



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

G. SACCONI¹ , A. KHALIL^{2,3} , B. THILAGANATHAN^{2,3} , S. V. GLINIANAIA⁴,
V. BERGHELLA⁵ and F. D'ANTONIO⁶, for the MONOMONO, NorSTAMP and STORK research collaboratives[#]

¹Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy; ²Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust, University of London, London, UK; ³Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK; ⁴Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK; ⁵Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA; ⁶Department of Obstetrics and Gynecology, University Hospital of Northern Norway, Tromsø, Norway

KEYWORDS: Cesarean delivery; chorionicity; cord accident; cord entanglement; healthcare; monochorionic; multiple gestation; perinatal death; respiratory distress syndrome; twin pregnancy

CONTRIBUTION

What are the novel findings of this work?

The risk of intrauterine death is significantly increased in monochorionic monoamniotic twin pregnancies with birth-weight discordance $\geq 10\%$ and this risk is further increased at birth-weight-discordance cut-offs $\geq 20\%$, with an odds ratio of 2.4 (95% CI, 1.1–5.6) at $\geq 20\%$ and an odds ratio of 4.4 (95% CI, 1.3–14.4) at $\geq 30\%$.

What are the clinical implications of this work?

Monochorionic monoamniotic twin pregnancies with birth-weight discordance are at increased risk of fetal death, signaling a need for increased levels of monitoring. The current data do not demonstrate an advantage of inpatient over outpatient management in these cases.

ABSTRACT

Objectives The primary objective was to quantify the risk of perinatal mortality in non-anomalous monochorionic monoamniotic (MCMA) twin pregnancies complicated by birth-weight (BW) discordance. The secondary objectives were to investigate the effect of inpatient vs outpatient fetal monitoring on the risk of mortality in weight-discordant MCMA twin pregnancies, and to explore the predictive accuracy of BW discordance for perinatal mortality.

Methods This analysis included data on 242 MCMA twin pregnancies (484 fetuses) from three major research collaboratives on twin pregnancy (MONOMONO, STORK and NorSTAMP). The primary outcomes were the risks of intrauterine (IUD), neonatal (NND) and perinatal (PND) death, according to weight discordance at birth from $\geq 10\%$ to $\geq 30\%$. The secondary outcomes were the association of inpatient vs outpatient fetal monitoring with the risk of mortality in weight-discordant pregnancies, and the accuracy of BW discordance in predicting mortality. Logistic regression and receiver-operating-characteristics-curve analyses were used to analyze the data.

Results The risk of IUD was significantly increased in MCMA twin pregnancies with BW discordance $\geq 10\%$ (odds ratio (OR), 2.2; 95% CI, 1.1–4.4; $P = 0.022$) and increased up to an OR of 4.4 (95% CI, 1.3–14.4; $P = 0.001$) in those with BW discordance $\geq 30\%$. This association remained significant on multivariate logistic regression analysis for BW-discordance cut-offs $\geq 20\%$. However, weight discordance had low predictive accuracy for mortality, with areas under the receiver-operating-characteristics curve of 0.60 (95% CI, 0.46–0.73), 0.52 (95% CI, 0.33–0.72) and 0.57 (95% CI, 0.45–0.68) for IUD, NND and PND, respectively. There was no difference in the risk of overall IUD, single IUD, double IUD, NND or PND between pregnancies managed as an

Correspondence to: Dr F. D'Antonio, Department of Obstetrics and Gynecology, Department of Medical and Surgical Sciences, University of Foggia, Viale Luigi Pinto, 71100 Foggia, Italy (e-mail: dantoniofra@gmail.com)

[#]Collaborators are listed at end of article.

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inpatient compared with those managed as an outpatient, for any BW-discordance cut-off.

Conclusions MCMA twin pregnancies with BW discordance are at increased risk of fetal death, signaling a need for increased levels of monitoring. Despite this, the predictive accuracy for mortality is low; thus, detection of BW discordance alone should not trigger intervention, such as iatrogenic delivery. The current data do not demonstrate an advantage of inpatient over outpatient management in these cases. Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

Monoamniotic twinning is a rare event that 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 with monochorionic diamniotic and dichorionic twin pregnancies, especially as a 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 older literature^{3–7}. Recently, several multinational studies showed a substantially improved chance of perinatal survival, with mortality rates ranging from 10% to 30%^{8–11}, although the optimal type of monitoring has still to be defined⁷.

There is no randomized trial comparing the different types 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 MCMA twin pregnancies managed mainly as in- compared with outpatients⁸. However, there was large heterogeneity in the timing of initiation and intensity of outpatient surveillance among the participating centers, thus potentially undermining the robustness of the results.

Fetal and perinatal death in MCMA twin pregnancies seems to be related mainly to complications unique to MCMA placentae, such as acute twin-to-twin transfusion syndrome (TTTS), twin reversed arterial perfusion (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.

Birth-weight (BW) discordance is one of the major determinants of perinatal mortality and morbidity in dichorionic and monochorionic twin pregnancies. Although it may represent normal physiological variation, a high degree of intertwin discrepancy in fetal growth has been associated with poor perinatal outcome¹². In view of this association, clinicians commonly report the degree of estimated-weight discordance detected on ultrasound examination.

In a recent systematic review, we reported that both dichorionic and monochorionic twin pregnancies

discordant for fetal growth are at higher risk of intrauterine death (IUD), especially when one fetus is small-for-gestational age (SGA)¹². Besides mortality, BW discordance has also been associated with an increased risk of neonatal morbidity, such as respiratory distress syndrome, sepsis, intraventricular hemorrhage and admission to the neonatal intensive care unit¹¹. However, the association between BW 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 BW discordance. The secondary objectives were to investigate the effect of inpatient *vs* outpatient fetal monitoring on the risk of mortality in BW-discordant MCMA twin pregnancies, and to explore the predictive accuracy of BW discordance for mortality.

METHODS

Study design and participants

This analysis included data from three major multicenter research collaboratives on twin pregnancy (MONO-MONO, STORK and NorSTAMP) from four different countries, including the UK, Italy, Spain and the USA^{8,10,11}. Details of 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}. Only non-anomalous MCMA twin pregnancies with a prenatal diagnosis of monoamniocity were considered suitable for inclusion in the present study. Pregnancies affected by chromosomal or structural anomalies, those with a postnatal diagnosis of monoamniocity and those undergoing *in-utero* treatment (either cord occlusion or laser coagulation of placental anastomoses) were excluded.

Outcomes

The primary outcomes were the risks of IUD, neonatal death (NND; defined as death of a neonate within 0–27 days following delivery) and perinatal death (PND; defined as fetal death ≥ 24 weeks of gestation or NND), according to different cut-offs of BW discordance ($\geq 10\%$, $\geq 15\%$, $\geq 20\%$, $\geq 25\%$ and $\geq 30\%$). BW discordance was defined as the percentage discrepancy in BW between the larger and smaller twin, and was calculated using the following equation: BW discordance (%) = $(BW_{\text{larger twin}} - BW_{\text{smaller twin}}) / BW_{\text{larger twin}} \times 100$.

Secondary outcomes were the association of inpatient *vs* outpatient fetal monitoring with the risk of mortality in BW-discordant pregnancies, and the diagnostic performance of BW 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, use of assisted reproductive technology, ethnicity, type of monitoring, and delivery of at least one SGA twin, defined as BW $< 10^{\text{th}}$ percentile.

Statistical analysis

Statistical analysis was performed using SPSS v. 19.0 (IBM Corp., Armonk, NY, USA). Data are shown as mean \pm SD or median with interquartile range (IQR) for continuous variables, and as n (%) for categorical variables. Univariate comparisons of dichotomous variables were performed using the chi-square test with continuity correction. Comparisons of continuous variables were performed using Student's t -test to assess the difference between means.

The association between the study outcomes and relevant risk factors was investigated using multivariate logistic regression analysis and presented as odds ratio (OR) with 95% CI. The predictive accuracy of weight discordance for mortality was assessed using the area under the receiver-operating-characteristics curve (AUC). Sensitivity, specificity, positive and negative likelihood ratios, and diagnostic ORs were calculated for BW-discordance cut-offs of $\geq 10\%$, $\geq 15\%$, $\geq 20\%$, $\geq 25\%$ and $\geq 30\%$.

Two-sided P -values were calculated. A P -value ≤ 0.05 was considered to indicate statistical significance. This study was reported following the STROBE guidelines¹³.

RESULTS

Characteristics of study population

Two hundred and forty-two MCMA twin pregnancies (484 fetuses) were included in the analysis. The general characteristics of the study population are reported in Tables 1 and S1. Mean maternal age was 29.5 ± 4.6 years and mean gestational age at delivery was 31.7 ± 2.0 weeks. Mean BW discordance was 10.3 ± 8.5 g and the prevalence of BW discordance $\geq 10\%$, $\geq 15\%$, $\geq 20\%$, $\geq 25\%$ and $\geq 30\%$ was 41.3%, 19.4%, 11.6%, 6.6% and 3.3%, respectively. The majority (69%) of the included pregnancies were managed mainly as outpatients, while 31% had elective admission to the hospital for inpatient management.

Primary and secondary outcomes

The risk of IUD was significantly increased in MCMA twin pregnancies with BW discordance $\geq 10\%$ (OR, 2.2; 95% CI, 1.1–4.4; $P=0.022$), $\geq 20\%$ (OR, 2.3; 95% CI, 1.0–5.3; $P=0.050$), $\geq 25\%$ (OR, 3.9; 95% CI, 1.6–9.8; $P=0.003$) and $\geq 30\%$ (OR, 4.4; 95% CI, 1.3–14.4; $P=0.001$) (Table 2).

When stratifying the analysis according to the type of IUD (single *vs* double), the risk of single IUD was significantly increased in MCMA pregnancies presenting with BW discordance $\geq 10\%$ (OR, 3.9; 95% CI, 1.0–14.9; $P=0.046$), $\geq 15\%$ (OR, 5.3; 95% CI, 1.6–17.6; $P=0.007$), $\geq 20\%$ (OR, 4.6; 95% CI, 1.3–16.3; $P=0.017$), $\geq 25\%$ (OR, 9.1; 95% CI, 2.5–32.9; $P=0.001$) and $\geq 30\%$ (OR, 7.3; 95% CI, 1.4–36.9; $P=0.016$), while there was no significant

Table 1 General characteristics of study population of 242 mono-chorionic monoamniotic twin pregnancies from MONOMONO, NorSTAMP and STORK multiple-pregnancy cohorts

Characteristic	Value
Maternal age (years)	29.5 \pm 4.6
Parity	0 (0–1)
Body mass index	25.6 \pm 5.4
Smoker*	20 (9.3)
Assisted reproductive technology*	15 (7.0)
Ethnicity†	
Caucasian	188 (85.5)
African	12 (5.5)
Other	20 (9.1)
GA at delivery (weeks)	31.7 \pm 2.0
Prenatal management	
Inpatient	75 (31.0)
Outpatient	167 (69.0)
Birth-weight discordance (g)	10.3 \pm 8.5
Birth-weight discordance	
< 10%	142 (58.7)
$\geq 10\%$	100 (41.3)
$\geq 15\%$	47 (19.4)
$\geq 20\%$	28 (11.6)
$\geq 25\%$	16 (6.6)
$\geq 30\%$	8 (3.3)

Data are given as mean \pm SD, median (interquartile range) or n (%).

*Information available for 215 pregnancies (195 for MONOMONO, 0 for NorSTAMP and 20 for STORK). †Information available for 220 pregnancies (195 for MONOMONO, 25 for NorSTAMP and 0 for STORK). GA, gestational age.

association between the risk of double IUD and BW discordance (Table S2). The risk of NND was not increased in BW-discordant, compared with BW-concordant, MCMA pregnancies, irrespective of the BW-discordance cut-off used (Table 2). Table S3 shows the incidence of IUD in BW-discordant *vs* BW-concordant pregnancies, according to gestational age.

When exploring the association between inpatient *vs* outpatient antenatal fetal monitoring and mortality in MCMA pregnancies at different cut-offs of BW discordance, there was no significant difference in the risk of overall IUD, single IUD, double IUD, NND or PND between pregnancies managed as an inpatient and those managed as an outpatient at any BW-discordance cut-off (Tables 3 and S4).

On multivariate logistic regression analysis, BW discordance $\geq 20\%$ (OR, 3.8; 95% CI, 1.2–11.8; $P=0.019$), $\geq 25\%$ (OR, 7.8; 95% CI, 2.0–29.7; $P=0.003$) and $\geq 30\%$ (OR, 9.7; 95% CI, 1.6–58.9; $P=0.014$), but not delivery of at least one SGA neonate ($P=0.456$) or type of fetal monitoring (inpatient *vs* outpatient, $P=0.075$), was associated independently with the occurrence of IUD. Conversely, gestational age at delivery (OR, 2.6; 95% CI, 1.5–4.5; $P=0.001$) was associated significantly with NND (Table S5).

BW discordance had low predictive accuracy for mortality, with AUCs of 0.596 (95% CI, 0.46–0.73), 0.527 (95% CI, 0.34–0.71), 0.524 (95% CI, 0.33–0.72) and 0.566 (95% CI, 0.45–0.68) for overall IUD, double IUD, NND and PND, respectively, while the diagnostic

Table 2 Association between birth-weight (BW) discordance and intrauterine, neonatal and perinatal death in 484 monochorionic monoamniotic twins, according to BW-discordance cut-off

BW-discordance cut-off	Death (n/N)		Odds ratio (95% CI)	P
	BW-discordant twins	BW-concordant twins		
Intrauterine death				
≥ 10%	22/200	15/284	2.22 (1.1–4.4)	0.022
≥ 15%	10/94	27/390	1.60 (0.7–3.4)	0.227
≥ 20%	8/56	29/428	2.29 (1.0–5.3)	0.050
≥ 25%	7/32	30/452	3.94 (1.6–9.8)	0.003
≥ 30%	4/16	33/468	4.39 (1.3–14.4)	0.001
Neonatal death				
≥ 10%	6/200	7/284	1.22 (0.4–3.7)	0.720
≥ 15%	3/94	10/390	1.25 (0.3–4.6)	0.736
≥ 20%	1/56	12/428	0.63 (0.1–4.9)	0.660
≥ 25%	1/32	12/452	1.18 (0.1–9.4)	0.874
≥ 30%	1/16	12/468	2.53 (0.3–20.8)	0.387
Perinatal death				
≥ 10%	28/200	22/284	1.94 (1.1–3.5)	0.028
≥ 15%	13/94	37/390	1.53 (0.8–3.0)	0.217
≥ 20%	9/56	41/428	1.81 (0.8–4.0)	0.138
≥ 25%	8/32	42/452	3.25 (1.7–7.7)	0.007
≥ 30%	5/16	45/468	4.27 (1.4–12.8)	0.010

Table 3 Association between inpatient vs outpatient fetal monitoring and intrauterine, neonatal and perinatal death in 200 birth-weight (BW)-discordant monochorionic monoamniotic twins, according to BW-discordance cut-off

BW-discordance cut-off	Death (n/N)		Odds ratio (95% CI)	P
	Inpatients	Outpatients		
Intrauterine death				
≥ 10%	4/54	18/146	0.57 (0.2–1.8)	0.329
≥ 15%	4/32	6/62	1.33 (0.3–5.1)	0.675
≥ 20%	4/14	4/42	3.80 (0.8–17.8)	0.090
≥ 25%	3/10	4/22	1.93 (0.3–10.9)	0.458
≥ 30%	2/4	2/12	5.00 (0.4–59.7)	0.203
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	1/42	0.95 (0.04–24.8)	0.978
≥ 25%	0/10	1/22	0.68 (0.03–18.29)	0.820
≥ 30%	0/4	1/12	0.85 (0.03–25.0)	0.926
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	5/42	2.96 (0.7–13.1)	0.153
≥ 25%	3/10	5/22	1.46 (0.3–7.8)	0.661
≥ 30%	2/4	3/12	3.00 (0.3–31.6)	0.361

performance for single IUD was better (AUC, 0.729; 95% CI, 0.57–0.89) (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 moderate to good specificity for IUD when a cut-off of ≥ 20% was used to define BW discordance (Table S6).

DISCUSSION

Main findings

This large multicenter study quantified the risk of perinatal mortality in 242 MCMA twin pregnancies, including 484 fetuses, according to intertwin weight discordance at birth. The study showed a consistently

higher risk of IUD in fetuses with BW discordance of ≥ 10% and at higher cut-offs. The association remained significant for BW-discordance cut-offs ≥ 20% after adjusting for confounders. The risk of mortality did not differ according to whether the pregnancy was managed as an inpatient or outpatient. We also explored the ability of BW discordance alone to predict perinatal mortality in MCMA twin pregnancies, demonstrating a low diagnostic performance, apart from for single IUD.

Strengths and limitations

Our study has several strengths. The number of included women in our cohort is substantially higher

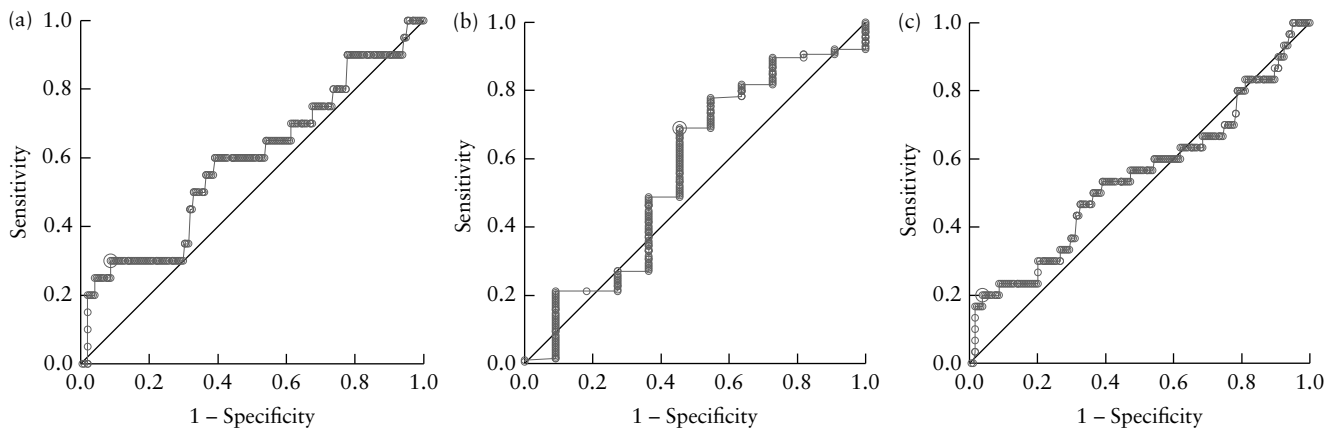


Figure 1 Receiver-operating-characteristics curves for prediction of intrauterine (a), neonatal (b) and perinatal (c) death by intertwin birth-weight discordance in monochorionic monoamniotic twin pregnancies.

than that in previous relevant studies. The multicenter nature of this study makes our results generalizable. The most important limitation of our study is its retrospective design and the use of BW discordance rather than estimated-fetal-weight discordance. Furthermore, the practice of iatrogenic preterm delivery of MCMA pregnancies presenting with weight discordance may have introduced intervention bias, potentially affecting the reported strength of association between BW discordance and mortality. Finally, we acknowledge that analyses for some study outcomes were underpowered; however, they are uncommon outcomes (e.g. neonatal mortality) with an overall incidence of less than 5%. It is important to acknowledge that each center is likely to have few MCMA twin pregnancies, and therefore this study is one of the largest in the literature.

Interpretation of study findings and comparison with existing literature

The optimal type of monitoring of MCMA twin pregnancies has still to be ascertained. There are no randomized controlled trials comparing the different management protocols in MCMA pregnancies and there is large heterogeneity with regard to the type, frequency and timing of initiation of fetal monitoring among recently published studies. Recently, the MONOMONO working group⁸ showed that management involving elective admission for inpatient monitoring started at around 26–27 weeks, with non-stress tests two to three times daily, was associated with several fetal and neonatal benefits in MCMA pregnancies. More importantly, the study also reported that, in cases of non-anomalous uncomplicated MCMA twins, the fetal and neonatal death rates from 31 + 6 weeks to 36 + 6 weeks are not increased, irrespective of whether inpatient or outpatient management is followed⁸. Despite this, the large heterogeneity in protocols for antenatal surveillance of MCMA pregnancies among the different centers did not allow the extrapolation of robust evidence on the optimal type and frequency of prenatal monitoring in these pregnancies.

BW discordance is one of the major determinants of perinatal outcome in both monochorionic and dichorionic twin pregnancies, and this association seems to persist even when considering pregnancies delivered close to term. We have reported previously 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 that growth discrepancy is associated with adverse perinatal outcome even at later gestational ages¹¹. The findings from this study support a practice of intensive fetal monitoring when discordant intertwin growth is detected *in utero*.

BW discordance should not be the only indication for iatrogenic delivery, and other factors, such as gestational age and fetal Doppler, should be considered in the determination of timing of delivery in growth-discordant twins. Monoamniotic placentae are characterized by a peculiar vascular arrangement in which there is a higher number of arterioarterial, lower number of arteriovenous and similar number of venovenous anastomoses compared with in monochorionic diamniotic pregnancies, which seems to reduce the risk of TTTS. However, prenatal diagnosis of TTTS in MCMA twin gestations is challenging as 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 twin¹⁴. The unique vascular arrangement in MCMA twins can predispose to acute hemodynamic events which can potentially lead to sudden unpredictable fetal death. Similarly, the large diameter of the arterioarterial anastomoses between the two umbilical cords may predispose to acute transfusion events, leading to sudden fetal loss followed by cotwin death or severe neurological damage. In this scenario, the diagnostic accuracy of arterial and venous Doppler in anticipating adverse events is reduced, which could partially explain the large number of deaths reported as unexpected in the published literature.

Conclusions

MCMA twin pregnancies affected by BW discordance are at increased risk of fetal loss, justifying the need for increased fetal monitoring. BW discordance alone should not be an indication for iatrogenic delivery, and other factors, such as gestational age and fetal Doppler, should be taken into account when assessing growth-discordant MCMA 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 ultrasound-estimated-fetal-weight discordance.

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Collaborators

The MONOMONO working group

Fulvio Zullo¹, Mariavittoria Locci¹, Maurizio Guida¹, Hannah Anastasio², Tullio Ghi³, Tiziana Frusca³, Andrea Dall'Asta³, Letizia Galli³, Nicola Volpe³, Mariano Lanna⁴, Stefano Faiola⁴, Anna Fichera⁵, Federico Prefumo⁵, Giuseppe Rizzo⁶, Silvana Arduino⁷, Elisabetta Cantanna⁷, Giuliana Simonazzi⁸, Viola Seravalli⁹, Elena Rita Magro-Malosso⁹, Mariarosaria Di Tommaso⁹, Jena L. Miller¹⁰, Ahmet A. Baschat¹⁰, Amerigo Vitagliano¹¹, Silvia Visentin¹¹, Erich Cosmi¹¹, Claudia Caissutti¹², Lorenza Driul¹², Daniele Di Mascio¹³, Pierluigi Benedetti Panici¹³, Flaminia Vena¹³, Roberto Brunelli¹³, Andrea Ciardulli¹⁴, Corina Schoen¹⁵, Anju Suhag¹⁶, Zita Maria Gambacorti-Passerini¹⁷, Maria Angeles Anaya Baz¹⁷, Giulia Magoga¹⁸, Enrico Busato¹⁹, Elisa Filippi¹⁹, María José Rodríguez Suárez²⁰, Francisco Gamez Alderete²¹, Paula Alonso Ortuno²¹, Marianne Vendola²², Preethi Navaneethan²², Ruwan Wimalasundera²², Raffaele Napolitano²², Antonio Mollo²³, Carmen Imma Aquino²³, Serena D'Agostino²⁴, Cinzia Gallo²⁴, Roberta Venturella²⁴ and Mariaelena Flacco²⁵.

¹Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy; ²Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA; ³Department of Obstetrics and Gynecology, University of Parma, Parma, Italy; ⁴Fetal Therapy Unit 'U Nicolini', Buzzi Children's Hospital University of Milan, Milan, Italy; ⁵Department of Obstetrics and Gynecology, University of Brescia, Brescia, Italy; ⁶University of Rome Tor Vergata, Division

of Maternal Fetal Medicine, Ospedale Cristo Re Roma, Rome, Italy; ⁷Department of Obstetrics and Gynecology, 2nd University of Turin, AO Town of Health and Science, Turin, Italy; ⁸Department of Medical Surgical Sciences, Division of Obstetrics and Prenatal Medicine, St Orsola Malpighi Hospital, University of Bologna, Bologna, Italy; ⁹Department of Health Science, Division of Pediatrics, Obstetrics and Gynecology, Careggi Hospital University of Florence, Florence, Italy; ¹⁰Johns Hopkins Center for Fetal Therapy, Department of Gynecology & Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA; ¹¹Department of Woman's and Child's Health, University of Padua, Padua, Italy; ¹²Department of Experimental Clinical and Medical Science, DISM, Clinic of Obstetrics and Gynecology, University of Udine, Udine, Italy; ¹³Department of Gynecological, Obstetrical and Urological Sciences, Sapienza University of Rome, Rome, Italy; ¹⁴Department of Obstetrics and Gynecology, Catholic University of Sacred Heart, Rome, Italy; ¹⁵Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Massachusetts-Baystate, Springfield, MA, USA; ¹⁶Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX, USA; ¹⁷Department of Obstetrics and Gynecology, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain; ¹⁸Department of Obstetrics and Gynecology, Hospital of Treviso, Treviso, Italy; ¹⁹Department of Obstetrics and Gynecology, Santa Maria di Ca' Foncello Hospital, Treviso, Italy; ²⁰Department of Obstetrics and Gynecology, Hospital Universitario Central de Asturias (HUCA), Oviedo, Spain; ²¹Department of Obstetrics and Gynecology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; ²²University College Hospital, London, UK; ²³School of Medicine, University of Salerno, Salerno, Italy; ²⁴Department of Obstetrics and Gynaecology, School of Medicine, Magna Graecia University of Catanzaro, Catanzaro, Italy; ²⁵Local Health Unit, University of Pescara, Pescara, Italy.

NorSTAMP collaborators

Therese Hannon¹, Stephen N. Sturgiss¹, Judith Rankin², Nicola Miller³ and Danielle Martin³.

¹Department of Fetal Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; ²Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK; ³NCARDRS, National Congenital Anomaly and Rare Disease Registration Service, Public Health England, Newcastle upon Tyne, UK.

STORK collaborators

Arash Bahamie¹, Amar Bhide², Aris Papageorghiou², Anne Deans³, Kim Morgan³, Michael Egbor⁴, Adetunji Matiluko⁴, Cheryl Ellis⁵, Hina Gandhi⁶, Rosol Hamid⁷,

Renata Hutt⁸, Lesley Roberts⁸, Faz Pakarian⁹ and Elisabeth Peregrine¹⁰.

¹St Peter's Hospital, London, UK; ²St George's University of London, London, UK; ³Frimley Park Hospital, Frimley, UK; ⁴St Helier's Hospital, Carshalton, UK; ⁵Epsom General Hospital, Epsom, UK; ⁶East Surrey Hospital, Redhill, UK; ⁷Mayday University Hospital, London, UK; ⁸Royal Surrey County Hospital, Guildford, UK; ⁹Worthing Hospital, Worthing, UK; ¹⁰Kingston Hospital, London, UK.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Table S1 General characteristics of study population of 242 monochorionic monoamniotic twin pregnancies, according to cohort

Table S2 Association of birth-weight discordance with single and double intrauterine fetal death in monochorionic monoamniotic twin pregnancies

Table S3 Occurrence of single and double intrauterine death in birth-weight-discordant vs -concordant monochorionic monoamniotic twin pregnancies, according to gestational age

Table S4 Association of inpatient vs outpatient monitoring with single and double intrauterine death in birth-weight (BW) discordant monochorionic monoamniotic twins, according to BW-discordance cut-off

Table S5 Multivariate logistic regression analysis of association of pregnancy characteristics and birth-weight discordance with single or double intrauterine fetal death in monochorionic monoamniotic twin pregnancies

Table S6 Diagnostic accuracy of birth-weight discordance for perinatal mortality in monochorionic monoamniotic twin pregnancies