CLINICAL RESEARCH ARTICLE

Maternal hypertension and survival in singletons and twins born at 23–29 weeks: not just one answer...

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BACKGROUND: To describe the association between maternal hypertension (chronic and gestational, MH) and mortality in very preterm singletons and twins, focusing on how estimates depend on gestational age (GA) and size at birth.

METHODS: We estimated relative risks of in-hospital death in 12,320 singletons (MH: 22.4%) and 4381 twins (MH: 10.6%) born at 23–29 weeks in the Italian Neonatal Network (89 hospitals, 2008–2016).

RESULTS: Babies with MH had higher GA and were more frequently small-for-gestational age (SGA), especially singletons. In crude analyses, MH was associated with lower mortality in singletons. In multivariable analyses, the effects of GA and size differed between twins and singletons with and without MH. The best-fitting models included continuous birth weight (rather than SGA) and were stratified by GA. In these models, MH was associated with lower mortality in singletons—but not twins—born after week 25.

CONCLUSIONS: In this cohort of very preterm infants, the association between MH and mortality differed between singletons and twins and across strata of GA at birth. These estimates cannot be interpreted causally, but suggest that, from a descriptive/predictive standpoint, singletons with MH born after week 25 have lower mortality than singletons born to women without MH.

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INTRODUCTION

Very preterm births represent a small fraction of all births, but contribute disproportionately to infant mortality and morbidity. Hence, these infants are often the focus of studies aimed at identifying prognostic factors. As maternal hypertension (MH) is a common reason for medically induced preterm birth, the survival of babies born following this complication has been examined in several studies, with conflicting results.^{1–15} Although studies restricted to very preterm births (which, by design, condition on gestational age (GA) at birth) yield estimates that cannot be interpreted causally,^{16–20} they are important for descriptive and predictive purposes.

A possible explanation for the discrepancies across studies may be the choice of predictors included in the models, such as GA and size at birth, and the way they are modeled. An additional source of variability may be due to whether twins, which represent a non-negligible proportion of very preterm infants, are part of the study population (and how they are examined when included). Several studies have suggested that, overall, twins born after MH have better outcomes than twins born from normotensive pregnancies.^{2,10,14,21–24} These observations have led to the hypothesis that gestational hypertension may be an adaptive condition in multifetal pregnancies.^{2,10,14,22,23}

Three reports have suggested that, among very preterm twins, gestational hypertension is associated with lower mortality.^{2,10,14} These studies were all based on data from US birth certificates using different time periods, inclusion criteria, analyses, and relatively broad categories of GA at birth, comprising 9 or more weeks (20–28 or 20–31 weeks). Even from a non-causal perspective, a problem with this approach is that preeclampsia

is commonly diagnosed relatively late in pregnancy; therefore, assessing mortality from 20 weeks—when risk of death is very high but incidence of hypertensive disorders is very low—can result in exaggerating the appearance of a survival advantage, due to immortal time bias.²⁵

In this paper, we examine the association between MH (pre-existing or pregnancy-induced) and in-hospital mortality in very preterm singletons and twins, focusing on how the analytic approach affects estimates, in order to provide suggestions for analyzing this type of data.

MATERIALS AND METHODS

Study population

The study population comprised neonates born between 23 and 29 weeks of gestation in 2008–2016. All infants had been admitted to one of the 89 Italian hospitals participating in the Italian Neonatal Network (INN, www.neonatalnet.org), a voluntary collaboration of neonatal units across Italy. The INN aims at coordinating national data collection and maintains an anonymized database comprising all infants admitted to hospitals adhering to the Vermont Oxford Network (VON, www.vtoxford.org). The INN records information on all infants born <30 weeks of gestation; babies born at later gestational weeks are included only if they have a birth weight <1501 g. The network covers about 80% of all infants with the above characteristics born in Italy during the study period. This study was carried out as an analysis of the INN database, for which all hospitals sought local ethics committee approval. Parents provided informed consent to data collection, as required by Italian law. No protected healthcare information was collected.

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Fig. 1 Identification of study population. ZBW: z-score of birth weight for gestation

From the 34,085 babies comprising the INN database for 2008–2016 (Fig. 1), we excluded infants born before 161 days (23 weeks), because MH is rare at these early weeks and live birth is inconsistently registered. To avoid systematically including small but more mature infants, we considered only births up to 29 weeks of gestation. As this analysis focuses on singletons and twins, we further excluded triplets and higher order multiples, as well as babies with recorded congenital anomalies. From the 17,510 eligible infants, we further excluded 809 (4.6%) because of missing or implausible values in key variables, as shown in Fig. 1.

Definitions

All entities were defined per the VON data collection protocol (www.vtoxford.org). MH required the medical diagnosis of chronic or pregnancy-induced hypertension, recorded before or during the current pregnancy and defined as a systolic blood pressure above 140 or a diastolic blood pressure above 90 mmHg, with or without edema and proteinuria. The best estimate of GA used the following hierarchy: (i) obstetrical measures based on last menstrual period, obstetrical parameters, and prenatal ultrasound as recorded in the maternal chart; (ii) neonatologist's estimate based on physical criteria, neurologic examination, or combined physical and GA exam.

The primary outcome in this study was death before discharge from the neonatal intensive care unit (NICU), including death in the delivery room ($N = 171$).

Singletons and twins below the 10th centile of sex-specific birth weight for GA Fenton's centiles²⁶ were classified as being small-for-gestational age (SGA).

All data undergo automated data checks for quality, and participating centers certify completeness at the time of submission to the network.

Statistical analysis

We initially modeled the exposure as a categorical variable reflecting the four possible combinations of MH and twinning

status (as shown in Table 1), to obtain an estimate for each stratum. In choosing the factors to be included in the models, we focused on characteristics of the pregnancy until delivery, including GA and weight at birth, but excluding conditions of the neonate.

We estimated relative risks (RR) and 95% confidence intervals (CI) using Poisson generalized estimating equations, with a robust variance estimator to account for the clustering by hospital. However, we treated each twin as an independent observation, because the anonymous data prevented us from identifying the co-twin with certainty.

To highlight how estimates change depending on how size at birth is accounted for, we compared two models adjusted for the same set of covariates, one with SGA and the other with continuous birth weight + birth weight squared (to account for non-linearity), alongside the model with only MH/twinning status.

We next explored whether the association between MH and mortality changed across strata of twinning and GA at birth by adding interaction terms (MH–twinning–GA) to the models. Finally, we stratified the analyses by GA at birth and twinning, in a model that mirrored the one used by McBride et al.¹¹ (which, however, did not include twins). The latter study, based on US data from the VON, had the same definitions and data collection protocol as ours, making it an ideal candidate for comparison. However, we omitted infants born at 23 weeks, due to our smaller sample size and the low incidence of MH in this group. We examined singletons and twins separately and for each 2-week stratum of GA at birth, we ran three regression models on the same sets of singletons and twins including different predictors: (i) “MH only,” (ii) MH, SGA, and covariates (sex, antenatal steroids, inborn/outborn status, race/ethnicity, and mode of delivery) (“MH + SGA, Cov”), and (iii) the same predictors as in (ii) but with continuous birth weight and birth weight squared instead of SGA (“MH + BW, Cov”). In a sensitivity check, we repeated the above analysis after excluding outborn infants, who may differ from inborn ones in terms of risk factors and prognosis—and who had to survive transfer to be included in the database.

Table 1. Characteristics of the study population, by maternal hypertension and twinning

Characteristic	Singletons, no MH	Singletons, MH	Twins, no MH	Twins, MH
	N = 9566 %	N = 2754 %	N = 3917 %	N = 464 %
Boys	53.9	47.8	53.8	47.4
Gestational age (weeks)				
23–25	29.9	14.6	24.7	16.2
26–27	30.3	30.2	28.0	29.3
28–29	39.8	55.3	47.3	54.5
Chorioamnionitis (980 missing values)	27.0	5.2	17.1	11.6
Prenatal steroids	78.8	86.7	85.0	88.8
Vaginal delivery	40.5	5.6	18.5	7.5
Outborn	9.8	6.4	7.7	7.5
Oxygen	88.1	89.0	87.4	88.1
Endotracheal tube	60.6	50.9	54.6	56.9
In-hospital death	20.3	17.3	21.6	18.8
Of which, delivery room death	1.14	0.58	1.10	0.65
Missing ^a	1.14	1.23	1.12	1.47
Small for gestation	9.0	34.2	8.9	18.5
Large for gestation	8.2	1.3	3.4	2.2
	Median (IQR)			
Birth weight (g)	945 (444)	830 (349)	970 (440)	900 (384)
Birth weight z-score	0.19 (1.1)	−0.96 (1.1)	−0.03 (1.0)	−0.33 (1.2)
Apgar 1 min	5 (4)	6 (3)	6 (3)	6 (3)
Missing %	0.6	0.3	0.4	0.2
Apgar 5 min	8 (2)	8 (1)	8 (1)	8 (1)
Missing %	2.4	1.7	2.5	1.7
Length of hospital stay (days) (105 missing)	62 (46)	65 (39)	59 (42)	63 (41)

IQR interquartile range, MH maternal hypertension

^a Out of 17,146 eligible

To assess the predictive ability of the models, we computed the area under the ROC curves (ROC-AUC, or C-statistic), which provides a measure of the model's ability to discriminate between those with and without the outcome.²⁷ A value of 0.5 indicates that the model predicts the outcome no better than a toss of a coin would, while a value of 1 indicates perfect prediction. As a model may provide an overall good prediction over the entire sample, but behave poorly for subsets of infants, we also assessed the goodness of fit of all the models by calculating their Hosmer–Lemeshow statistic. A higher value indicates poor fit.²⁸

All analyses were carried out using Stata 11.2 (College Station, TX, USA).

RESULTS

Of the 16,701 babies in the study population, 26.2% were twins. MH was reported in 22.4% of singletons and 10.6% of twins. In singletons, the proportion of births with MH rose steadily by gestational week of birth, from <10% at 23 weeks to nearly 30% at week 29; in twins, the increase was less pronounced (Fig. 2). Table 1 shows the characteristics of the neonates by twinning and MH status. Babies born following MH, particularly singletons, tended to be born later than those without MH and were more frequently female and delivered by cesarean section. Both singletons and twins born after MH were smaller than their peers without MH, but the proportion of SGA babies was substantially higher in singletons than in twins (47.0% in singletons vs. 20.4% in

Fig. 2 Proportion of singleton and twin births with maternal hypertension by gestational age at birth

twins, among births at 23–26 weeks, and 29.8% vs. 17.7%, respectively, among births at 27–29 weeks).

In total, 20.7% of infants without MH died in hospital, vs. 17.5% of those with MH. Table 2 shows the estimated RRs of death in the various groups, and how they changed depending on the predictors included in the analyses. Singletons without MH serve

Table 2. Estimated RR and 95% CIs of in-hospital death by MH and twinning

	MH-twinning		MH-twinning+GA, SGA, Cov		MH-twinning + GA, BW, Cov	
	RR	95% CI	RR	95% CI	RR	95% CI
Singletons, no MH	1.00		1.00		1.00	
Singleton, MH	0.86	[0.78,0.95]	0.97	[0.89,1.06]	0.83	[0.76,0.91]
Twins, no MH	1.07	[0.99,1.16]	1.17	[1.10,1.25]	1.14	[1.07,1.21]
Twins, MH	0.92	[0.73,1.15]	1.17	[1.01,1.35]	1.07	[0.92,1.25]
ROC-AUC	0.521		0.839		0.851	
Hosmer–Lemeshow statistic	—		142.36 ^a		75.37 ^a	

MH maternal hypertension, GA gestational age at birth, SGA small-for-gestational age, BW birth weight (linear + squared), Cov covariates: infant sex, antenatal steroids, inborn/outborn status, race/ethnicity, mode of delivery (vaginal vs, cesarean), RR relative risk, CI confidence interval, ROC-AUC area under the ROC curve

^a $P < 0.00001$

as the reference category. In models including only MH/twinning status, singletons with MH had lower mortality (RR 0.86, 95% CI 0.78–0.95), but twins with MH did not (RR 0.92, 95% CI 0.73–1.15). After we included GA at birth, MH was associated with higher mortality in both singletons and twins (data not shown). Further addition of SGA plus covariates yielded a null association in singletons, while twins had higher mortality, similar by MH status. Including actual birth weight (+birth weight squared) instead of SGA as a predictor resulted in a slightly lower RR associated with MH in both singletons and twins. In both the models that included GA and a measure of size at birth, twins had higher mortality than singletons. Including continuous birth weight, as opposed to SGA, resulted in a marginally higher predictive ability (ROC-AUC curve). Both sets of adjustments yielded a very poor fit, however, as evidenced by the high (and highly significant) Hosmer–Lemeshow statistic.

There was evidence of effect-measure modification of both twinning and GA on the association of MH with mortality ($p < 0.05$ for MH-twinning and for twinning-GA, and $p = 0.11$ for MH-GA interactions), even though inclusion of the three-way interaction MH-twinning-GA did not improve model fit (p -value: 0.63). Figure 3 shows the differences between singletons and twins (left vs. right panel), between strata of GA, and between different models within each stratum. These analyses suggested that the choice of predictors matters more for singletons than for twins. Specifically, in singletons (left panel), estimates from models with no additional factor suggested a higher mortality in infants with MH at 24–25 and 26–27 weeks, and a null association in babies born at 28–29 weeks. After adding other covariates, MH was associated with lower mortality in singletons from weeks 26–27 when continuous birth weight, instead of SGA, was in the model. In twins (right panel), the gradient across GA strata was much less pronounced, as were the differences between models. At weeks 28–29, the pattern was closer to that of singletons, but all estimates in twins were highly imprecise.

Similar to the analyses shown in Table 2, inclusion of continuous birth weight in lieu of SGA resulted in both estimates further away from the crude ones, and in a higher discriminative ability (ROC-AUC, Supplementary Table S1, online). The exclusion of outborn babies resulted in very similar estimates as those shown in Fig. 3. However, although mortality of outborn and inborn singletons was very similar (19.1% vs. 19.7%, respectively), outborn twins had lower mortality than inborn ones (14.5% vs. 21.9%).

DISCUSSION

In this large cohort of very preterm infants, the association between MH and mortality varied as a function of gestational

week of birth and twinning status. When size at birth was included in the models, MH was associated with better survival in singletons born from week 26. Discrimination was always slightly higher when models included continuous birth weight, rather than SGA. The modeling approach appeared to matter less in twins, possibly indicating a weaker association between MH and mortality at the same GA/birth size, although our estimates were limited by low precision.

Because of effect-measure modification by twinning and GA on the association between MH and mortality, models that account for (but are not stratified by) GA at birth yield estimates that are averaged over the GA span. Thus, these models obscure the fact that the associations vary depending on GA at birth (and this clearly worsens their goodness of fit). Such dependency on GA may be due in part to the fact that the mix of factors (other than MH) that cause very preterm birth changes across gestation.^{18,29} Another reason is that, at the lowest GAs, mortality is largely due to immaturity and related morbidity, and the contribution of the factors causing preterm birth is comparatively small.

Although it may be tempting to interpret these results as suggesting a protective effect of MH on mortality, such a conclusion would be wrong. In this study, we compared babies born very preterm after a specific complication with a more heterogeneous group of babies born very preterm due to several other (unmeasured) factors that likely had varying effects on mortality. It is well established that, in analyses aimed at estimating a causal association, adjusting for (or stratifying by) factors that are intermediates of the association—such as GA or birth weight—can result in substantial bias,^{16,17,19,30–34} due to opening of colliders paths. The problems associated with adjusting for mediators have been specifically described in the context of perinatology.^{16,19,20,30} Thus, while our results have descriptive (or prognostic) value, they provide no information on the causal effect of preeclampsia on neonatal mortality and should not be interpreted as such. Moreover, both MH and fetal growth restriction can trigger medically indicated preterm delivery, thus determining the very presence of these babies in analyses restricted to preterm births.

We initially included SGA as an indicator of disrupted fetal growth, as this dichotomy identifies (somewhat arbitrarily) a high-risk group of infants to whom neonatologists pay particular attention.^{35,36} SGA status is included in several risk-adjustment scores and algorithms, including SNAPPE,³⁷ and the risk-adjustment model of the VON.³⁸ However, using continuous birth weight always resulted in a better discriminative ability and in estimates further away from the null. The relatively small sample size in twins limited our ability to draw conclusions on this aspect; nevertheless, the results suggest that, at least until week 27,

Fig. 3 Estimated relative risk and 95% confidence intervals of in-hospital death by maternal hypertension, stratified by gestational age. RR, risk ratios; SGA, small-for-gestational age; BW: birth weight; Cov: covariates: sex, antenatal steroids, inborn/outborn status, race/ethnicity, mode of delivery (vaginal vs. cesarean)

estimates in twins may be less susceptible to how size at birth is modeled. This conclusion is supported by the fact that, in twins, MH has limited impact on fetal growth,^{10,21,23,24} even among very preterm births.²²

The main strengths of this study are the large sample size, the fact that we were able to examine a span of several years over a recent period, and the standardized data collection protocol for all participating hospitals. Several limitations should also be noted. The diagnosis of MH was not specific as to whether it referred to de novo hypertension or to pre-existing hypertension. However, the MH frequency of 22.4% in singletons births in our study was comparable to the rate of preeclampsia in the ELGAN¹² (18% in births at 23–27 weeks) and Epipage2⁴ (23.9% in births at 24–34 weeks) studies, and to the rate estimated in the total VON database (based on the same definition as our study).¹¹ We did not have information on the putative causes of preterm delivery for the infants in our study, which, to the extent that they affected mortality, would likely have improved the fit of the models. We also did not have outcome information for about 1.2% of eligible infants, primarily those lost to follow-up after transfer. Nevertheless, the proportion of missing was small, and there were no differences by MH status. We could not account for dependency in twins, likely resulting in underestimating standard errors. However, given that we adjusted the analysis for clustering on hospital, this would account for at least some of the unmeasured shared characteristics of twins.³⁹ Furthermore, these limitations would not influence our demonstration of how results are sensitive to GA and size at birth. As our aim was to describe mortality given live birth, the fact that we lacked information on fetal deaths is not a major limitation.

Other sources of variability, beyond geographical differences, operate in studies examining outcomes in very preterm babies born after MH. For example, definitions of preeclampsia vary, from the broad one in our study to those that incorporate SGA in the definition.^{1,4,6} Some studies include all preterm babies born up to a given week of gestation (usually 29), as well as more mature babies with a birth weight <1501 g,^{5,7} leading to a mix of infants (and pathologies) different from that of studies based on all eligible babies born in a specified interval of GA. The prevailing

obstetric practices in different settings, and particularly the balance of expectant management vs. early induction of pregnancies with MH, are also likely to play a role in explaining differences between studies.

In sum, our study shows that the way in which strong predictors of neonatal outcome (GA and birth weight) are modeled influences estimates of the association between MH and neonatal mortality (and, presumably, other predictor–outcome relations) in very preterm infants. The fact that, especially in singletons, the association between MH and mortality appears to be dependent on the analytic approach goes some way towards explaining why findings across studies have been inconsistent.

Not only is GA a strong predictor of outcome, but its association with mortality varies within the limited range examined in this study. Therefore, simply including it as a covariate in the models obscures how the association between MH and mortality changes as GA increases. The same is true for twinning. Based on these results, we suggest that, when analyzing data from neonatal networks or NICUs, researchers specifically assess whether singletons and twins should be examined separately. In addition, given that—especially among very preterm infants—GA at birth is strongly predictive of virtually every outcome, stratifying by GA at birth will generally yield more accurate estimates. Similarly, including actual birth weight instead of SGA will likely result in a better fit and discriminatory ability.

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AUTHOR CONTRIBUTIONS

Both authors have participated in the concept and design; analysis and interpretation of data; and the drafting or revising of the manuscript. Both have approved the

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ADDITIONAL INFORMATION

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