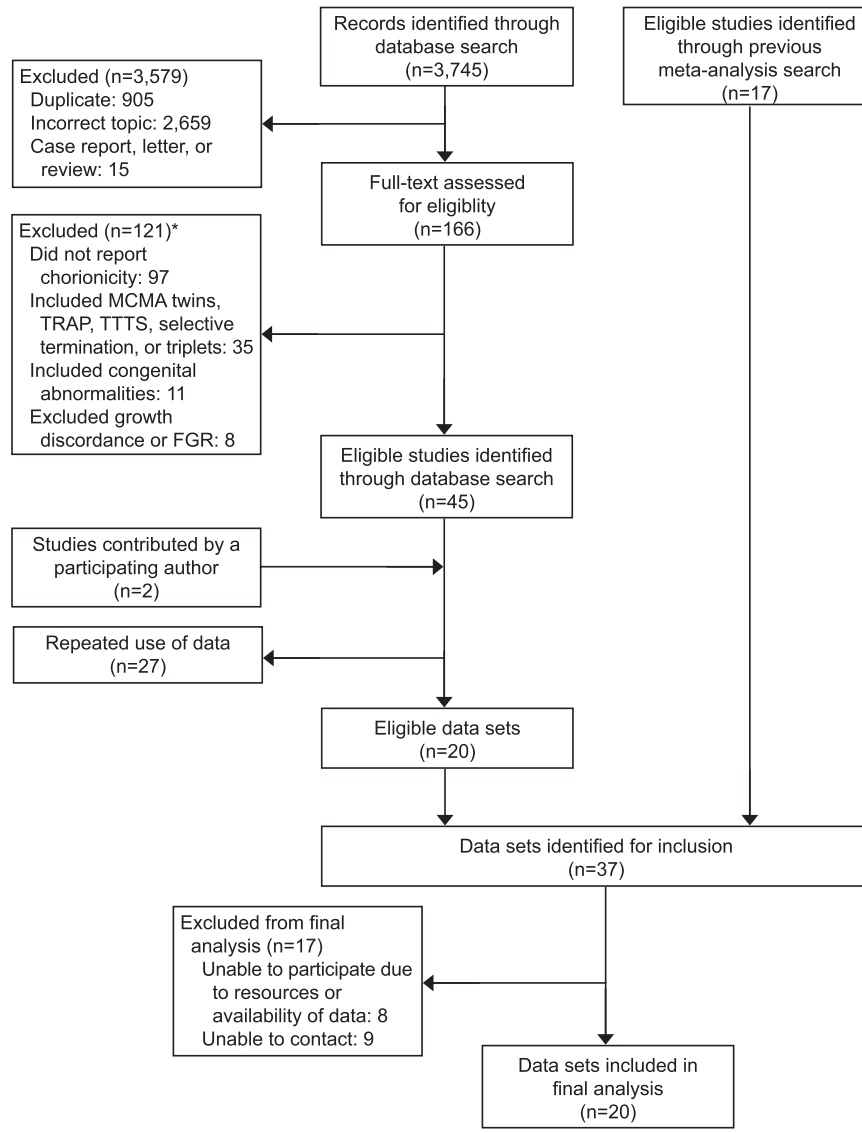

Fig. 1. MOOSE (Meta-analysis of Observational Studies in Epidemiology) flowchart for assessment of studies for eligibility. *Items not mutually exclusive. MCMA, monochorionic–monoamniotic; TRAP, twin reversed arterial perfusion; TTTS, twin–twin transfusion syndrome; FGR, fetal growth restriction.

Koch. Time of Delivery in Twins With Growth Disorders. Obstet Gynecol 2022.

Table 1. Perinatal Death in Weekly Intervals in Dichorionic Twin Pregnancies From 32 Weeks of Gestation

Gestational Age (wk)	All Levels of Growth Discordance: No. of Stillbirths/No. of Ongoing Pregnancies	All Levels of Growth Discordance: No. of Neonatal Deaths/No. of Women Who Delivered*	All Levels of Growth Discordance: Pooled RD† (/1,000 Pregnancies) (95% CI)	Less Than 10% Growth Discordance: No. of Stillbirths/No. of Ongoing Pregnancies	Less Than 10% Growth Discordance: No. of Neonatal Deaths/No. of Women Who Delivered*	Less Than 10% Growth Discordance: Pooled RD† (/1,000 Pregnancies) (95% CI)
All birth weights						
32 0/7–6/7	4/7,474	6/241	**−25.6 (−45.9 to−5.3)**	1/3,832	1/103	−9.8 (−27.6 to 8.1)
33 0/7–6/7	5/7,229	5/354	**−13.5 (−26 to−1.0)**	0/3,728	1/174	−5.9 (−16.8 to 5.0)
34 0/7–6/7	8/6,871	8/695	**−8.9 (−16.6 to−1.2)**	1/3,555	2/312	−6.3 (−15.3 to 2.6)
35 0/7–6/7	3/6,169	10/971	**−9.6 (−15.9 to−3.3)**	0/3,242	3/496	−5.8 (−12.3 to 0.7)
36 0/7–6/7	5/5,196	6/1,362	−3.3 (−6.9 to 0.3)	4/2,746	3/687	−3.1 (−8.4 to 2.3)
37 0/7–6/7	6/3,828	6/1,937	−1.0 (−4.0 to 1.9)	½,054	3/1,027	−2.3 (−5.7 to 1.2)
38 0/7–6/7	7/1,887	3/1,449	3.4 (−2.1 to 8.9)	0/1,026	0/797	Insufficient data
39 0/7–6/7	0/434	2/334	−6.1 (−14.4 to 2.3)	0/227	0/173	Insufficient data
40 0/7–6/7	1/101	0/88	18.1 (−16.9 to 53.1)	0/54	0/47	Insufficient data
Birth weight less than the 10th percentile						
32 0/7–6/7	4/1,814	4/68	**−66.7 (−124.8 to−8.5)**	1/396	1/7	−202.4 (−679.9 to 275.2)
33 0/7–6/7	5/1,742	5/78	**−76.1 (−134.3 to−17.9)**	0/388	1/15	−124.2 (−488.7 to 240.2)
34 0/7–6/7	4/1,660	3/174	−8.7 (−26.3 to 8.9)	0/374	1/30	−35.5 (−167.9 to 97.0)
35 0/7–6/7	2/1,483	6/233	**−24.4 (−44.3 to−4.6)**	0/344	1/35	−27.7 (−66.2 to 10.7)
36 0/7–6/7	1/1,249	4/349	−10.1 (−20.7 to 0.5)	0/309	2/83	−22.4 (−51.6 to 6.8)
37 0/7–6/7	1/899	3/479	−5.1 (−12.7 to 2.4)	0/226	1/116	−7.6 (−20.5 to 5.3)
38 0/7–6/7	3/421	2/332	4.5 (−12.8 to 21.8)	0/110	0/92	Insufficient data
39 0/7–6/7	0/89	0/76	Insufficient data	0/18	0/17	Insufficient data
40 0/7–6/7	0/14	0/14	Insufficient data	0/1	0/1	Insufficient data
Birth weight 10th percentile or higher						
32 0/7–6/7	0/5,654	2/173	−11.8 (−27.6 to 4.0)	0/3,433	0/96	Insufficient data
33 0/7–6/7	0/5,481	0/276	Insufficient data	0/3,337	0/159	Insufficient data
34 0/7–6/7	4/5,205	5/521	**−9.0 (−17.4 to−0.6)**	1/3,178	1/282	−3.3 (−10.2 to 3.7)
35 0/7–6/7	1/4,680	4/738	−5.1 (−10.6 to 0.4)	0/2,895	2/461	−4.5 (−10.7 to 1.6)
36 0/7–6/7	4/3,941	2/1,013	−0.9 (−4.0 to 2.1)	4/2,434	1/604	−0.1 (−4.0 to 3.9)
37 0/7–6/7	5/2,923	3/1,458	0.3 (−2.8 to 3.4)	1/1,825	2/911	−1.4 (−4.7 to 1.8)
38 0/7–6/7	4/1,460	1/1,117	3.5 (−1.7 to 8.7)	2/913	0/705	3.9 (−1.5 to 9.3)
39 0/7–6/7	0/339	2/258	−7.8 (−18.4 to 2.9)	0/206	0/156	Insufficient data
40 0/7–6/7	1/81	0/74	23.5 (−21.7 to 68.7)	0/50	0/46	Insufficient data

Gestational Age (wk)	10–30% Growth Discordance: No. of Stillbirths/ No. of Ongoing Pregnancies	10–30% Growth Discordance: No. of Neonatal Deaths/No. of Women Who Delivered*	10–30% Growth Discordance: Pooled RD† (/1,000 Pregnancies) (95% CI)	Greater Than 30% Growth Discordance: No. of Stillbirths/ No. of Ongoing Pregnancies	Greater Than 30% Growth Discordance: No. of Neonatal Deaths/No. of Women Who Delivered*	Greater Than 30% Growth Discordance: Pooled RD† (/1,000 Pregnancies) (95% CI)
All birth weights						
32 0/7–6/7	0/3,244	5/105	**−52.2 (−92.7 to−11.6)**	3/398	0/33	7.6 (−2.1 to 17.3)
33 0/7–6/7	1/3,139	2/134	−14.1 (−33.3 to 5.1)	4/362	2/46	−29.2 (−91.0 to 32.7)
34 0/7–6/7	2/3,004	4/319	−12.1 (−24.4 to 0.1)	5/312	2/64	8.3 (−32.4 to 49.0)
35 0/7–6/7	1/2,683	5/421	**−11.2 (−21.4 to−1.0)**	2/244	2/54	−27.5 (−72.7 to 17.7)
36 0/7–6/7	1/2,261	2/607	−2.6 (−7.1 to 1.9)	0/189	1/68	−9.8 (−27.7 to 8.2)
37 0/7–6/7	5/1,653	2/835	1.5 (−3.3 to 6.4)	0/121	1/75	−12.4 (−36.0 to 11.2)
38 0/7–6/7	2/814	2/616	0.2 (−7.9 to 8.4)	3/47	1/36	77.9 (−42.0 to 197.8)

(*continued*)

Table 1. Perinatal Death in Weekly Intervals in Dichorionic Twin Pregnancies From 32 Weeks of Gestation (*continued*)

	10–30% Growth Discordance			Greater Than 30% Growth Discordance		
Gestational Age (wk)	No. of Stillbirths/ No. of Ongoing Pregnancies	No. of Neonatal Deaths/No. of Women Who Delivered*	Pooled RD† (/1,000 Pregnancies) (95% CI)	No. of Stillbirths/ No. of Ongoing Pregnancies	No. of Neonatal Deaths/No. of Women Who Delivered*	Pooled RD† (/1,000 Pregnancies) (95% CI)
39 0/7–6/7	0/196	2/152	−14.2 (−33.3 to 4.9)	0/11	0/9	Insufficient data
40 0/7–6/7	0/44	0/38	Insufficient data	0/3	0/3	Insufficient data
Birth weight less than the 10th percentile						
32 0/7–6/7	0/1,062	3/34	**−113.3 (−186.5 to−40.1)**	3/356	0/27	9.7 (−2.5 to 21.9)
33 0/7–6/7	1/1,028	2/27	−80.1 (−163.3 to 3.1)	4/326	2/36	−41.8 (−119.6 to 35.9)
34 0/7–6/7	0/1,000	1/86	−12.7 (−36.7 to 11.4)	4/286	1/58	26.0 (−2.4 to 54.4)
35 0/7–6/7	0/914	3/145	−20.2 (−42.4 to 2.0)	2/225	2/53	−26.9 (−72.6 to 18.9)
36 0/7–6/7	1/769	1/200	−3.7 (−13.4 to 6.1)	0/171	1/66	−10.4 (−29.3 to 8.6)
37 0/7–6/7	1/568	1/298	−1.5 (−8.9 to 5.9)	0/105	1/65	−14.8 (−42.8 to 13.2)
38 0/7–6/7	0/270	1/208	−5.0 (−14.3 to 4.4)	3/41	1/32	87.3 (−34.4 to 209.0)
39 0/7–6/7	0/62	0/52	Insufficient data	0/9	0/7	Insufficient data
40 0/7–6/7	0/9	0/10	Insufficient data	0/3	0/3	Insufficient data
Birth weight 10th percentile or higher						
32 0/7–6/7	0/2,179	2/71	−28.7 (−65.4 to 8.1)	Insufficient data		
33 0/7–6/7	0/2,108	0/107	Insufficient data	Insufficient data		
34 0/7–6/7	2/2,001	3/233	−11.8 (−26.1 to 2.5)	Insufficient data		
35 0/7–6/7	1/1,766	2/276	−6.3 (−16.4 to 3.8)	Insufficient data		
36 0/7–6/7	0/1,489	1/407	−2.4 (−7.1 to 2.3)	Insufficient data		
37 0/7–6/7	4/1,082	1/537	3.3 (−3.1 to 9.7)	Insufficient data		
38 0/7–6/7	2/541	1/408	3.2 (−7.9 to 14.2)	Insufficient data		
39 0/7–6/7	0/131	2/100	−23.4 (−53.9 to 7.0)	Insufficient data		
40 0/7–6/7	1/31	0/28	64.3 (−58.5 to 187.1)	Insufficient data		

RD, risk difference.
Bold indicates statistical significance.
* Number of women who delivered at least one liveborn twin.
† Individual studies' RDs pooled by fixed effect model meta-analysis (see text).

participants. *Small for gestational age* (SGA) was defined as birth weight less than the 10th percentile for gestation using twin-specific growth charts.[16] *Stillbirth* was defined as the death of the fetus before birth; *perinatal loss* included stillbirth and neonatal death within the first 7 days. Birth weight discordance was calculated as 100×(larger birth weight−smaller birth weight)/larger birth weight.

A two-step approach was used for study selection.[17] First, the abstracts and titles of citations were assessed for eligibility followed by a 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[14] were added to the updated search if they met the inclusion criteria.

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 they could 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 before delivery, occurrence of stillbirth, onset of labor, indication for delivery, mode of delivery, gestational age at delivery, birth weight, neonatal

death, and neonatal morbidity (including necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity, respiratory distress syndrome [RDS], meningitis, and septicemia). Additional efforts were made to contact the original authors to obtain data about gestational age at fetal death (if applicable) wherever possible. Agreement approval to use the data was given by the authors of each included study. The data were deidentified and protected by a password that was accessible only to certain investigators.

Quality assessment was performed using the Newcastle-Ottawa Scale for assessing the quality of cohort studies in meta-analyses[18] to estimate the risk of bias of each individual study. The Newcastle-Ottawa Scale assesses studies on three domains: selection, comparability, and outcome. The maximum score is 9 points.

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

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 (from 32 weeks through 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 less than 0 indicates that the risk of neonatal death outweighs that of stillbirth if delivery occurs, and, thus, expectant management is preferred. A positive risk difference indicates the opposite. 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 necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity, 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, birth weight (less than the 10th percentile and 10th percentile or higher) and growth discordance (less than 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.[14] 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 death was used to calculate prospective stillbirth risks and estimate birth weight percentile. For the risk of neonatal death and composite neonatal morbidity, the number of neonatal deaths or composite outcomes was divided by the number of liveborn neonates 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 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 0 events were expected.[19] For the composite neonatal morbidity outcome, because we expected heterogeneity of absolute risks between studies, we used a logistic-normal random-effects model for the estimation.[20] In the event of nonconvergence, we used a random-effects model with inverse-variance weights and exact CIs.

Sensitivity analyses were performed using a moving average for growth discordance (0–10%, 0–20%, 10–30%, 20–40%, and 30–50%) in both dichorionic and monochorionic twin pregnancies. A post hoc sensitivity analysis that included only cohorts entirely after 2004 was performed in all twins to assess the effect of improved neonatal care over time. The analyses were performed using IBM SPSS Statistics 26 and Stata 17.0.

RESULTS

From the 3,762 articles identified through the search strategy and our previous meta-analysis, we included 20 unique studies on 9,755 women with 7,474 dichorionic (from 17 studies) and 2,281 monochorionic twin gestations (from 13 studies) in our current analysis (Fig. 1) (Soliman et al. Am J Obstet Gynecol 2015;212:S261–2.).[6–11,21–37]

Of the 17 studies on dichorionic twins, 15 provided data on stillbirth and neonatal mortality and two provided data on neonatal mortality only. For monochorionic twins, 12 studies provided data on stillbirth and neonatal mortality and one provided data on neonatal mortality only. In 1,814

(24.3%) of the dichorionic twins and 699 (30.6%) of the monochorionic twins, one or both neonates were SGA; in 1,327 (17.7%) dichorionic twins and 458 (20.0%) monochorionic twins, birth weight discordance was greater than 20%. There were no cases of major congenital anomalies in all twins or twin–twin transfusion syndrome in monochorionic twins. The mean gestational age at delivery was 36.6 (SD 1.7) for dichorionic and 36.0 (SD 1.8) for monochorionic twin pregnancies. Additional characteristics of the population and study characteristics are provided in Appendix 2, available online at http://links.lww.com/AOG/C689. The number of deliveries per gestational week is displayed in Appendix 3, available online at http://links.lww.com/AOG/C689.

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 (Appendix 4, available online at http://links.lww.com/AOG/C689). Most studies used consecutive or random sampling methods (18/20) and achieved adequate follow-up (greater than 80%). Twenty studies had a low risk of bias for determining assessment of gestational age at delivery and chorionicity (Appendix 5, available online at http://links.lww.com/AOG/C689).

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 per 1,000 (95% CI 0.6/1,000–2.4/1,000) at 34 0/7–6/7 weeks of gestation to 6.0 per 1,000 (95% CI 2.9/1,000–12.4/1,000) at 38 0/7–6/7 weeks, whereas the risk of neonatal death decreased from 11.5 per 1,000 (95% CI 5.8/1,000–22.5/1,000) at 34 0/7–6/7 weeks of gestation to 2.1 per 1,000 (95% CI 0.7/1,000–6.1/1,000) at 39 0/7–6/7 weeks (Appendix 6, available online at http://links.lww.com/AOG/C689). Perinatal risks are likely balanced between 36 0/7–6/7 and 37 0/7–6/7 weeks of gestation (Table 1 and Fig. 2).

In dichorionic pregnancies in which one or both twins were SGA (n=1,814), the absolute risk of stillbirth increased from 2.5 per 1,000 (95% CI 1.0/1,000–6.5/1,000) to 11.8 per 1,000 (4.0/1,000–34.0/1,000) from 34 0/7–6/7 to 38 0/7–6/7 weeks of gestation, whereas the risk of neonatal mortality decreased from 17.2 per 1,000 (95% CI 5.9/1,000–49.5/1,000) to 6.0 per 1,000 (95% CI 1.7/1,000–21.7/1,000) (Appendix 6, http://links.lww.com/AOG/C689). The perinatal risk was likely balanced at 37 0/7–6/7 weeks of gestation (risk difference −5.1/1,000, 95% CI −12.7/1,000–2.4/1,000; I^2 0%, 95% CI 0–46%). From 38 0/7–6/7 weeks of gestation, the stillbirth risk was statistically comparable with the neonatal mortality risk (risk difference 4.5/1,000, 95% CI −12.8 to 21.8; I^2=0%, 95% CI 0–47%). Similar findings with balanced perinatal risks at 37 0/7–6/7 weeks of gestation were seen among twins with different levels of growth discordance (Table 1 and Fig. 2).

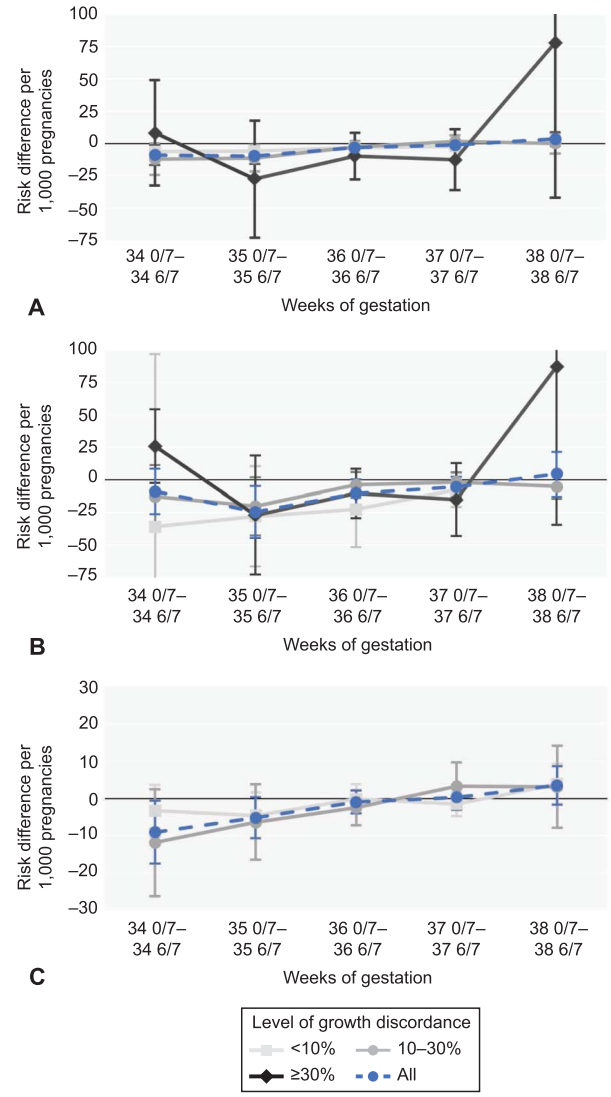

Fig. 2. Prospective risk of stillbirth from expectant management vs risk of neonatal mortality from delivery at weekly intervals from 34 weeks of gestation in dichorionic twin pregnancies, by birth weight centile and level of growth discordance. Statistically significant results are shown in bold in Table 1. All neonates (**A**), small-for-gestational age neonates (birth weight less than the 10th percentile) (**B**), and appropriate-for-gestational age neonates (birth weight at the 10th percentile or greater) (**C**).

Koch. Time of Delivery in Twins With Growth Disorders. Obstet Gynecol 2022.

Table 2. Perinatal Death in Weekly Intervals in Monochorionic Twin Pregnancies From 32 Weeks of Gestation

Gestational Age (weeks)	All Levels of Growth Discordance			Less Than 10% Growth Discordance		
	No. of Stillbirths/ No. of Ongoing Pregnancies	No. of Neonatal Deaths/No. of Women Who Delivered*	Pooled RD† (/1,000 Pregnancies) (95% CI)	No. of Stillbirths/ No. of Ongoing Pregnancies	No. of Neonatal Deaths/No. of Women Who Delivered*	Pooled RD† (/1,000 Pregnancies) (95% CI)
All birth weights						
32 0/7–6/7	4/2,281	4/144	−22.9 (−46.9 to 1.1)	1/1,215	0/43	12.2 (−4.7 to 29.1)
33 0/7–6/7	2/2,133	1/169	−4.7 (−14.0 to 5.3)	2/1,171	0/66	1.6 (−0.6 to 3.9)
34 0/7–6/7	3/1,963	4/252	−11.0 (−25.8 to 3.8)	0/1,103	2/109	−17.7 (−39.7 to 4.2)
35 0/7–6/7	2/1,708	1/344	−1.2 (−7.0 to 4.5)	1/994	0/187	1.0 (−0.9 to 2.9)
36 0/7–6/7	1/1,362	6/549	**−11.6 (−21.6 to−1.7)**	0/806	4/316	**−14.5 (−28.3 to−0.6)**
37 0/7–6/7	4/812	2/495	2.5 (−5.9 to 11.0)	1/490	1/301	−0.7 (−9.6 to 8.2)
38 0/7–6/7	2/314	0/258	11.0 (−4.0 to 26.0)	0/188	0/153	Insufficient data
39 0/7–6/7	0/55	0/41	Insufficient data	0/35	0/28	Insufficient data
40 0/7–6/7	0/12	1/13	Insufficient data	0/7	0/7	Insufficient data
Birth weight less than the 10th percentile						
32 0/7–6/7	0/699	4/70	**−60.7 (−112.1 to−9.3)**	0/163	0/3	Insufficient data
33 0/7–6/7	0/629	1/61	−15.8 (−45.2 to 13.6)	0/160	0/5	Insufficient data
34 0/7–6/7	3/568	1/93	4.5 (−15.0 to 24.0)	0/155	0/13	Insufficient data
35 0/7–6/7	1/472	1/91	−4.9 (−25.5 to 15.7)	0/142	0/19	Insufficient data
36 0/7–6/7	1/380	1/148	−4.7 (−19.2 to 9.7)	0/123	0/47	Insufficient data
37 0/7–6/7	2/231	1/139	3.0 (−15.9 to 22.0)	1/76	0/45	18.2 (−17.1 to 53.5)
38 0/7–6/7	1/91	0/77	21.1 (−18.1 to 60.2)	0/30	0/25	Insufficient data
39 0/7–6/7	0/14	0/11	Insufficient data	0/5	0/5	Insufficient data
40 0/7–6/7	0/3	1/3	Insufficient data	0/0	0/0	Insufficient data
Birth weight 10th percentile or higher						
32 0/7–6/7	4/1,581	0/74	9.7 (−3.5 to 22.9)	1/1,052	0/40	13.1 (−5.1 to 31.3)
33 0/7–6/7	2/1,503	0/108	1.3 (−0.5 to 3.1)	2/1,011	0/61	2.0 (−0.8 to 4.7)
34 0/7–6/7	0/1,394	3/159	−18.7 (−38.7 to 1.3)	0/948	2/96	−20.0 (−44.5 to 4.5)
35 0/7–6/7	1/1,235	0/253	0.8 (−0.7 to 2.3)	1/852	0/168	1.2 (−1.1 to 3.4)
36 0/7–6/7	0/981	5/401	**−14.2 (−26.5 to−2.0)**	0/683	4/269	**−16.9 (−33.0 to−0.7)**
37 0/7–6/7	2/580	1/356	1.8 (−7.2 to 10.7)	0/414	1/256	−4.2 (−12.3 to 4.0)
38 0/7–6/7	1/222	0/181	8.4 (−8.0 to 24.8)	0/158	0/128	Insufficient data
39 0/7–6/7	0/40	0/30	Insufficient data	0/30	0/23	Insufficient data
40 0/7–6/7	0/10	0/10	Insufficient data	0/7	0/7	Insufficient data

Gestational Age (weeks)	10–30% Growth Discordance			Greater Than 30% Growth Discordance		
	No. of Stillbirths/ No. of Ongoing Pregnancies	No. of Neonatal Deaths/No. of Women Who Delivered*	Pooled RD† (/1,000 Pregnancies) (95% CI)	No. of Stillbirths/ No. of Ongoing Pregnancies	No. of Neonatal Deaths/No. of Women Who Delivered*	Pooled RD† (/1,000 Pregnancies) (95% CI)
All birth weights						
32 0/7–6/7	3/877	3/57	−43.9 (−93 to 5.2)	0/189	1/44	−27.3 (−70.9 to 16.4)
33 0/7–6/7	0/817	0/69	Insufficient data	0/145	1/34	−33.2 (−92.5 to 26.2)
34 0/7–6/7	2/749	1/103	−3.8 (−26.1 to 18.6)	1/111	1/40	−8.1 (−54.7 to 38.4)
35 0/7–6/7	0/644	0/127	Insufficient data	1/70	1/30	−4.3 (−75.1 to 66.5)
36 0/7–6/7	0/517	2/216	−10.1 (−22.9 to 2.8)	1/39	0/17	20.2 (−15.2 to 55.7)
37 0/7–6/7	3/301	1/181	6.3 (−11 to 23.5)	0/21	0/13	Insufficient data
38 0/7–6/7	2/118	0/100	31.9 (−10.1 to 73.9)	0/8	0/5	Insufficient data
39 0/7–6/7	0/17	0/12	Insufficient data	0/3	0/1	Insufficient data

(*continued*)

Table 2. Perinatal Death in Weekly Intervals in Monochorionic Twin Pregnancies From 32 Weeks of Gestation (*continued*)

	10–30% Growth Discordance			Greater Than 30% Growth Discordance		
Gestational Age (weeks)	No. of Stillbirths/ No. of Ongoing Pregnancies	No. of Neonatal Deaths/No. of Women Who Delivered*	Pooled RD† (/1,000 Pregnancies) (95% CI)	No. of Stillbirths/ No. of Ongoing Pregnancies	No. of Neonatal Deaths/No. of Women Who Delivered*	Pooled RD† (/1,000 Pregnancies) (95% CI)
40 0/7–6/7	0/5	0/4	Insufficient data	0/2	1/2	Insufficient data
Birth weight less than the 10th percentile						
32 0/7–6/7	0/363	3/26	**−121.9 (−238.0 to −5.9)**	0/173	1/41	−30.1 (−78.3 to 18.1)
33 0/7–6/7	0/337	0/25	Insufficient data	0/132	1/31	−36.4 (−101.6 to 28.8)
34 0/7–6/7	2/312	0/45	17.2 (−5.6 to 40.0)	1/101	1/35	−9.1 (−61.5 to 43.2)
35 0/7–6/7	0/265	0/46	Insufficient data	1/65	1/26	−4.8 (−84.7 to 75.0)
36 0/7–6/7	0/219	1/84	−12.7 (−35.4 to 10.0)	1/38	0/17	24.4 (−17.0 to 65.8)
37 0/7–6/7	1/135	1/82	−8.7 (−32.4 to 15.1)	0/20	0/12	Insufficient data
38 0/7–6/7	1/53	0/47	38.6 (−26.9 to 104.1)	0/8	0/5	Insufficient data
39 0/7–6/7	0/6	0/5	Insufficient data	0/3	0/1	Insufficient data
40 0/7–6/7	0/1	0/1	Insufficient data	0/2	1/2	Insufficient data
Birth weight 10th percentile or higher						
32 0/7–6/7	3/513	0/31	14.4 (−1.7 to 30.6)	Insufficient data		
33 0/7–6/7	0/479	0/44	Insufficient data	Insufficient data		
34 0/7–6/7	0/436	1/58	−23.0 (−62.0 to 16.0)	Insufficient data		
35 0/7–6/7	0/378	0/81	Insufficient data	Insufficient data		
36 0/7–6/7	0/297	1/132	−8.7 (−24.4 to 7.1)	Insufficient data		
37 0/7–6/7	2/165	0/99	17.0 (−6.4 to 40.4)	Insufficient data		
38 0/7–6/7	1/64	0/53	31.6 (−29.4 to 92.6)	Insufficient data		
39 0/7–6/7	0/10	0/7	Insufficient data	Insufficient data		
40 0/7–6/7	0/3	0/3	Insufficient data	Insufficient data		

RD, risk difference.
Bold indicates statistical significance.
* Number of women who delivered at least one liveborn twin.
† Individual studies' RDs pooled by fixed effect model meta-analysis (see text).

In dichorionic pregnancies in which both twins had birth weights appropriate for gestational age (birth weights in the 10th percentile or higher; n=5,654), the absolute risk of stillbirth ranged from 0.8 per 1,000 (95% CI 0.3/1,000–2.1/1,000) to 4.4 per 1,000 (1.7/1,000–11.4/1,000) between 34 0/7–6/7 and 38 0/7–6/7 weeks of gestation. The risk of neonatal mortality was highest at 34 0/7–6/7 weeks of gestation (9.6/1,000, 95% CI 4.1/1,000–22.3/1,000) and lowest at 38 0/7–6/7 weeks (0.9/1,000, 95% CI 0.2/1,000–5.1/1,000) (Appendix 6, http://links.lww.com/AOG/C689). The perinatal risk was balanced between 36 0/7–6/7 weeks of gestation (risk difference −0.9/1,000, 95% CI −4.0/1,000 to 2.1/1,000; I^2=0%, 95% CI 0–45%) and 37 0/7–6/7 weeks (risk difference 0.3/1,000, 95% CI −2.8/1,000–3.4/1,000; I^2=0%, 95% CI 0–45%). From 38 0/7–6/7 weeks of gestation, the stillbirth risk seems to outweigh the neonatal mortality risk (risk difference 3.5/1,000, 95% CI −1.7 to 8.7; I^2=0%, 95% CI 0–46%), though results were not statistically significant. Similar findings with balanced perinatal risks between 36 0/7–6/7 and 37 0/7–6/7 weeks of gestation were seen among twins with less than 10% (n=3,433) and 10–30% growth discordance (n=2,179; Table 1 and Fig. 2).

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 per 1,000 (95% CI 0.6/1,000–4.8/1,000) at 34 0/7–6/7 weeks of gestation and 7.1 per 1,000 (95% CI 2.8/1,000–18.1/1,000) at 37 0/7–6/7 weeks. The risk of

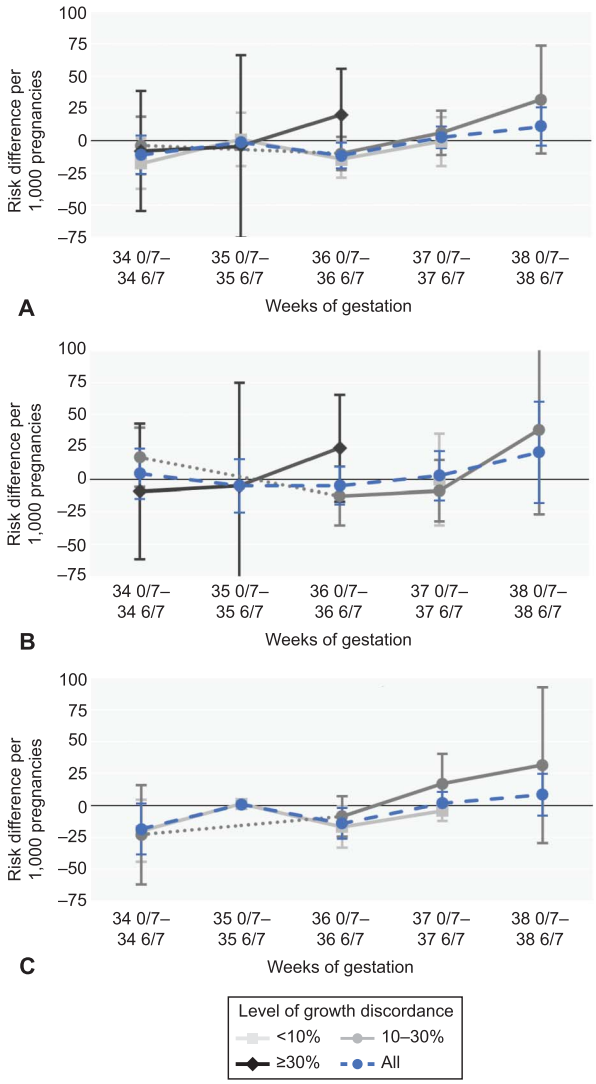

Fig. 3. Prospective risk of stillbirth from expectant management vs risk of neonatal mortality from delivery at weekly intervals from 34 weeks of gestation in monochorionic twin pregnancies, by birth weight centile and level of growth discordance. Statistically significant results are shown in bold in Table 2. All neonates (**A**), small-for-gestational age neonates (birth weight less than the 10th percentile) (**B**), and appropriate-for-gestational age neonates (birth weight at the 10th percentile or greater) (**C**).

Koch. Time of Delivery in Twins With Growth Disorders. Obstet Gynecol 2022.

neonatal death decreased from 15.9 per 1,000 (95% CI 6.2/1,000–40.1/1,000) at 34 0/7–6/7 weeks of gestation to 4.0/1,000 (95% CI 1.1/1,000–14.6/1,000) at 37 0/7–6/7 weeks (Appendix 7, available online at http://links.lww.com/AOG/C689). Perinatal risks are likely balanced between 36 0/7–6/7 and 37 0/7–6/7 weeks of gestation (Table 2 and Fig. 3).

In monochorionic pregnancies in which one or both twins were SGA (n=699), the absolute risk of stillbirth increased from 5.8 per 1,000 (95% CI 2.0/1,000–16.8/1,000) to 12.4 per 1,000 (3.4/1,000–44.2/1,000) from 34 0/7–6/7 to 37 0/7–6/7 weeks of gestation, whereas the risk of neonatal mortality decreased from 10.8 per 1,000 (95% CI 1.9/1,000–58.4/1,000) to 7.2 per 1,000 (95% CI 1.3/1,000–39.6/1,000) (Appendix 7, http://links.lww.com/AOG/C689). The perinatal risk was balanced between 36 0/7–6/7 weeks of gestation (risk difference −4.7/1,000, 95% CI −19.2/1,000 to 9.7/1,000; I^2=0%, 95% CI 0–49%) and 37 0/7–6/7 weeks (risk difference 3.0/1,000, 95% CI −15.9/1,000 to 22.0/1,000; I^2=0%, 95% CI 0–50%). From 38 0/7–6/7 weeks of gestation, the stillbirth risk was statistically comparable with the neonatal mortality risk (risk difference 21.1/1,000, 95% CI −18.1 to 60.2; I^2=0%, 95% CI 0–56%). In SGA twins with 10–30% growth discordance (n=363), a similar finding was observed, with balanced perinatal risks between 36 0/7–6/7 and 37 0/7–6/7 weeks of gestation (Table 2 and Fig. 3). For SGA twins with more than 30% growth discordance (n=173), stillbirth risk seemed to outweigh neonatal mortality risk at 36 0/7–6/7 weeks of gestation (risk difference 24.4/1,000, 95% CI −17.0 to 65.8; I^2=0%, 95% CI 0–58%), although this was not statistically significant; after 36 0/7–6/7 weeks, data were insufficient to estimate perinatal risks.

In monochorionic pregnancies in which both twins were appropriate for gestational age (birth weights of 10th percentile or higher; n=1,581), the prospective risk of stillbirth was 1.4 per 1,000 (95% CI 0.4/1,000–5.0/1,000) at 33 0/7–6/7 weeks of gestation and 5.0 per 1,000 (95% CI 1.4/1,000–18.0/1,000) at 37 0/7–6/7 weeks. The risk of neonatal death decreased from 18.9 per 1,000 (95% CI 6.4/1,000–54.0/1,000) at 34 0/7–6/7 weeks of gestation to 2.8 per 1,000 (95% CI 0.5/1,000–15.7/1,000) at 37 0/7–6/7 weeks (Appendix 7, http://links.lww.com/AOG/C689). The perinatal risk was balanced between 36 0/7–6/7 weeks of gestation (risk difference −14.2/1,000, 95% CI −26.5/1,000 to −2.0/1,000; I^2=0%, 95% CI 0–49%) and 37 0/7–6/7 weeks (risk difference 1.8/1,000, 95% CI −7.2/1,000 to 10.7/1,000; I^2=0%, 95% CI 0–50%). From 38 0/7–6/7 weeks of gestation, the stillbirth risk was statistically comparable with the neonatal mortality risk (risk difference 8.4/1,000, 95% CI −8.0 to 24.8; I^2=0%, 95% CI 0–54%). Similar findings with balanced perinatal risks between 36 0/7–6/7 and 37 0/7–6/7 weeks of gestation were seen among twins with less than 10% (n=1,052) and 10–30% growth discordance (n=513; Fig. 3).

Sensitivity analyses in both dichorionic and monochorionic twin pregnancies that used a moving average for growth discordance showed similar results as described above (Appendix 8, available online at http://links.lww.com/AOG/C689). Including only cohorts entirely after 2004 resulted in similar findings as the main analysis (Appendix 9, available online at http://links.lww.com/AOG/C689).

The risk of a neonatal morbidity outcome in one or both twins decreased consistently with advancing gestational age up to 39 0/7–6/7 weeks of gestation in dichorionic twin pregnancies and 37 0/7–6/7 weeks in monochorionic twin pregnancies, after which no adverse events occurred. However, there were insufficient data after 37 0/7–6/7 weeks of gestation for meaningful interpretation. Findings were similar in different levels of growth restriction and growth discordance (Appendices 10 and 11, available online at http://links.lww.com/AOG/C689).

DISCUSSION

In this study of twin pregnancies, we have demonstrated that although growth discordance and SGA were associated with higher stillbirth and neonatal mortality risks, they largely did not influence the optimal timing of birth. Perinatal risk balanced between 36 0/7–6/7 and 37 0/7–6/7 weeks of gestation in both dichorionic and monochorionic twin pregnancies and for different level of growth discordance and birth weight, which is largely in line with previous meta-analyses of twin pregnancies not complicated by growth disorders.[14,36] As expected, the risk of adverse neonatal morbidity outcome decreased consistently with advancing gestational age.[6,10]

This individual participant data meta-analysis allowed us to analyze different subgroups based on chorionicity, growth discordance and birth weight, 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 effect that delivery has on neonatal mortality. Wherever possible the gestational age at death was used for calculation of stillbirth rates and birth weight percentile. Levels of growth discordance and birth weight percentile were calculated from gestational age and birth weight, avoiding inter-study variability in calculations and cutoffs 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 policies of planned delivery beyond 37 and 38 weeks of gestation in most studies. Another limitation is that many of the included studies did not report on factors that indicated pathology, such as umbilical artery Doppler measurements and placental pathology that indicated placental insufficiency. Consequently, we were not able to distinguish those constitutionally small from those with actual growth disorders.[38] 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, because preterm cesarean delivery is associated with increased risk of RDS compared with vaginal delivery.[30,39] 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 cases of single intrauterine fetal death, clinical management varies largely, creating substantial variation in the time between fetal death 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,[38] and could lead 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 two thirds of the stillbirths.

The analysis of the collated data sets was based on the use of birth weight; however, the decision to deliver, in practice, is based on estimated fetal weight from ultrasonography. The percentage of birth weight predictions from ultrasonography for twins within 10% and 15% accuracy is 49.7% and 68.5%, respectively; the accuracy declines for twin fetuses less than 2,000 g and at lower gestational ages.[40] Twin birth weight charts were used; they are known to have better predictive value for perinatal mortality[41] but use a higher cutoff for defining SGA compared with singleton growth charts. Using

singleton growth charts would classify a greater proportion of twins with SGA, compared with using twin-specific charts.[11,42]

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 counseling for parents about the prospective outcome of expectant management compared with delivery. We acknowledge that the best evidence to determine the optimal timing should be sourced from randomized trials and observational studies may be subject to confounding. Interventions including antenatal fetal testing and Doppler measurements may affect the timing of delivery in practice. However, given the low rate of perinatal death, performing such a trial would be incredibly challenging even if using an adaptive design and composite outcomes. Our study provides the best available evidence in the absence of such trials.

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.

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