Weight discordance and perinatal mortality in monoamniotic twin pregnancies: analysis of the MONOMONO, NorSTAMP and STORK multiple pregnancy cohorts

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Key words: multiple gestation, twin pregnancy, health care, perinatal death, cord accident, cesarean delivery, cord entanglement, respiratory distress syndrome, monochorionic, chorionicity

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.20357

CONTRIBUTION

A **What does this study add to what is already known?** The risk of IUD in MCMA twin pregnancies increased significantly ($p<0.05$) from an odds ratio (OR) 2.4 (95% CI 1.1 to 5.6) for a ≥20% discordance to an OR of 4.4 (95% CI 1.3 to 14.4) for a ≥30% discordance.

B **What are the clinical implications of this work?** MCMA twin pregnancies with weight discordances ≥20% are at increased risk of fetal demise, signaling a need for increased levels of monitoring. The current data does not demonstrate an advantage for inpatient over outpatient management in these cases.

ABSTRACT

Objectives: To explore the risk of perinatal mortality in monochorionic monoamniotic (MCMA) twin pregnancies complicated by inter-twin birthweight (BW) discordance.

Methods. This analysis includes data on 242 MCMA twin pregnancies (484 fetuses) from three major research collaboratives on twin pregnancies (MONOMONO, STORK and NorSTAMP). The primary aim was to quantify the risk of intrauterine (IUD), neonatal (NND) and perinatal (PND) death comparing weight discordance at birth from ≥ 10% up to ≥30%. The secondary objectives were to investigate the role of fetal monitoring (inpatient vs outpatient) in modifying the risk of mortality in weight discordant pregnancies, and to explore the diagnostic accuracy of BW in predicting mortality. Logistic regression and AUC analyses were used to analyze the data.

Results. The risk of IUD in MCMA twin pregnancies increased significantly from an OR=2.4 (95% CI 1.1 to 5.6, p=0.050) for a ≥20% discordance to an OR=4.4 (95% CI 1.3 to 14.4, p=0.001) for a ≥30% discordance compared to lower cut-off groups. This association remained significant on logistic regression analysis. However, weight discordance had a low predictive accuracy for mortality with an AUC of 0.60 (95% CI 0.46 to 0.73), 0.52 (95% CI 0.33 to 0.724) and 0.57 (95% CI 0.45 to 0.68) for IUD, NND and PND, respectively. There was no difference in the risk of overall IUD, single IUD, double IUD, NND and PND between pregnancies managed as inpatient compared to outpatient for all levels of discordance.

Conclusion: MCMA twin pregnancies with birthweight discordances ≥20% are at increased risk of fetal demise, signaling a need for increased levels of monitoring. Despite this, its predictive accuracy for mortality is low, thus detection of BW alone should not trigger intervention (eg: iatrogenic delivery). Finally, the current data does not demonstrate an advantage for inpatient over outpatient management in these cases.

INTRODUCTION

Monoamniotic twinning is a rare event, and occurs in about 1% of all monozygotic twin gestations.[1,2] Monochorionic monoamniotic (MCMA) twin pregnancies are at increased risk of perinatal mortality and morbidity compared to monochorionic diamniotic and dichorionic twin pregnancies, especially as the consequence of preterm birth, fetal anomalies and acute transfusion events.[2,3] These risks have been associated with a loss rate as high as 70% in the older literature.[3-7] Recently, several multinational studies showed a substantially improved perinatal survival with mortality rates ranging from 10% to 30%,[8-11] although the optimal type of monitoring is still to be defined.[7]

There is no randomized trial comparing the type of prenatal monitoring in MCMA twin gestations. Published studies differ significantly in the type and frequency of fetal monitoring. A recent retrospective multicenter study published by a large research collaborative reported that the incidence of perinatal mortality and morbidity was lower in monoamniotic twin pregnancies managed mainly as in- compared to outpatient.[8] However, there was a large heterogeneity in the timing of initiation of the outpatient surveillance and intensity of outpatient surveillance among the participating centers, thus potentially affecting the robustness of the results.

The fetal and perinatal death in MCMA twin pregnancies seems to be related mainly to complications unique to MCMA placentas, such as acute twin to twin transfusion syndrome (TTTS), twin reversed arterial perfusion sequence (TRAP) sequence, cord entanglement, conjoined twins and other major congenital anomalies,[1,2] while factors associated with poor prognosis in non-anomalous MCMA twins are still a subject of debate.

Birthweight discordance is one of the major determinants of perinatal mortality and morbidity in dichorionic and monochorionic twin pregnancies. Although it may represent a normal physiological variation, high degrees of discrepancy in fetal growth have been associated with poor perinatal outcome.[12] In view of this association, clinicians commonly report the degree of estimated weight discordance detected on ultrasound.

In a recent systematic review, we have reported that both dichorionic and monochorionic twin pregnancies discordant for fetal growth are at higher risk of intrauterine death, especially as a result of growth restriction.[13] Besides mortality, BW discordance has also been associated with an increased risk of neonatal morbidity such as respiratory distress syndrome, sepsis, intra-ventricular hemorrhage and admission to neonatal intensive care unit.[12] However, the association between weight discordance and perinatal mortality in MCMA twin pregnancies is yet to be elucidated.

The primary objective of this study was to quantify the risk of perinatal mortality in non-anomalous MCMA twin pregnancies affected by weight discordance at birth. The secondary objectives were to

investigate the role of fetal monitoring (inpatient vs outpatient) in modifying the risk of mortality in weight discordant MCMA twin pregnancies, and to explore the predictive accuracy of weight discordance for perinatal mortality.

MATERIALS and METHODS

Study design and participants

This analysis included data from three major multicentre research collaboratives on twin pregnancies (MONOMONO, STORK and NorSTAMP) from four different countries, including United Kingdom, Italy, Spain, and United Stated.[8,10,11] Details for inclusion and exclusion criteria, and type of management, including antepartum management and timing of delivery, in the collaborative centers have been reported previously.[8-11] Briefly, only non-anomalous MCMA twin pregnancies with a prenatal diagnosis of monoamnionicity were considered suitable for the inclusion in the present study. Pregnancies affected by chromosomal or structural anomalies, those with a post-natal diagnosis of monoamnionicity and those undergoing in utero treatment (either cord occlusion or laser coagulation of placental anastomoses) were excluded.

Outcomes

The primary outcome was the risk of intrauterine (IUD), neonatal (NND – death of a live birth within 0-27 days of life) and perinatal (PND – fetal death from ≥24 weeks of gestation? and NND) death according to different cut-offs of birthweight (BW) discordance (≥10%, ≥15%, ≥20%, ≥25% and ≥30) compared to the reference group of <10%. BW discordance was defined as the percentage of discrepancy in birthweight between the larger and the smaller twin and calculated using the following equation: BW discordance (%) = (larger twin BW – smaller twin BW)/ larger twin BW) x100.

The secondary outcome was to elucidate the role of fetal monitoring (inpatient vs outpatient) in modifying the risk of mortality on birth weight discordant pregnancies, and to explore the diagnostic performance of birth weight discordance in predicting mortality.

We also planned to include other risk factors of perinatal mortality in the analysis, including maternal age, parity, body mass index, smoking, assisted reproductive technology (ART), ethnicity, type of monitoring, and small for gestational age (SGA) of at least one twin, defined as birth weight <10th percentile.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc., Armonk, NY, USA). Data are shown as means ± standard deviation (SD) or median (interquartile range, IQR) where there was a non-linear association for continuous variables, or as percentage (numbers) for categorical variables. Univariate comparisons of dichotomous data were performed with the use of the chi-square with continuity correction. Comparisons between groups

were performed with the use of the T-test to test group means with SD by assuming equal within-group variances.

The association between the study outcomes and relevant risk factors was investigated using multivariate logistic regression and presented as odds ratio (OR) with the 95% of confidence interval (CI). The predictive accuracy of weight discordance for mortality was also analyzed and presented as the area under the curve (AUC). Finally, the predictive accuracy was reported as sensitivity, specificity, positive and negative likelihood ratio and diagnostic OR calculated for BW discordance cut-offs of ≥10%, ≥15%, ≥20%, ≥25% and ≥30% respectively. Furthermore, the figures for diagnostic accuracy of the optimal BW discordance cut-off, defined as the threshold of weight discordance showing the best combination of sensitivity and specificity as extrapolated from the ROC curve analysis, were also computed.

We calculated two-sided p-values. A p-value <0.05 was considered to indicate statistical significance. This study was reported following the STROBE guidelines.[12]

RESULTS

Characteristics of the study population

Two hundred and forty-two MCMA twin pregnancies (484 fetuses) were included in the analysis. General characteristics of the study population are reported in Table 1 and Supplementary Table 1. Mean maternal age was 29.5±4.6 years, while the mean gestational age at delivery was 31.7±2.0 weeks. The mean weight discordance was 10.3±8.5%, while the prevalence of weight discordance ≥10%, ≥15%, ≥20%, ≥25% and ≥30% was 41.3%, 19.4%, 11.16%, 6.6% and 3.3%, respectively. The majority (69%) of the included pregnancies were managed mainly as outpatient, while 35% had elective admission to the hospital for inpatient management.

Primary and secondary outcomes

The risk of IUD was significantly higher in MCMA twin pregnancies with BW discordance ≥20% (OR 2.4, 95% CI 1.1 to 5.6; p=0.050), ≥25% (OR 4.9, 95% CI 2.0 to 11.0; p= 0.001) and ≥30% (OR 4.4, 95% CI 1.3 to 14.4; p=0.001) (Table 2).

When stratifying the analysis according to the type of IUD (single vs double), the risk of single IUD was significantly increased in either MCMA pregnancies presenting with weight discordance ≥15% (OR 5.3, 95% CI 1.6 to 17.6; p=0.007), ≥20% (OR 4.7, 95% CI 1.3 to 16.7; p= 0.016), ≥25% (OR 5.0, 95% CI 1.4 to 18.1; p=0.014) and ≥30% (OR 7.3, 95% CI 1.4 to 36.9; p=0.016), while the strength of association between BW discordance and mortality was lower for double IUD (Supplementary Table 2 and 3). Conversely, the risk of NND was not increased in weight discordant, compared to concordant MCMA pregnancies, irrespective of the BW discordance cut-off used (Table 2).

When exploring the association of antenatal fetal monitoring (inpatient vs outpatient) in MCMA pregnancies with different cut-offs of BW discordance, there was no significant difference in the risk of overall IUD, single IUD, double IUD, NND, and perinatal death between pregnancies managed as inpatient compared to those managed as outpatient for all the weight discordance cut-offs (Table 3, Supplementary Table 4).

In the multiple logistic regression analysis, BW discordance ≥20% (OR 3.8, 95% CI 1.2 to 11.8; p=0.019), ≥25% (OR 7.8, 95% CI 2.0 to 29.7; p=0.003) and ≥30% (OR 9.7, 95% CI 1.6 to 58.9; p=0.014), but not the presence of at least one SGA fetus in the twin pair (p=0.456) or the type of fetal monitoring (inpatient vs outpatient, p=0.07) were independently associated with the occurrence of IUD. Conversely, gestational age at birth (OR 2.6, 95% CI 1.5 to 4.5; p=0.001) was significantly associated with NND (Supplementary Table 5).

BW discordance had a low predictive accuracy for overall mortality with an AUC of 0.60 (95% CI 0.46 to 0.73), 0.53 (95% CI 0.34 to 0.71) and 0.57 (95% CI 0.45 to 0.68) for IUD, NND and PND respectively, while the diagnostic performance for single IUD was better (AUC: 0.73, 95% CI 0.6 to 0.9) (Table 4 and Figure 1). The low predictive accuracy of BW discordance as a standalone test for mortality was mainly due to its low sensitivity, while it had a moderate to good specificity in ruling out the risk of IUD when a cut-off of ≥20% was used to define discrepancy (Supplementary Table 6).

DISCUSSION

Main findings

This large multicenter study quantified the risk of perinatal mortality in 242 MCMA twin pregnancies, including 484 fetuses, according to intertwine weight discordance at birth. The study showed a consistently higher risk of IUD for fetuses with BW discordance of ≥20% and higher. The adjustment for confounders strengthened this association. This risk did not differ according to whether the pregnancy was managed as inpatient or outpatient. We also explored the role of weight discordance alone in predicting perinatal mortality in MCMA twin pregnancies, demonstrating a low diagnostic performance, except for single IUD.

Strengths and limitations

Our study has several strengths. The number of included women in our cohort is substantially higher than in previous relevant studies. The multicenter nature of this study makes our results generalizable. The most important limitation of our study is the retrospective design and the use of BW rather than estimated fetal weight discordant. Furthermore, the practice of iatrogenic preterm delivery of MCMA pregnancies presenting with discordance may have likely introduced an intervention bias potentially affecting the reported strength of association between weight discordance and mortality. Finally, we do acknowledge that analyses for some outcomes were underpowered; however, those are indeed uncommon outcomes (eg neonatal mortality) with an overall rate of less than 5%. It is important to acknowledge that each centre is likely to have a few MCMA twin pregnancies, and therefore, this study is considered one of the largest in the literature.

Interpretation of study findings and comparison with existing literature

The optimal type of monitoring of monoamniotic twin pregnancies has still to be ascertained. There are no randomized controlled trials comparing the different management protocols in MCMA pregnancies and a large heterogeneity as regard as type and frequency of fetal monitoring and timing at initiation of fetal surveillance among the recently published studies. Recently, Saccone et al. for the MONOMONO working group,[8] showed that MCMA pregnancies managed with elective admission for inpatient managed started at around 26-27 weeks, with nonstress tests (NST) 2-3 times daily, was associated with several fetal and neonatal benefits. More importantly, the study also reported that in case of non-anomalous uncomplicated monoamniotic twins the fetal death rate and the neonatal death rate after 31^{+6} weeks are not increased, even up to 36^{+6} weeks.[8] Despite this, the large heterogeneity in the protocol for antenatal surveillance of MCMA pregnancies among the

different centers did not allow to extrapolate a robust evidence on the type and frequency of prenatal monitoring of these pregnancies.

BW discordance is one of the major determinants of perinatal outcome in both MC and DC twin pregnancy and this association seems to persist even when considering pregnancies delivered close to term. We have previously reported that BW discordance was associated with an increased risk of morbidity even when only pregnancies delivered from 34 weeks of gestation were included in the analysis thus suggesting the growth discrepancy is associated with adverse perinatal outcome, even at later gestational ages. The findings from this study support a practice of intensive fetal monitoring when discordant growth is detected in utero.

Despite this, BW discordance should not be the only indication for iatrogenic delivery and other factors such as gestational age and fetal Doppler should be considered for determining the timing of delivery in growth discordant twins. Monoamniotic placentas are characterized by a peculiar vascular arrangement with a higher number of arterio-arterial, lower number of arterio-venous, and a similar number of veno-venous anastomoses compared to monochorionic diamniotic pregnancies, which seems to reduce the risk of TTTS. However, prenatal diagnosis of TTTS in MCMA twin gestations is challenging since the polyhydramnios-oligohydramnios sequence cannot be detected and diagnosis should be based on other signs, including polyhydramnios, discordance in bladder size, cardiomegaly and abnormal Doppler flow patterns in either twin.[15] Conversely, the large-diameter of arterio-arterial anastomoses between the two umbilical cords may predispose to acute transfusion events leading to sudden fetal loss followed by co-twin death or severe neurological damage. In this scenario, the diagnostic accuracy of arterial and venous Doppler in anticipating adverse events is reduced, thus partially explained the large number of deaths reported as unexpected in the published literature.

Conclusions

MCMA twin pregnancies affected by severe discordance are at increased risk of fetal loss, justifying the need for increased fetal monitoring. BW discordance alone should not be the only indication for an iatrogenic delivery and other factors, such as gestational age and fetal Doppler should be taken into account when assessing growth discordant MA twins. Although no advantage seemed to be conferred by inpatient over outpatient management, future studies are needed in order to elucidate the optimal type and frequency of monitoring in MCMA pregnancies presenting with significant weight discordance.

***Financial Support**: SVG was funded by a 2015-16 bursary from the British Maternal & Fetal Medicine Society (BMFMS) and the Twins and Multiple Births Association (TAMBA).*

ACKNOWLEDGEMENTS

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Figure legend

Figure 1 Receiver operating characteristics curve analysis of weight discordance in predicting intra-uterine, neonatal and perinatal death in monochorionic monoamniotic twin pregnancies

Table 1. General characteristics of the study population (n = 242 monochorionic monoamniotic twin pregnancies).

Characteristics	**Value**
Mean maternal age (year) (SD)	29.5 (4.6)
Median parity (IQR)	0 (0-1)
Mean BMI (SD)	25.6 (5.4)
Smoking -% (n)[a]	9.3 (20)
ART - % (n)[a]	6.2 (15)
Ethnicity - % (n)[b]	
• Caucasian	85.5 (188)
• African	5.5 (12)
• Other	9.1 (20)
Mean GA at delivery (week) (SD)	31.7 (2.0)
Prenatal management - % (n)	
• Inpatient	31.0 (75)
• Outpatient	69.0 (167)
Mean BW discordance (gram) (SD)	10.3 (8.5)
BW discordance -% (n)	
• <10%	17.8 (43)
• ≥10%	41.3 (100)
• ≥15%	19.4 (47)
• ≥20%	11.6 (28)
• ≥25%	6.6 (16)
• ≥30%	3.3 (8)

SD: standard deviation; IQR: interquartile range; GA: gestational age; BW: birth weight, BMI: body mass index; ART: assisted reproduction techniques
a: Information available for 215 pregnancies (195 for MONOMONO, 0 for NorStamp and 25 for STORK).
b: Information available for 221 pregnancies (195 for MONOMONO, 25 for NorStamp and 0 for STORK).

Table 2. Odd ratios for the occurrence of overall intrauterine fetal death, neonatal death, and perinatal death in monochorionic monoamniotic twin pregnancies according to the different cut-offs of birthweight (BW) discordance.

BW discordance cut-off	Fetuses (n=484)	OR (95% CI)	p-values
Intrauterine death (overall)			
≥10%	22/200 vs 15/284	2.22 (1.1-4.4)	0.022
≥15%	10/94 vs 27/390	1.60 (0.7-3.4)	0.227
≥20%	8/56 vs 29/428	2.43 (1.1-5.6)	0.050
≥25%	8/32 vs 29/452	4.86 (2.0-11.0)	0.001
≥30%	4/16 vs 33/468	4.39 (1.3-14.4)	0.001
Neonatal death			
≥10%	6/200 vs 7/284	1.22 (0.4-3.7)	0.720
≥15%	3/94 vs 10/390	1.25 (0.3-4.6)	0.736
≥20%	1/56 vs 12/428	0.63 (0.1-4.9)	0.660
≥25%	1/32 vs 12/452	1.18 (0.1-9.4)	0.874
≥30%	1/16 vs 12/468	2.53 (0.3-20.8)	0.387
Perinatal death			
≥10%	28/200 vs 22/284	1.94 (1.1-3.5)	0.028
≥15%	13/94 vs 37/390	1.53 (0.8-3.0)	0.217
≥20%	8/56 vs 41/428	1.57 (0.7-3.6)	0.276
≥25%	9/32 vs 41/452	3.92 (1.7-9.0)	0.001
≥30%	5/16 vs 45/468	4.27 (1.4-12.8)	0.010

BW, birthweight; OR, odds ratio; CI, confidence interval.

Table 3. Odd ratios for the occurrence of overall, single and double intrauterine fetal death in birthweight discordant monochorionic monoamniotic twin pregnancies managed as inpatient compared to outpatient.

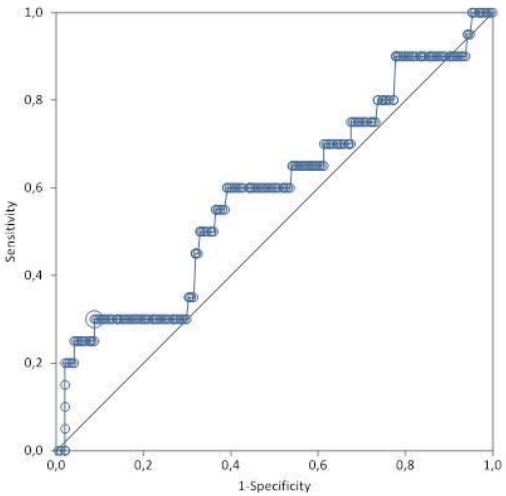
BW discordance cut-off	Inpatient monitoring	Outpatient monitoring	OR (95% CI)	p-value
Intrauterine death (overall)				
≥10%	4/54	18/146	0.57 80.2-1.8)	0.329
≥15%	4/32	6/62	1.33 (0.3-5.1)	0.675
≥20%	4/14	4/40	3.60 (0.8-17.1)	0.106
≥25%	3/10	4/22	1.93 (0.3-10.9)	0.458
≥30%	2/4	2/16	7.00 (0.6-81.7)	0.121
Neonatal death				
≥10%	1/54	5/146	0.53 (0.1-4.7)	0.569
≥15%	1/32	2/62	0.97 (0.1-11.1)	0.979
≥20%	0/14	1/40	0.91 (0.03-23.6)	0.954
≥25%	0/10	1/22	0.68 (0.03-18.29)	0.820
≥30%	0/4	1/16	1.15 (0.04-33.3)	0.936
Perinatal death				
≥10%	5/54	23/146	0.55 (0.2-1.5)	0.246
≥15%	5/32	8/62	1.25 (0.4-4.2)	0.718
≥20%	4/14	5/40	2.80 (0.6-12.4)	0.176
≥25%	3/10	5/22	1.46 (0.3-7.8)	0.661
≥30%	2/4	3/16	4.33 (0.4-44.4)	0.217

BW, birthweight; OR, odds ratio; CI, confidence interval.

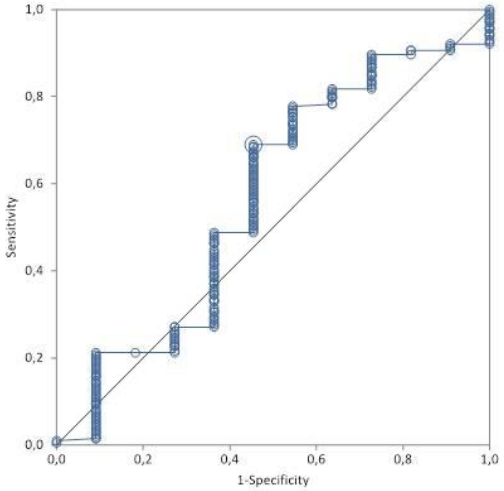
Table 4. Diagnostic accuracy of birthweight discordance in detecting perinatal mortality in monochorionic monoamniotic twin pregnancies.

Outcome	AUC (95% CI)
Overall IUD	0.596 (0.46-0.73)
Single IUD	0.729 (0.57-0.89)
Double IUD	0.527 (0.34-0.71)
NND	0.524 (0.33-0.72)
PND	0.566 (0.45-0.68)

IUD



NND



PND