


Article

Prevalence and Factors Associated With Intertwin Birth Weight Discordance Among Same-Sex Twins in Lombardy, Northern Italy

Giovanna Esposito¹ , Anna Cantarutti^{2,3}, Paola Agnese Mauri^{1,4}, Matteo Franchi^{2,3}, Francesco Fedele¹, Giovanni Corrao^{2,3}, Fabio Parazzini¹ and Nicola Persico^{1,4}

¹Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, ²Unit of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy, ³National Centre for Healthcare Research and Pharmacoepidemiology, Milan, Italy and ⁴Department of Woman, Newborn and Child, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Abstract

This population-based cohort study investigated the prevalence, potential risk factors, and consequences of birth weight discordance (BWD) among same-sex twins. We retrieved data from the automated system of healthcare utilization databases of Lombardy Region, Northern Italy (2007–2021). BWD was defined as 30% or more disparity in birth weights between the larger and the smaller twin. Multivariate logistic regression was used to analyze the risk factors of BWD in deliveries with same-sex twins. In addition, the distribution of several neonatal outcomes was assessed overall and according to BWD level (i.e., $\leq 20\%$, 21–29, and $\geq 30\%$). Finally, a stratified analysis by BWD was performed to assess the relationship between assisted reproductive technologies (ART) and neonatal outcomes. We identified 11,096 same-sex twin deliveries; 556 (5.0%) pairs of twins were affected by BWD. Multivariate logistic regression analysis showed that maternal age ≥ 35 years (OR 1.26, 95% CI [1.05, 5.51]), low level of education (OR 1.34, 95% CI [1.05, 1.70]), and ART (OR 1.16, 95% CI [0.94, 1.44], almost significant due to the low power) were independent risk factors for BWD in same-sex twins. Conversely, parity (OR 0.73, 95% CI [0.60, 0.89]) was inversely related. All the adverse outcomes observed were more common among BWD pairs than non-BWD ones. Instead, a protective effect of ART was observed for most neonatal outcomes considered among BWD twins. Our results suggest that conception after ART increases the risk of developing a high disparity between the weights of the two twins. However, the presence of BWD may complicate twin pregnancies, compromising neonatal outcomes, regardless of the modality of conception.

Keywords: Same-sex twins; birth weight discordance

(Received 23 January 2023; revise received 20 March 2023; accepted 20 March 2023; First Published online 16 May 2023)

Twin pregnancy represents a health issue as it is well known to be more prone to maternal and fetal complications and perinatal mortality than a singleton pregnancy (Cheetham, 2007; Rankin et al., 2005; Vogel et al., 2013). Furthermore, during the last 40 years, a marked increase in the incidence of twin pregnancies — in particular, dizygotic ones — has been observed in most industrialized countries (Dawson et al., 2015; Eriksson & Fellman, 2007), due to the widespread use of assisted reproductive technologies (ART; Dawson et al., 2015; Fuster et al., 2008). Given the diffusion and the clinical implications, the study of twin pregnancies is of utmost epidemiological interest.

Among other adverse conditions typical of twin pregnancies, birth weight discordance (BWD), defined as the disparity of 15% and 40% in birth weights between the larger and the smaller twin respectively (Breathnach et al., 2011; Breathnach & Malone, 2012), complicates about 10% to 29% of pregnancies, according to

the cut-off value used to describe discordance (Blickstein & Goldman, 2003; Miller et al., 2012). Up to a certain degree of discordance, the discrepancy in the birth weights of twins should be considered physiological; the mechanism whereby two fetuses exposed to the same intrauterine environment adopt significantly different growth patterns represents a final common pathway for several twin pregnancy conditions.

The presence of opposite-sex twins (Azcorra et al., 2021; Blickstein & Weissman, 1990), placental dysfunction (Victoria et al., 2001), older maternal age, (Konar et al., 2016; Sannoh et al., 2003; Tan et al., 2005) low maternal socioeconomic profile (Azcorra et al., 2021; Kim et al., 2019; Luo et al., 2006; Tan et al., 2005), primiparity (Blickstein et al., 2000; Sannoh et al., 2003), and lower total twin birth weight (Blickstein et al., 1999; Tan et al., 2005) are factors that have been associated with BWD. Also chorionicity represents a relevant factor influencing BWD; in mono-chorionic pregnancies, vascular anastomoses due to the sharing of a single placenta may lead to an unbalanced intertwin transfusion and consequent asymmetric growth of twins (Denbow et al., 2000; Homola et al., 2019; Lewi et al., 2007).

Further, given the significant contribution of ART to twin pregnancies, it appears interesting to investigate the role of ART on

Corresponding Author: Giovanna Esposito, Email: giovanna.esposito@unimi.it

Cite this article: Esposito G, Cantarutti A, Mauri PA, Franchi M, Fedele F, Corrao G, Parazzini F, Persico N. (2023) Prevalence and Factors Associated With Intertwin Birth Weight Discordance Among Same-Sex Twins in Lombardy, Northern Italy. *Twin Research and Human Genetics* 26: 177–183, <https://doi.org/10.1017/thg.2023.17>



BWD. An increased risk of BWD was reported in ART versus spontaneous twins (Daniel *et al.*, 2000; Koudstaal *et al.*, 2000; Pinborg *et al.*, 2004; Zadori *et al.*, 2004; Zhang *et al.*, 2013), but the evidence is still scarce and controversial (Suzuki & Murata, 2007; Yang *et al.*, 2011).

Some studies have identified discordant twin growth as an independent risk factor for adverse perinatal consequences (Blickstein *et al.*, 2006; Harper *et al.*, 2013; Wen *et al.*, 2005; Yinon *et al.*, 2005), neonatal morbidity (D'Antonio, Thilaganathan *et al.*, 2018; Di Mascio *et al.*, 2019), and intrauterine death (D'Antonio, Odibo *et al.*, 2018). Others have attributed the morbidity and mortality observed in discordant pairs to confounding factors (Cooperstock *et al.*, 2000; Fraser *et al.*, 1994; Frezza *et al.*, 2011; Konar *et al.*, 2016; Patterson & Wood, 1990), such as gestational age at delivery, as a strong association between BWD and preterm births was observed, actual birth weight, gender discordance, and chorionicity. However, no clear picture of this issue has been defined.

In order to shed more light on this unfavorable condition, we analyzed the prevalence, potential risk factors and consequences of BWD in a cohort of same-sex twins in Lombardy, Northern Italy, during the period 2007 to 2021. In addition, we evaluated whether ART influences the outcomes of BWD twins.

Methods

Data Source and Study Cohort

Data for this study were retrieved from the automated system of healthcare utilization (HCU) databases from Lombardy, the largest region of Italy (about 10 million inhabitants), which includes a variety of information on residents who receive National Health System (NHS) assistance. We collected data about maternal socio-demographic characteristics, reproductive history, the current mode of conception, pregnancy course, delivery and newborns' outcomes from the certificate of delivery assistance (Certificato di Assistenza Al Parto [CedAP]) database. We linked records from CedAP and standard discharge form (Scheda di Dimissione Ospedaliera [SDO]) databases through a unique anonymized identification code for each subject. The analysis of the anonymous administrative database does not require ethics committee approval in Italy.

We identified twin births in Lombardy between January 1, 2007 and December 31, 2021. We included deliveries for which there was a SDO related to childbirth coded according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) and/or the Diagnosis-Related Groups (DRG) code, of mothers aged 15 to 55 years, and occurring between 22 to 42 gestational weeks. Deliveries with a lack of information concerning the mode of conception (*i.e.*, spontaneous, nonspontaneous), birth weight, sex of at least one of the twins, and opposite-sex deliveries were excluded. For the cohort selection, the regional databases were accessed until March 2023.

Birth Weight Discordance (BWD) Definition

Information about the birth weight of each twin was collected from CedAP. Intertwin discordance was obtained by the formula $100 * \frac{\text{larger twin weight} - \text{smaller twin weight}}{\text{larger twin weight}}$. Pregnancy was considered complicated by the BWD when the disparity was 30% or more (Jahanfar *et al.*, 2016; Vergani *et al.*, 2004).

Statistical Analysis

First, univariate and multivariate logistic regression were performed to determine the potential factors (*i.e.*, maternal age; nationality; level of education — university, high school, middle or primary school; parity; and mode of conception) associated with BWD. Odds ratios (ORs) and 95% confidence intervals (CIs) were subsequently calculated. Stratified analysis by sex was also conducted.

Second, we compared the distribution of the adverse neonatal outcomes of interest, including preterm birth (36 gestational weeks or less), low birth weight (2500 grams or less), small for gestational age (SGA; having a birth weight below the 10th percentile for gestational age, according to the sex-specific Italian reference curve for normal fetal growth; Parazzini *et al.*, 1995), low Apgar score (7 or less), perinatal mortality, according to the BWD level (*i.e.*, $\leq 20\%$, 21–29%, and $\geq 30\%$). The trend test was used to test differences in the above-mentioned outcomes according to the BWD's levels. The same analysis was repeated, excluding preterm births from the cohort ($N = 7009$ pairs of twins).

Finally, we assessed the relative risks (RRs) and 95% CIs of the neonatal outcomes of interest and the mode of conception according to the presence or absence of BWD. Models were adjusted by maternal age, nationality, level of education, and parity.

We performed analysis using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA).

Results

We identified 17,786 twin births that occurred in Lombardy between January 1, 2007 and December 31, 2021. Of these, we subsequently excluded: 145 deliveries that did not match with a SDO related to childbirth and/or with the DRG code, 13 deliveries of mothers aged less than 15 years or more than 55 years of age, 32 deliveries occurred before 22 completed weeks or after 42 completed weeks. Out of 17,596 twin births, 89 without information concerning the mode of conception, birth weight, or sex of at least one twin were excluded. Finally, we considered only same-sex twins for a total of 11,096 deliveries.

Couples of females twins were 5620 (50.6%), and ones of males were 5476 (49.4%). In general, males were heavier in comparison to females; the average birth weight was 2309.2 g and 2232.8 g, respectively ($p < .0001$).

Births affected by BWD (*i.e.*, discordance of 30% between the largest and smallest twin weight) were 556 (5.0%), 279 (5.0%) among females and 277 (5.0%) among males ($p = .8204$). More in particular, 6,175 (55.7%) twin deliveries presented a discordance of less than 10%, 3144 (28.3%) between 10 and 19%, 1221 (11.0%) between 20 and 29%, 377 (3.4%) between 30 and 39% and 179 (1.6%) over 40%.

ORs of BWD cases according to selected potential risk factors are provided in Table 1. Maternal age >35 years (OR 1.23, 95% CI [1.01, 1.50]), parous (OR 0.73, 95% CI [0.61, 0.88]), and non-spontaneous conception (OR 1.33, 95% CI [1.10, 1.61]) were significant factors for BWD in univariate analysis. After adjusting for all potential risk factors, gestational age >35 years (OR 1.26, 95% CI [1.05, 1.51]), low level of education (OR 1.34, 95% CI [1.05, 1.70]), and parous (OR 95% CI [0.73, 0.60, 0.89]) were significantly associated with BWD. However, nonspontaneous conception was confirmed as a risk factor even if the estimate was not statistically significant due to the low statistical power (OR 1.16, 95% CI [0.94, 1.44]). The results were consistent in the subsets of males and

Table 1. Odds ratios (ORs) of birth weight discordance (BWD) couples of twins according to selected potential risk factors. Lombardy, 2007–2021

Potential Risk Factors	Overall			Males			Females		
	BWD n (%)	OR ^a (95% CI)	OR ^b (95% CI)	BWD, n (%)	OR ^a (95% CI)	OR ^b (95% CI)	BWD, n (%)	OR ^a (95% CI)	OR ^b (95% CI)
Maternal age									
<35	289 (4.5)	1.00 (Ref.)	1.00 (Ref.)	144 (4.6)	1.00 (Ref.)	1.00 (Ref.)	145 (4.5)	1.00 (Ref.)	1.00 (Ref.)
≥35	267 (5.6)	1.26 (1.06, 1.49)	1.26 (1.05, 1.51)	133 (5.7)	1.26 (0.99, 1.61)	1.27 (0.98, 1.65)	134 (5.6)	1.25 (0.98, 1.59)	1.24 (0.96, 1.60)
Nationality									
Italian	434 (5.1)	1.00 (Ref.)	1.00 (Ref.)	220 (5.2)	1.00 (Ref.)	1.00 (Ref.)	214 (5.0)	1.00 (Ref.)	1.00 (Ref.)
Foreign	122(4.7)	0.92 (0.75, 1.13)	0.99 (0.79, 1.22)	57 (4.5)	0.86 (0.66, 1.16)	0.94 (0.68, 1.28)	65 (4.9)	0.98 (0.74, 1.31)	1.04 (0.77, 1.40)
Level of education^c									
University	181 (4.7)	1.00 (Ref.)	1.00 (Ref.)	87 (4.5)	1.00 (Ref.)	1.00 (Ref.)	94 (4.9)	1.00 (Ref.)	1.00 (Ref.)
High school	237 (5.0)	1.07 (0.87, 1.30)	1.12 (0.92, 1.37)	119 (5.2)	1.15 (0.87, 1.53)	1.22 (0.92, 1.63)	118 (4.9)	0.99 (0.75, 1.30)	1.03 (0.84, 1.37)
Middle/primary school	137 (5.5)	1.18 (0.94, 1.48)	1.34 (1.05, 1.70)	71 (5.7)	1.29 (0.94, 1.78)	1.52 (1.09, 2.13)	66 (5.3)	1.08 (0.78, 1.48)	1.18 (0.84, 1.66)
Parity									
Nulliparous	377 (5.6)	1.00 (Ref.)	1.00 (Ref.)	197 (5.9)	1.00 (Ref.)	1.00 (Ref.)	180 (5.2)	1.00 (Ref.)	1.00 (Ref.)
Parous	179 (4.1)	0.73 (0.61, 0.88)	0.73 (0.60, 0.89)	80 (3.7)	0.62 (0.48, 0.81)	0.62 (0.46, 0.82)	99 (4.5)	0.86 (0.67, 1.11)	0.87 (0.66, 1.14)
Conception									
Spontaneous	402 (4.7)	1.00 (Ref.)	1.00 (Ref.)	196 (4.6)	1.00 (Ref.)	1.00 (Ref.)	206 (4.7)	1.00 (Ref.)	1.00 (Ref.)
Nonspontaneous	154 (6.1)	1.33 (1.10, 1.61)	1.16 (0.94, 1.44)	81 (6.5)	1.41 (1.09, 1.85)	1.18 (0.88, 1.58)	73 (5.8)	1.25 (0.95, 1.64)	1.15 (0.85, 1.55)

Note: BWD, birth weight discordance.

^aUnivariate logistic regression model.

^bMultivariate logistic regression model.

^c9 missing values.

Table 2. Modality of delivery and adverse neonatal outcomes according to the degree of birth weight discordance (BWD), Lombardy, 2007–2021

	BWD			<i>p</i> value for trend
	<20% (<i>n</i> = 9319)	20-29% (<i>n</i> = 1221)	≥30% (<i>n</i> = 556)	
Modality of delivery^a				
Spontaneous	1273 (13.7)	137 (11.2)	47 (8.5)	
Instrumental	99 (1.1)	7 (0.6)	2 (0.4)	
Elective CS	5463 (58.6)	756 (61.9)	347 (62.4)	
CS during labour	2120 (22.7)	269 (22.0)	108 (19.4)	
CS without labour	337 (3.6)	49 (4.0)	47 (8.8)	<.0001
Neonatal outcomes				
Preterm birth				
No	3618 (38.8)	378 (31.0)	91 (16.4)	
Yes	5701 (61.2)	843 (69.0)	465 (83.6)	<.0001
Low birth weight				
No/No	2608 (28.0)	64 (5.2)	2 (0.4)	
Yes/No	1816 (19.5)	530 (43.4)	178 (32.0)	
Yes/Yes	4895 (52.5)	627 (51.4)	376 (67.6)	<.0001
SGA				
No/No	7648 (82.1)	651 (53.3)	107 (19.2)	
Yes/No	691 (7.4)	410 (33.6)	325 (58.5)	
Yes/Yes	980 (10.5)	160 (13.1)	124 (22.3)	<.0001
Low Apgar score				
No/No	8679 (93.1)	1090 (89.3)	426 (76.6)	
Yes/No	462 (5.0)	97 (7.9)	102 (18.4)	
Yes/Yes	178 (1.9)	34 (2.8)	28 (5.0)	<.0001
Perinatal mortality				
No/No	9266 (99.4)	1206 (98.8)	500 (89.9)	
Yes/No	36 (0.4)	10 (0.8)	52 (9.4)	
Yes/Yes	17 (0.2)	5 (0.4)	4 (0.7)	<.0001

Note: SGA, small for gestational age; CS, cesarian section.

^aThe sum did not add up to the total because of missing data.

females; however, most of the significance was lost, probably due to the lower statistical power.

Lowering the cut-off of discordance — BWD defined as 20% or more disparity in birth weights — in the multivariate analysis, advanced maternal age (*OR* 1.19, 95% *CI* [1.07, 1.33]) and ART (*OR* 1.17, 95% *CI* [1.03, 1.32]) remained associated with an increased risk of BWD and parity (*OR* 0.77, 95% *CI* [0.69, 0.87]) with a reduced risk (data not shown).

Table 2 shows the distribution of the modality of delivery and the adverse neonatal outcomes according to the degree of weight discordance. Regarding the modality of delivery, in the group of BWD equal to 30% or more, cesarean sections during labor and cesarean sections without labor were over two-fold more common in comparison to the group of non-BWD. Preterm birth (61.2% vs. 69.0% vs. 83.6%, *p* trend ≤ .0001), low birth weight (when both twins experienced the outcome, 52.5% vs. 51.4% vs 67.7%, *p* trend

≤ .0001), small for gestational age (at least one twin, 17.9% vs. 46.7% vs. 80.8%, *p* trend ≤ .0001), low Apgar score (7 or less; at least one twin, 6.9% vs. 10.7% vs. 23.4%, *p* trend ≤ .0001), and perinatal mortality (at least one twin, 0.6% vs. 1.2% vs. 10.1%, *p* trend ≤ .0001) were more common in twins with a discordance equal to 30% or more with respect to those with discordance between 20–29%, with respect to those with a discordance less than 20%. Excluding preterm births from the cohort, the positive association between adverse outcomes and BWD was still observed (data not shown).

ART was inversely related to worst outcomes among both non-BWD and BWD twins (*RR* ranging from 14% to 6% from small for gestational age to preterm birth). No association was observed for perinatal mortality, probably due to the low statistical power (Table 3). Results were confirmed, also lowering the cut-off of discordance to 20% (data not shown).

Discussion

In the current study, pairs of twins affected by a 30% or more disparity in birth weights between the larger and the smaller twin represented about 5% of a cohort of same-sex twins in Lombardy, Northern Italy, during the period 2007–2021. BWD was more common in women aged 35 years or more and those undergoing ART, but less frequent in parous women. The adverse neonatal outcomes observed (i.e., preterm birth, low birth weight, low Apgar score, SGA, and perinatal mortality) were more frequent among BWD twins.

As a concern for potential risk factors, we found that advanced maternal age (i.e., ≥35 years) was related to proneness to have a BWD, even if the association was of borderline significance. This finding is consistent with previous analyses conducted in populations from the United States and, more recently, from a tertiary care center in India (Konar *et al.*, 2016; Sannoh *et al.*, 2003; Wen *et al.*, 2005). All over the world, especially in high-income countries, maternal age at birth is rising. Thus, the evaluation of the consequences of this trend represents an issue of utmost importance because older maternal age has been associated with an increased risk of several adverse perinatal outcomes (Frick, 2021). We also observed a positive relation between lower educational levels and BWD, as previous studies found (Azcorra *et al.*, 2021; Kim *et al.*, 2019; Luo *et al.*, 2006; Tan *et al.*, 2005). This condition may reflect lower incomes and unhealthier behaviors and influence the access to perinatal care, compromising the management of the course of pregnancy and delaying appropriate interventions. We also found that advanced maternal age (i.e., ≥35 years) was related to proneness to have a BWD, even if the association was of borderline significance. Regarding the use of ART, we confirmed the previously observed (Koudstaal *et al.*, 2000; Pinborg *et al.*, 2004; Zadori *et al.*, 2004) increased risk of BWD among women undergoing these techniques versus those conceiving spontaneously. In addition, we also confirm primiparity findings (Blickstein *et al.*, 2000; Sannoh *et al.*, 2003); in our cohort, parous women had about 25% reduced risk of BWD. Regarding the chorionicity, if dichorionic twins have completely separate circulation systems during intrauterine life, about 95% of monochorionic twins have vascular anastomoses on the single placental surface that connects the two circulations (Denbow *et al.*, 2000; Lewi *et al.*, 2007). In monochorionic pregnancies, placental vascular anastomoses leads to twin-to-twin transfusion in 15% of cases, resulting in an asymmetric growth of the fetus (Hack *et al.*, 2008). On the other hand, opposite-sex twins also showed an increased risk for BWD compared to

Table 3. Adverse neonatal outcomes among birth weight discordance (BWD) and non-BWD pairs of twins according to mode of conception (i.e., spontaneous and after assisted reproductive technologies [ART]), Lombardy, 2007–2021

	BWD			Non-BWD		
	Spontaneous <i>n</i> (%)	ART <i>n</i> (%)	RR (95% CI)	Spontaneous <i>n</i> (%)	ART <i>n</i> (%)	RR
Preterm birth	678 (84.3)	252 (81.8)	0.94 (0.92, 0.96)	10262 (62.7)	2826 (60.0)	0.93 (0.91-0.96)
Low birth weigh	672 (83.6)	258 (83.8)	0.94 (0.92, 0.96)	10418 (63.7)	2972 (63.1)	0.93 (0.91-0.96)
Small for gestational age	420 (52.2)	153 (49.7)	0.86 (0.80, 0.92)	2660 (16.3)	721 (15.3)	0.84 (0.77-0.90)
Apgar score	123 (15.3)	35 (11.4)	0.82 (0.71, 0.96)	798 (4.9)	185 (3.9)	0.82 (0.69-0.97)
Perinatal mortality	46 (5.7)	14 (4.6)	0.82 (0.53, 1.29)	76 (0.5)	12 (0.3)	0.67 (0.36-1.28)

Note: RR, relative risk.

same-sex twins (Azcorra et al., 2021), and it has been reported that females of opposite-sex twin pairs have a significantly increased risk of being growth discordant (Blickstein & Weissman, 1990); this finding may be justified by the higher measures of males in terms of birth weight and length (Parazzini et al., 1995). The debate regarding the influence of the own sex and also of the sex of cotwin on the birth weight is still ongoing.

The management of BWD is challenging since no evidence assessing the different management options (expectant and intervention management) is available. In particular, prenatal identification of BWD may lead to a iatrogenic delivery before the term of pregnancy, attributing the aftermath of prematurity on both twins, regardless of whether one of the two may have a physiological growth.

Although some studies have identified BWD as an independent risk factor for adverse perinatal consequences (Blickstein et al., 2006; D'Antonio, Odibo et al., 2018; D'Antonio, Thilaganathan et al., 2018; Di Mascio et al., 2019; Harper et al., 2013; Hartley et al., 2002; Wen et al., 2005; Yinon et al., 2005) others have attributed the morbidity and mortality observed in discordant pairs to confounding factors (Cooperstock et al., 2000; Fraser et al., 1994; Frezza et al., 2011; Konar et al., 2016; Patterson & Wood, 1990), especially to preterm birth.

In our study we also evaluated the relationship between BWD and selected adverse outcomes. As shown previously by other studies and as can be expected from BWD management alternatives mentioned above, we observed that preterm births were more common among BWD twins compared with non-BWD twins. In general, all the other outcomes considered (i.e., low birth weight, SGA, low Apgar score, and perinatal mortality) were more frequent among BWD births. A recent study found that BWD infants had a higher antibiotic prescription rate than the concordant ones, even though the strep test results and newborn septicemia rates were similar, showing that BWD twins required early respiratory support (Jahanfar et al., 2017). As we found that BWD twins frequently obtained a low Apgar score, our results are consistent with this finding. We also observed a higher proportion of perinatal deaths among BWD twins. A systematic review investigating perinatal mortality reported that both dizygotic and monozygotic twin pregnancies discordant were at higher risk of intrauterine death but not of neonatal death compared with pregnancies with concordant ones, especially when at least one fetus was SGA (D'Antonio, Odibo et al., 2018).

Given the widespread use of ART, its great contribution to the conception of twins, and the evidence that ART may increase the risk of BWD (Daniel et al., 2000; Koudstaal et al., 2000; Pinborg et al., 2004; Zadori et al., 2004; Zhang et al., 2013), we investigated

the role of ART on BWD outcomes. An analysis focusing on this topic suggested that the possible differences in the management of pregnancies after ART and spontaneous ones could moderate the sequelae of BWD (Zadori et al., 2004). In our cohort, the proportion of all adverse outcomes investigated was higher among spontaneous than ART pregnancies in both discordant and nondiscordant twins.

Some study limitations need to be considered. First, data for this study were exclusively based on inpatient information, thus clinical diagnoses given in an outpatient setting or not recorded as one of the patient diagnoses in hospitalizations for delivery or during pregnancy were missing. Thus, no hypotheses could be made about the pathophysiological clinical pathway leading to BWD, such as unequal placental sharing, abnormalities of umbilical cord insertion, placental dysfunctions, and twin-to twin-transfusion. We tried to identify births reported in the corresponding SDO a code, in the main or in the secondary diagnoses, related to such conditions, but often even if reporting poor fetal growth, the underlying mechanism was not specified. Second, we decided to include only same-sex twins in the study cohort due to the well-known disparity in terms of birth weight and length between males and females. In this way, we included all the monozygotic pregnancies in a higher proportion than in the general population. In addition, another limitation of the study was the inability to distinguish the dizygotic from monozygotic pregnancies. According to the probabilistic Weinberg's method (Weinberg, 1901) assuming that sex gender is independently distributed in dizygotic, compared to monozygotic pregnancies, in our cohort, the difference between the total number of twins and twice the number of opposite-sex twins provides an estimated number of monozygotic twins of 4460, resulting in a proportion of 40.2%, higher compared with the proportion observed in the general population (31.7% estimated in spontaneously conceived twins in Lombardy, 2007–2017; Esposito et al., 2022). The major strength of the study is its population-based design, whereby a large cohort of twins is available over a span of more than 10 years.

In conclusion, the presence of BWD complicates twin pregnancies, compromising neonatal outcomes. Further evidence is needed to better identify potential risk factors and interventions to limit adverse consequences in order to improve the management strategy in BWD twins.

Availability of data and materials. The data that support the findings of this study are available from Lombardy Region, but restrictions apply to the availability of these data, which were used under license for the current study. The data used in this study cannot be made available in the manuscript, the supplemental files or in a public repository due to Italian data protection laws.

The anonymized datasets generated during and/or analyzed during the current study can be provided on reasonable request, from the corresponding author, after written approval by the Lombardy region.

Funding. This work was supported by a research grant from the Italian Ministry of Education, University and Research (“PRIN” 2017, project 2017728JPK). The grant provides financial support for the analysis of data.

Disclosure of interests. Giovanni Corrao received research support from the European Community (EC), the Italian Agency of Drugs (AIFA), and the Italian Ministry for University and Research (MIUR). He took part in a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN and BMS). He also received honoraria as a member of the advisory board to Roche. The other authors declare that they have no conflicts of interest to disclose.

Ethics approval and consent to participate. According to Italian law, studies based entirely on registry data do not require approval from an ethics review board.

References

- Azcorra, H., Rodriguez, L., & Mendez, N. (2021). The association between maternal and foetal factors with birth weight discordance in twins from Yucatan, Mexico. *Annals of Human Biology*, 48, 153–156. <https://doi.org/10.1080/03014460.2021.1921847>
- Blickstein, I., & Goldman, R. D. (2003). Intertwin birth weight discordance as a potential adaptive measure to promote gestational age. *Journal of Reproductive Medicine*, 48, 449–454.
- Blickstein, I., Goldman, R. D., & Mazkereth, R. (2000). Adaptive growth restriction as a pattern of birth weight discordance in twin gestations. *Obstetrics and Gynecology*, 96, 986–990. doi: [10.1016/S0029-7844\(00\)01079-6](https://doi.org/10.1016/S0029-7844(00)01079-6)
- Blickstein, I., Goldman, R. D., Smith-Levitin, M., Greenberg, M., Sherman, D., & Rydstroem, H. (1999). The relation between inter-twin birth weight discordance and total twin birth weight. *Obstetrics and Gynecology*, 93, 113–116. doi: [10.1016/S0029-7844\(98\)00343-3](https://doi.org/10.1016/S0029-7844(98)00343-3)
- Blickstein, I., Mincha, S., Goldman, R. D., Machin, G. A., & Keith, L. G. (2006). The Northwestern twin chorionicity study: testing the ‘placental crowding’ hypothesis. *Journal of Perinatal Medicine*, 34, 158–161. <https://doi.org/10.1515/jpm.2006.028>
- Blickstein, I., & Weissman, A. (1990). Birth-weight discordancy in male-1st and female-1st pairs of unlike-sexed twins. *American Journal of Obstetrics and Gynecology*, 162, 661–663. [https://doi.org/10.1016/0002-9378\(90\)90977-F](https://doi.org/10.1016/0002-9378(90)90977-F)
- Breathnach, F. M., McAuliffe, F. M., Geary, M., Daly, S., Higgins, J. R., Dornan, J., Morrison, J. J., Burke, G., Higgins, S., Dicker, P., Manning, F., Mahony, R., Malone, F. D., & Perinatal Ireland Research Consortium. (2011). Definition of intertwin birth weight discordance. *Obstetrics and Gynecology*, 118, 94–103. <https://doi.org/10.1097/AOG.0b013e31821fd208>
- BreathnachMd, F. M., & Malone, F. D. (2012). Fetal growth disorders in twin gestations. *Seminars in Perinatology*, 36, 175–181. <https://doi.org/10.1053/j.semperi.2012.02.002>
- Cheetham, C. (2007). Perinatal death in twins ¼ Absolute risk: Better basis for decision making. *British Medical Journal*, 334, 651–652. doi: [10.1136/bmj.39164.420150.1F](https://doi.org/10.1136/bmj.39164.420150.1F)
- Cooperstock, M. S., Tummaru, R., Bakewell, J., & Schramm, W. (2000). Twin birth weight discordance and risk of preterm birth. *American Journal of Obstetrics and Gynecology*, 183, 63–67. [https://doi.org/10.1016/S0002-9378\(00\)55604-X](https://doi.org/10.1016/S0002-9378(00)55604-X)
- D’Antonio, F., Odibo, A. O., Prefumo, F., Khalil, A., Buca, D., Flacco, M. E., Liberati, M., Manzoli, L., & Acharya, G. (2018). Weight discordance and perinatal mortality in twin pregnancy: Systematic review and meta-analysis. *Ultrasound in Obstetrics & Gynecology*, 52, 11–23. <https://doi.org/10.1002/uog.18966>
- D’Antonio, F., Thilaganathan, B., Laoreti, A., Khalil, A., Bahamie, A., Bhide, A., Deans, A., Egbor, M., Ellis, C., Gandhi, H., Hamid, R., Hutt, R., Matiluko, A., Morgan, K., Pakarian, F., Papageorgiou, A., Peregrine, E., Roberts, L., & Southwest Thames Obstetric Research Collaborative (STORK). (2018). Birth-weight discordance and neonatal morbidity in twin pregnancy: Analysis of STORK multiple pregnancy cohort. *Ultrasound in Obstetrics & Gynecology*, 52, 586–592. <https://doi.org/10.1002/uog.18916>
- Daniel, Y., Ochshorn, Y., Fait, G., Geva, E., Bar-Am, A., & Lessing, J. B. (2000). Analysis of 104 twin pregnancies conceived with assisted reproductive technologies and 193 spontaneously conceived twin pregnancies. *Fertility and Sterility*, 74, 683–689. [https://doi.org/10.1016/S0015-0282\(00\)01491-6](https://doi.org/10.1016/S0015-0282(00)01491-6)
- Dawson, A. L., Tinker, S. C., Jamieson, D. J., Hobbs, C. A., Rasmussen, S. A., Reefhuis, J., & National Birth Defects Prevention Study. (2015). Epidemiology of twinning in the National Birth Defects Prevention Study, 1997 to 2007. *Birth Defects Research Part A: Clinical and Molecular Teratology*, 103, 85–99. <https://doi.org/10.1002/bdra.23325>
- Denbow, M. L., Cox, P., Taylor, M., Hammal, D. M., & Fisk, N. M. (2000). Placental angioarchitecture in monochorionic twin pregnancies: Relationship to fetal growth, fetofetal transfusion syndrome, and pregnancy outcome. *American Journal of Obstetrics and Gynecology*, 182, 417–426. doi: [10.1016/S0002-9378\(00\)70233-X](https://doi.org/10.1016/S0002-9378(00)70233-X)
- Di Mascio, D., Acharya, G., Khalil, A., Odibo, A., Prefumo, F., Liberati, M., Buca, D., Manzoli, L., Flacco, M. E., Brunelli, R., Benedetti Panici, P., & D’Antonio, F. (2019). Birthweight discordance and neonatal morbidity in twin pregnancies: A systematic review and meta-analysis. *Acta Obstetrica et Gynecologica Scandinavica*, 98, 1245–1257. <https://doi.org/10.1111/aogs.13613>
- Eriksson, A. W., & Fellman, J. (2007). Temporal trends in the rates of multiple maternities in England and Wales. *Twin Research and Human Genetics*, 10, 626–632. <https://doi.org/10.1375/twin.10.4.626>
- Esposito, G., Dalmartello, M., Franchi, M., Mauri, P. A., Cipriani, S., Corrao, G., & Parazzini, F. (2022). Trends in dizygotic and monozygotic spontaneous twin births during the period 2007–2017 in Lombardy, Northern Italy: A population-based study. *Twin Research and Human Genetics*, 25, 149–155. <https://doi.org/10.1017/thg.2022.19>
- Fraser, D., Picard, R., Picard, E., & Leiberman, J. R. (1994). Birth weight discordance, intrauterine growth retardation and perinatal outcomes in twins. *Journal of Reproductive Medicine*, 39, 504–508.
- Frezza, S., Gallini, F., Puopolo, M., De Carolis, M. P., D’Andrea, V., Guidone, P. I., Luciano, R., Zuppa, A. A., & Romagnoli, C. (2011). Is growth-discordance in twins a substantial risk factor in adverse neonatal outcomes? *Twin Research and Human Genetics*, 14, 463–467. <https://doi.org/10.1375/twin.14.5.463>
- Frick, A. P. (2021). Advanced maternal age and adverse pregnancy outcomes. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 70, 92–100. <https://doi.org/10.1016/j.bpobgyn.2020.07.005>
- Fuster, V., Zuluaga, P., Colantonio, S., & de Blas, C. (2008). Factors associated with recent increase of multiple births in Spain. *Twin Research and Human Genetics*, 11, 70–76. <https://doi.org/10.1375/twin.11.1.70>
- Hack, K. E. A., Nikkels, P. G. J., Koopman-Esseboom, C., Derks, J. B., Elias, S. G., van Gemert, M. J. C., & Visser, G. H. A. (2008). Placental characteristics of monochorionic diamniotic twin pregnancies in relation to perinatal outcome. *Placenta*, 29, 976–981. <https://doi.org/10.1016/j.placenta.2008.08.019>
- Harper, L. M., Weis, M. A., Odibo, A. O., Roehl, K. A., Macones, G. A., & Cahill, A. G. (2013). Significance of growth discordance in appropriately grown twins. *American Journal of Obstetrics and Gynecology*, 208, 393 e391–395. <https://doi.org/10.1016/j.ajog.2013.01.044>
- Hartley, R. S., Hitti, J., & Emanuel, I. (2002). Size-discordant twin pairs have higher perinatal mortality rates than nondiscordant pairs. *American Journal of Obstetrics and Gynecology*, 187, 1173–1178. <https://doi.org/10.1067/mob.2002.126961>
- Homola, W., Florjanski, J., Krolak-Olejnik, B., Fuchs, T., Lachowska, M., & Bek, W. (2019). The impact of chorionicity and the type of twin growth on the early neonatal outcome in twin pregnancies ¼ 20 years of experience from one tertiary perinatal center. *Taiwanese Journal of Obstetrics and Gynecology*, 58, 482–486. <https://doi.org/10.1016/j.tjog.2019.05.009>

- Jahanfar, S., Lim, K., & Ovideo-Joekes, E. (2017). Birth weight discordance and adverse perinatal outcomes. *Journal of Perinatal Medicine*, 45, 603–611. <https://doi.org/10.1515/jpm-2016-0089>
- Jahanfar, S., Lim, K., & Ovideo-Joekes, E. (2016). Optimal threshold for birth weight discordance: Does knowledge of chorionicity matter? *Journal of Perinatology*, 36, 704–712. <https://doi.org/10.1038/jp.2016.82>
- Kim, L. H., Caughey, A. B., Yee, L. M., & Cheng, Y. W. (2019). Association between the degree of twin birthweight discordance and perinatal outcomes. *American Journal of Perinatology*, 36, 969–974. <https://doi.org/10.1055/s-0038-1675769>
- Konar, H., Sarkar, M., & Paul, J. (2016). Perinatal outcome of the second twin at a tertiary care center in India. *Journal of Obstetrics and Gynecology of India*, 66, 441–447. <https://doi.org/10.1007/s13224-015-0724-7>
- Koudstaal, J., Bruinse, H. W., Helmerhorst, F. M., Vermeiden, J. P. W., Willemsen, W. N. P., & Visser, G. H. A. (2000). Obstetric outcome of twin pregnancies after in-vitro fertilization: A matched control study in four Dutch University hospitals. *Human Reproduction*, 15, 935–940. <https://doi.org/DOI10.1093/humrep/15.4.935>
- Lewi, L., Cannie, M., Blickstein, I., Jani, J., Huber, A., Hecher, K., Dymarkowski, S., Gratacos, E., Lewi, P., & Deprest, J. (2007). Placental sharing, birthweight discordance, and vascular anastomoses in monozygotic diamniotic twin placentas. *American Journal of Obstetrics and Gynecology*, 197, e1–8. doi: 10.1016/j.ajog.2007.05.009
- Luo, Z. C., Wilkins, R., Kramer, M. S., & Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. (2006). Effect of neighbourhood income and maternal education on birth outcomes: A population-based study. *CMAJ*, 174, 1415–1420. <https://doi.org/10.1503/cmaj.051096>
- Miller, J., Chauhan, S. P., & Abuhamad, A. Z. (2012). Discordant twins: Diagnosis, evaluation and management. *American Journal of Obstetrics and Gynecology*, 206, 10–20. <https://doi.org/10.1016/j.ajog.2011.06.075>
- Parazzini, F., Cortinovis, I., Bortolus, R., Fedele, L., & Decarli, A. (1995). Weight at Birth by Gestational-Age in Italy. *Human Reproduction*, 10, 1862–1863. doi: 10.1093/oxfordjournals.humrep.a136192
- Patterson, R. M., & Wood, R. C. (1990). What is twin birth-weight discordance. *American Journal of Perinatology*, 7, 217–219. doi: 10.1055/s-2007-999485
- Pinborg, A., Loft, A., Rasmussen, S., Schmidt, L., Langhoff-Roos, J., Greisen, G., & Andersen, A. N. (2004). Neonatal outcome in a Danish national cohort of 3438 IVF/ICSI and 10 362 non-IVF/ICSI twins born between 1995 and 2000. *Human Reproduction*, 19, 435–441. <https://doi.org/10.1093/humrep/deh063>
- Rankin, J., Pearce, M. S., Bell, R., Glinianaia, S. V., & Parker, L. (2005). Perinatal mortality rates: Adjusting for risk factor profile is essential. *Paediatric and Perinatal Epidemiology*, 19, 56–58. <https://doi.org/DOI10.1111/j.1365-3016.2004.00625.x>
- Sannoh, S., Demissie, K., Balasubramanian, B., & Rhoads, G. G. (2003). Risk factors for intrapair birth weight discordance in twins. *Journal of Maternal-Fetal and Neonatal Medicine*, 13, 230–236. <https://doi.org/10.1080/jmf.13.4.230.236>
- Suzuki, S., & Murata, T. (2007). The influence of assisted reproductive technology on growth discordance in dichorionic twin pregnancies. *Fetal Diagnosis and Therapy*, 22, 372–376. <https://doi.org/10.1159/000103299>
- Tan, H. Z., Wen, S. W., Fung, K. F. K., Walker, M., & Demissie, K. (2005). The distribution of intra-twin birth weight discordance and its association with total twin birth weight, gestational age, and neonatal mortality. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 121, 27–33. <https://doi.org/10.1016/j.ejogrb.2004.10.012>
- Vergani, P., Locatelli, A., Ratti, M., Scian, A., Pozzi, E., Pezzullo, J. C., & Ghidini, A. (2004). Preterm twins: What threshold of birth weight discordance heralds major adverse neonatal outcome? *American Journal of Obstetrics and Gynecology*, 191, 1441–1445. <https://doi.org/10.1016/j.ajog.2004.05.053>
- Victoria, A., Mora, G., & Arias, F. (2001). Perinatal outcome, placental pathology, and severity of discordance in monozygotic and dichorionic twins. *Obstetrics and Gynecology*, 97, 310–315. [https://doi.org/DOI10.1016/S0029-7844\(00\)01111-X](https://doi.org/DOI10.1016/S0029-7844(00)01111-X)
- Vogel, J. P., Torloni, M. R., Seuc, A., Betran, A. P., Widmer, M., Souza, J. P., & Merialdi, M. (2013). Maternal and perinatal outcomes of twin pregnancy in 23 low- and middle-income countries. *PLoS One*, 8, e70549. <https://doi.org/ARTNe7054910.1371/journal.pone.0070549>
- Weinberg, W. (1901). Beiträge zur physiologie und pathologie der mehrlingsgeburten beim Menschen. *Pflügers Archiv für Gesamte Physiologie*, 88, 346–350.
- Wen, S. W., Fung, K. F. K., Huang, L., Demissie, K., Joseph, K. S., Allen, A. C., Kramer, M. S., & Cana, F. I. H. S. G. (2005). Fetal and neonatal mortality among twin gestations in a Canadian population: The effect of intrapair birthweight discordance. *American Journal of Perinatology*, 22, 279–286. <https://doi.org/10.1055/s-2005-870899>
- Yang, H., Choi, Y. S., Nam, K. H., Kwon, J. Y., Park, Y. W., & Kim, Y. H. (2011). Obstetric and perinatal outcomes of dichorionic twin pregnancies according to methods of conception: Spontaneous versus in-vitro fertilization. *Twin Research and Human Genetics*, 14, 98–103. <https://doi.org/10.1375/twin.14.1.98>
- Yinon, Y., Mazkereth, R., Rosentzweig, N., Jarus-Hakak, A., Schiff, E., & Simchen, M. J. (2005). Growth restriction as a determinant of outcome in preterm discordant twins. *Obstetrics and Gynecology*, 105, 80–84. <https://doi.org/10.1097/01.AOG.0000146634.28459.e8>
- Zadori, J., Kozinszky, Z., Orvos, H., Katona, M., Kaali, S. G., & Pal, A. (2004). Birth weight discordance in spontaneous versus induced twins: Impact on perinatal outcome. *Journal of Assisted Reproduction and Genetics*, 21, 85–88. <https://doi.org/DOI10.1023/B:JARG.0000027019.87795.4e>
- Zhang, X. R., Liu, J., & Zeng, C. M. (2013). Perinatal risk factors and neonatal complications in discordant twins admitted to the neonatal intensive care unit. *Chinese Medical Journal*, 126, 845–849. <https://doi.org/10.3760/cma.j.issn.0366-6999.20121957>