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The impact of chorionicity on pregnancy outcome and neurodevelopment at 2 years old among twins born preterm: the EPIPAGE-2 cohort study.

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Short title: Chorionicity and short- and mid-term outcome

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Abstract

Objective: To compare the short and mid-term outcomes of preterm twins by chorionicity of pregnancy.

Design: Prospective nation-wide population-based EPIPAGE-2 cohort study.

Setting: 546 maternity units in France, between March and December 2011.

Population: A total of 1700 twin neonates born between 24-34 weeks of gestation.

Methods: The association of chorionicity with outcomes was analyzed using multivariate regression models.

Main Outcome Measures: First, survival at 2-years corrected age with or without neurosensory impairment and secondarily perinatal, short- and mid-term outcomes (survival at discharge, survival at discharge without severe morbidity) were described and compared by chorionicity.

Results: In the EPIPAGE 2 cohort, 1700 preterm births were included (850 twin pregnancies). 1220 (71.8%) were from Dichorionic (DC) pregnancies and 480 from monochorionic (MC) pregnancies. MC pregnancies had three times more medical terminations than DC pregnancies (1.67% vs 0.51%, $p < 0.001$) while there were three times more stillbirths in MC than in DC pregnancies (10.09% vs 3.78%, $p < 0.001$). Both twins were alive at birth in 86.6% of DC pregnancies compared to 80.0% among MC pregnancies ($p = 0.008$). No significant difference according to chorionicity was found regarding neonatal deaths and morbidities. Likewise, for children born earlier than 32 weeks, the two-year follow-up neurodevelopmental results were not significantly different between DC and MC twins.

Conclusions: This study confirms that MC pregnancies have a higher risk of adverse outcomes. However, the outcomes among preterm twins admitted to neonatal intensive care units are similar irrespective of chorionicity.

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Tweetable abstract:

Monochorionicity is associated with adverse perinatal outcomes but outcomes for preterm twins are comparable irrespective of their chorionicity.

Introduction

In 2016, the twin birth rate in France was 1.8%,[1] close to the European average, while the twin birth rate in the United States' was 3.5% .[2] Generally, 40 to 60% of twins are born before 37 weeks' gestational age (weeks) inducing subsequent neonatal complications and long term impacts on morbidity.[2,3] In France, 44.3% of twin births are preterm with a relative risk of preterm birth of 8.8 (95% IC 7.8-10.0) compared to singleton pregnancies.[1,3,4] The frequency of intrauterine growth restriction of one or both fetuses is significant among twin pregnancies.[5,6] Small size studies have shown evidence about the difference in outcome of preterm infant born from MC vs DC pregnancies, MC had with specific complications (twin-twin transfusion syndrome (TTTS), selective intrauterine growth restrictions, twin anemia polycythemia sequences (TAPS), and acute feto-fetal hemorrhages subsequent to a single intrauterine fetal death).[2-4,7] Over the long term, children born from twin pregnancies have an increased risk of neurological morbidity compared to singleton births.[7-10] Compared to dichorionic (DC) pregnancies, monochorionic (MC) pregnancies are likely to deliver more preterm and lower birth weight babies and to display an excess of neonatal morbidity and mortality (death, intraventricular hemorrhage (IVH) grade III or IV, necrotizing enterocolitis (NEC) and neonatal anemia).[11-15]At 2 years, neuro-developmental difficulties are more marked in MC twins compared to DC twins.[13-17]
However, there is a lack of current, reliable and relevant descriptive data concerning chorionicity at early gestational ages. Our objective was to compare outcomes of pregnancy in a population born preterm twins by chorionicity using data from the EPIPAGE 2 cohort (Etude épidémiologique sur les petits âges gestationnels). We hypothesised that MC preterm twins had more adverse outcomes in the perinatal period and at two-years than DC preterm twins.

Materials and Methods

Setting and data collection of the EPIPAGE-2 cohort study

This is a secondary analysis of EPIPAGE-2, a prospective, national, population-based cohort study of preterm infants born in France in 2011.[18] All live births, stillbirths and terminations of pregnancy at 22 $^{0/7}$ to 34 $^{0/7}$ weeks (when a fetus is diagnosed with a severe, lethal or incurable disease, French legislation authorizes a termination of pregnancy (TOP) for medical reasons, until full term (Law No. 75-17 of 17 January 1975 or Veil Law; Art. 162-12)), whose parents had not declined to participate, were included in 546 maternity units in 25 French administrative regions (all but one). The number of infants required according to our sample size calculations was provided by an 8-month recruitment period for births at 22 through 26 weeks, a 6-month period for 27 through 31 weeks, and a 5-week period for 32 through 34 weeks.[18]. Maternal, obstetric, and neonatal data were collected from medical records following a standardized protocol. Full details of the cohort recruitment and data collection were previously reported elsewhere.[18] The EPIPAGE-2 cohort study was implemented to describe short- as well as long-term outcomes among preterm infants. For that purpose, in children included in follow-up, a detailed neurological and sensory examination was performed by the referring physician at 2 years corrected age.[20]
This study was approved by the National Data Protection Authority (CNIL no.911009), the Consultative Committee on the Treatment of Data on Personal Health for Research Purposes (Reference no. 10.626), and the Committee for the Protection of People Participating in Biomedical Research (reference CPP SC-2873).

Patient involvement

Patients were not involved in designing the EPIPAGE-2 cohort study, or in making decisions about research questions and outcome measures. However, parents of preterm infants provided massive support to the study through high participation and follow-up rates. National parents' associations assisted with the dissemination of the results.

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Participants

Our twin pregnancy study's population encompassed all the women and their newborns whose attending obstetrician had confirmed chorionicity (MC or DC), defined ultrasonographically with a lambda or T-sign until 16 weeks of gestation.[18, 19] We excluded twin neonates born from a triple pregnancy, twin neonates whose chorionicity was not available, and twin neonates whose co-twin was not included in the EPIPAGE 2 study (intrauterine death before 22 weeks).

Outcomes

The primary outcome was two-year survival without neurosensory impairments, defined as cerebral palsy, deafness and blindness in children born < 32 weeks. We extracted data for cerebral palsy from the medical questionnaire, including information on major developmental steps (head control, sitting, standing, walking, and quality of gait), trunk and limb tone (low, normal, increased), and other abnormal neurological signs. Cerebral palsy was defined according to the criteria of the European Surveillance of Cerebral Palsy in Europe (SCPE) network.[22] Auditory and visual impairments were either unilateral or bilateral. Paediatricians in charge of routine follow-up performed the examinations. If a routine follow-up was unavailable, parents were asked to get their practitioner of choice to complete the medical questionnaire to ensure higher follow-up rates. The psychomotor development of those children free from cerebral palsy or sensory deficit was assessed using the 24-month Ages and Stages Questionnaire (ASQ). The ASQ was validated in France and completed by parents. A pathological ASQ score was defined as a score of less than two standard deviations in one of the five domains evaluated.[20]

Secondary outcomes were perinatal outcomes in all twin pregnancies and outcome preterm birth < 34 weeks included vital status, categorized as termination of pregnancy (TOP), antepartum stillbirth, death peripartum or in delivery room, death in neonatal intensive care unit (NICU) and survival at discharge. We also investigated survival at discharge without severe morbidity, i.e. without grades 3-4 IntraVentricular Haemorrhage (IVH),[23] cystic PeriVentricular Leukomalacia stages II or III (cPVL), Necrotizing EnteroColitis (NEC)[24] stage 3 or greater, retinopathy of prematurity (ROP)[25] stage 3 and/or laser treatment and severe bronchopulmonary dysplasia

(DBP), defined as requiring oxygen for at least 28 days in addition to the requirement of 30% or more oxygen and/or mechanical ventilator support or continuous positive airway pressure at 36 weeks' postmenstrual age.[26] We defined a neonatal morbidity criterion as a presence of: IVH 3 and/or IVH 4 and/or cPLV and/or DBP and/or ROP ≥3 and/or NEC ≥2. We defined the composite severity criterion as a neonatal morbidity and/or neonatal death.

Other perinatal data

Antenatal and obstetrical data were collected at birth. Gestational age was the best estimate based on the date of the last menstrual period and an early prenatal ultrasonogram. Complications related to MC twin gestations (TTTS is defined on ultrasound by the association of polyuric polyhydramnios in one sac with a deepest vertical pool of amniotic fluid (DVPAF) of at least 8 cm before or 10 cm after 20 weeks, together with oligouric oligohydramnios in the other sac with a DVPAF of at most 2 cm.[27]

Laser surgery was offered if TTTS was diagnosed before 26 weeks' gestation. Expectant management, serial amniodrainage, or elective preterm birth was offered for TTTS diagnosed after 26 weeks' gestation. Fetal weight discordancy was calculated according to the following formula = [(estimated weight of larger twin – estimated weight of smaller twin x 100) / estimated weight of larger twin]. Z-score birth weights were calculated from EPOPé intrauterine growth curves corrected for sex and gestational age.[21]

Classification of prematurity related to five causes in twins pregnancies[18] (Preterm labor, Preterm premature rupture of membranes, hypertensive disorders without suspected fetal growth restriction (FGR) or with suspected FGR, placental abruption after an uncomplicated pregnancy, suspected FGR without hypertensive disorders).

Statistical Analysis

Categorical variable data were described as numbers and percentages, and quantitative data were described by means and standard deviations or medians and inter-quartile ranges.

Analyses were based on the infant as the statistical unit, we thus estimated clustered robust standard errors that took into account the clustering of children within mother with twin pregnancies.

Comparative analysis was then carried out between MC and DC pregnancies.

Multiple linear regression analyses were performed to determine if outcomes were determined by chorionicity independently. These relations were studied without and then with adjustment for potential confounders identified in the literature: gender, weeks, growth restriction at birth (defined by a birthweight < 10th percentile according to Epopé curves),[21] maternal parity (primiparity versus multiparity), maternal educational level (number of completed years of education : some high school or less, high school diploma, some college, college diploma), language spoken at home (French only versus French and other language), assisted reproductive therapy, co-twin's death, TTTS, birth weight discordance and the cause of preterm.

In order to take into account the sampling strategy, observations were weighted with weights inversely proportional to the duration of the inclusion period of the gestational age class considered. Weights were 1.0 (35/35) for births at 24 to 26 weeks, 1.34 (35/26) at 27 to 31 weeks and 7.0 (35/5) at 32 to 34 weeks to ensure representativeness.

Attrition is a key issue in longitudinal cohort studies.[28,29] In this analysis, the proportion of infants alive at 2 years corrected age, eligible but lost to follow-up reached 17.7% (8.2% of all fetuses included). We performed multiple imputations with chained equations with a logistic regression imputation model for missing binary data and a multinomial imputation model for missing categorical data.

The association between chorionicity and outcomes was analyzed using multivariate regression models. This incorporated the explanatory confounding variables identified a priori, according to the literature data, as associated with the prognosis of preterm infants: sex, gestational age, birth weight <10th percentile, maternal education level, socio-economic level of the household. Outcomes were estimated within each of the 30 imputed datasets generated with 20 iterations, and results were pooled for a final analysis according to Rubin's rules. A sensitivity analysis was performed to take into account any missing data in the future or future explanatory variables by analyzing results after multiple imputations under the assumption of ignorable missing data. Analyzes were performed bilaterally, and the threshold of 0.05 was used to define significance. Statistical significance was set at two-tailed $p < .05$. Data were analyzed by use of Stata/SE 13.0 (StataCorp LP, College Station, TX, USA).

Results

There were 1.700 preterm births from 850 twin pregnancies with data regarding chorionicity. Of these, 1220 (71.8%) were from DC pregnancies, 480 (28.2%) from MC pregnancies. Among MC

pregnancies 52 (10.8%) neonates were from monoamniotic pregnancies and 428 (89.2%) from diamniotic pregnancies. Of the 1021 twins born < 32 weeks, who were alive at the discharge, we were able to evaluate 855 (83.7%) at the two years follow-up (225 (83.3%) were from MC and 630 (83.8%) from DC pregnancies) (Figure 1).

Pregnancy and neonatal outcomes by gestational age of live born preterm twin (table 1 and 2)

MC pregnancies had three times more medical terminations than DC pregnancies (1.67% vs 0.51%, p <0.001) while there were three times more stillbirths in MC than in DC pregnancies (10.09% vs 3.78%, p <0.001). Both twins were alive at birth in 86.6% of DC pregnancies compared to 80.0% among MC pregnancies (p = 0.008). If we consider all liveborn preterm twins, regardless of their gestational age, we found no significant differences according to the chorionicity regarding neonatal deaths and morbidities.

Among twins born before 28 weeks, the TTTS rate among MC pregnancies was 53.1%. There were no significant differences in the neonatal morbidity or in the mortality outcomes (Table S1). Among twins born between $28^{0/7}$ and $31^{6/7}$ weeks, there was a 30.6% TTTS. The rate of antenatal corticosteroid therapy at this period of gestational age was significantly higher in the MC group (83.3% vs 73.6%, p=0.04). By contrast, spontaneous prematurity (not induce labor) was significantly more common in the DC group (43.1% vs 26.0%, p<0.001). The discordance of estimated fetal weights greater than 20% and the birthweight <3°p were significantly more common in the MC group $28^{0/7}$ and $31^{6/7}$ weeks vs DC (respectively 37.9% vs 20.8, p=0.004 and 27.9% vs 15.9%, p<0.001). Between $28^{0/7}$ and $31^{6/7}$ weeks there was no statistically significant difference between groups regarding the neonatal morbidity and mortality. Beyond 32 weeks there were more newborns with birthweight <10°p in DC vs MC pregnancies (35.6 vs 21.8%, p=0.03).

Outcomes at 2 years corrected age of twin born before 32 weeks by chorionicity

The two-year follow-up neurodevelopmental results were not significantly different by chorionicity (Table 3) and by different gestational age intervals (Table S1). At 2 years, survival without neurosensory impairment was >96% with no significant difference after multivariate analysis (aOR 1.49 [0.44-5.07], p=0.52) and multiple imputation (aOR 2.42 [0.86-6.84], p=0.09) for MC compared to DC pregnancies. When excluding twins born from complicated TTTS pregnancies, the cerebral palsy rate was lower in MC vs DC pregnancies, but this difference was not significant (1.9% vs 3.0%, p=0.45) and confirmed after multivariate analysis and multiple imputation (Table 4).

We did not find any significant difference in perinatal twin's characteristics between those with and without follow-up at 2 years of corrected age, although more children born from pregnancies complicated by TTTS were lost to follow-up (19.25% vs 8.87%, p = 0.04) (Table S2).

Discussion

Main findings

Perinatal and two year outcomes of twins born before 32 weeks were not significantly different between MC and DC twin groups. In our study, while the probability of having two live births was significantly higher for DC twin pregnancies, MC and DC twins admitted to NICU had comparable survival and morbidity rates.

Strengths and Limitations

Strengths of our study include a very large sample of twins born very preterm, allowing us to report characteristics and outcomes stratified by week, and follow-up at 2 years corrected age. Unlike all published studies our sample is stemmed from a prospective population-based cohort at a national level, reflecting thus the diversity of antenatal management and outcomes from the "real-life" practices. We used standardized definitions for each outcome following international recommendations allowing to compare with the literature's data.

The main limitation of this study is the proportion of missing data related to loss to follow-up at 2 years corrected age, although attrition was moderate in relation to the cohort size and its geographical extent. The comparison of perinatal data between the follow-up and non-follow-up groups indicated that these children were comparable. Only the number of TTTSs differed significantly in the groups lost to follow-up. Appropriate statistical methods, with multiple imputations, enabled us to account for missing data and to obtain non-biased estimators.

Interpretation

The relative risk of intrauterine fetal death was 3.6 for MC twin compared to DC twin pregnancies.[30] For Hack in 2008, the risk of intrauterine fetal death was multiplied by 8.8 for MC twin pregnancy after 32 weeks.[13] Among the complication of MC pregnancies, the occurrence of TTTS is a risk factor of greater prematurity.[31] In our study, the TTTS rate was proportionally more

frequent in the subgroup less 28 weeks and between 28-31 $^{6/7}$ weeks (respectively 53.1 and 30.6%) in agreement with the literature's data.[32]

In the EPIPAGE 2 cohort study, growth discordance was significantly more common in the MC group, but the number of birth weight <10 ° p was significantly higher in the MC group only for the 28-31$^{6/7}$ weeks subgroup. Growth discordance, accompanied by an increased frequency of fetal growth restriction (FGR), is more common with MC twins. In cohort studies, with inclusion to term, the number of FGRs was higher among MC twins.[30, 32] FGR was found to be a risk factor for neonatal complications, which is neither independent of chorionicity[13] nor of the birth term.[33] The combination of MC and FGR was associated with negative neurological outcomes.[34] The FGR, more than the growth discrepancy was associated with a greater morbidity and mortality.[35, 36]

In our study, MC and DC twins admitted to NICU had a comparable survival and morbidity rate. The results in the literature are not consistent with some reporting a more negative perinatal outcome for MC twins.[33] A previous study, comparing to dichorionic twins (n = 29) and monochorionic twins without selective FGR (n = 32) delivered at 26-34 weeks, found more intraventricular Stage III and IV hemorrhages among MC twins.[37] In Hack et al., the occurrence of NEC was significantly higher in the MC group.[13] Conversely, in 2015 Garabedian et al found no differences in the occurrence of neonatal complications by chorionicity.[38] Acosta-Rojas et al, found similar perinatal outcomes for uncomplicated DC and MC twin pregnancies, after excluding TTTSs or FGRs.[14]

There are few longer-term neurodevelopment studies on twins based on chorionicity.

In this twin cohort, the rate of cerebral palsy was between 3-4%. It should be noted that nearly 40% of the children had a pathological ASQ at two years of age. These results are similar in singletons of EPIPAGE 2 cohort study.[20] Hack et al studied developmental outcomes and cerebral palsy rates in a cohort of twins (n= 366) who were born at term and showed no significant differences in developmental outcomes between MC and DC twins.[16] In 2009, a multicenter prospective cohort study, which excluded CP children, compared the outcome of 282 twins at 22 months of age. The authors found no significant differences between the psychomotor outcomes between the two groups MC and DC twin.[38]

Two more recent studies focused on the neurodevelopment of twins at three years of age according to their chorionicity. Kawamura et al, in a retrospective and single-center study of 162 twins born between 22 and 38 $^{6/7}$ weeks, found that monochorionicity was not an independent risk factor for a composite score (CP, mental retardation, death).[15] In 2018, Ichinomiya et al published

a retrospective and multicenter study of 1582 twins (50% follow-up rate). This study, which included children born with a birth weight of less than 1500 g, showed no significant differences on the overall development scores. Only the 'social-language' developmental quotient was significantly different to the detriment of the MC twins infants.[17] Halling et al, in a cohort of 230 preterm or term twins, reported a lower composite-language and motor score in growth-discordant MC vs. DC twins.[39]

Conclusion

This study confirms that monochorionic pregnancies are at increased risk of adverse perinatal outcomes but once admitted to neonatal intensive care units, the outcomes for preterm twins are comparable irrespective of their chorionicity. Likewise, the two year outcomes for twins born before 32 weeks and alive at discharge do not differ between MC and DC groups, even after adjusting for confounding factors. Our data could guide recommendations and tools for personalization in the domains of organization, decision-making, content, and style of prenatal counseling.

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Contribution to Authorship

Study concept and design of the EPIPAGE-2 study: FG.

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Ethics Approval

As required by French law and regulations, EPIPAGE 2 was approved by the national data protection authority (Comission Nationale de l'Informatique et des Libertés, CNIL n°911009), the appropriate ethics committees (CCTIRS: Comité Consultatif sur le Traitement de l'Information en matière de Recherche, approval granted November 18, 2010) and the committee for the protection of people participating in biomedical research (CPP: Comité de Protection des Personnes, approval granted March 18, 2011).

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Table S1. Comparison of twins with and without follow up at 2 years of corrected age.

Figure legend:

Figure 1 – flow chart

Description of figure 1:

The flow chart summarizes how the sample size of the analysis was reached.

Legends of figure 1:

Fetal loss: selective therapeutic interruption of pregnancy, spontaneous miscarriage, embryo reduction;

Table 1: Comparison of maternal, fetal and obstetric characteristics by chorionicity.

	Dichorionic pregnancies (n=610) N (%)	**Monochorionic pregnancies** (n=240) N (%)	**Weighted p-value**
Maternal characteristics			
Maternal Age (years, mean +/-SD)	31.21 (+/- 5.22)	29.24 (+/-5.66)	<0.001
Maternal Smoking	97 (15.67)	42 (18.94)	0.41
Mother's educational level			
≤ High school	195 (39.88)	78 (47.51)	
≤ 2 years post baccalaureate	104 (22.22)	34 (22.99)	0.34
Fetal and obstetric characteristics			
ART	251 (43.63)	16 (8.10)	<0.001
Prenatal diagnosis	20 (18.04)	28 (33.26)	0.08
Pregnancy outcome			
Embryo Reduction	3 (0.60)	0 (0)	0.86
Selective pregnancy termination	4 (0.66)	5 (1.12)	0.52
Spontaneous abortion of one of the fetuses	2 (0.15)	1 (0.19)	0.44
TTTS	-	77 (23.26)	-
Treatment of TTTS			
Laser	-	35 (54.57)	-
Amniodrainage	-	31 (49.40)	-
FGR			
1 fetus	95 (18.40)	58 (21.20)	0.49
2 fetuses	26 (4.53)	13 (6.41)	0.45
Discordancy EFW> 20%	68 (14.45)	47 (27.33)	0.008
Complete ACS	367 (68.10)	143 (70.22)	0.66
Magnesium sulfate	29 (3.40)	15 (3.63)	0.86
Cause of preterm birth			
Preterm labor	327 (62.04)	81 (50.03)	
PPROM	144 (21.29)	42 (28.28)	
Preterm labor + PPROM	3 (1.02)	2 (0.57)	0.29
Vascular Pathology	52 (9.24)	11 (10.45)	
FGR only	24 (6.41)	24 (10.67)	
Spontaneous Prematurity,	414 (69.52)	111 (50.88)	<0.001
Cesarean section	648 (53.84)	260 (58.65)	0.36
Gestational age (weeks, mean (+/-SD))	31.7 (+/-3.1)	31.4 (+/-3.3)	0.21
22-23 weeks	50 (8.1)	27 (11.2)	
24-27 weeks	160 (26.2)	51 (21.2)	0.28
28-31 weeks	253 (41.4)	118 (49.1)	
32-34 weeks	147 (24.0)	44 (18.3)	
Number of liveborn infants			
0	89 (5.69)	58 (11.17)	
1	85 (7.77)	35 (8.84)	0.008
2	436 (86.55)	147 (79.99)	

Abbreviations SD: standard deviation; ART: assisted reproductive therapy; PND: Prenatal diagnosis; TTTS: twin transfusion syndrome; FGR: intrauterine growth retardation; EFW: estimated fetal weight; ACS: Antenatal corticosteroid therapy; PPROM: Preterm prelabor rupture of membranes; FGR only: suspected fetal growth restriction without hypertensive disorders; Vascular Pathology hypertensive disorders without suspected fetal growth restriction or with suspected fetal growth restriction.
Data are presented as n (%) unless stated differently. Percentages and p-values are weighted according to gestational age**.**

Table 2: Perinatal complications and neonatal outcomes from twin pregnancies in the EPIPAGE 2 cohort.

	All twin live born infants, N (%)			**Live born 24-27$^{6/7}$ weeks, N (%)**			**Live born 28-31$^{6/7}$ weeks, N (%)**			**Live newborns 32-34$^{6/7}$ weeks, N (%)**		
Pregnancies	DC (n=543)	MC (n=191)	P value	DC (n=145)	MC (n=35)	P value	DC (n=251)	MC (n=112)	P value	DC (n=147)	MC (n=44)	P value
TTTS	0 (0)	56 (20.8)	-	-	18 (53.0)	-	-	33 (30.5)	-	-	5 (11.9)	-
Complete ACS	367 (71.0)	142 (77.6)	0.28	84 (60.1)	22 (64.4)	0.64	181 (73.5)	90 (83.3)	**0.04**	102 (71.8)	30 (75.0)	0.69
At least 1 FGR	89 (18.4)	47 (20.4)	0.65	21 (16.8)	5 (15.3)	0.88	42 (18.3)	37 (37.3)	**<0.001**	26 (18.7)	5 (12.8)	0.39
Preterm Labor	222 (43.5)	47 (20.1)	**0.001**	73 (53.5)	14 (40.4)	**0.03**	103 (43.1)	27 (25.9)	**<0.001**	46 (34.0)	6 (14.6)	**0.04**
Birthweight discordance > 0.20	63 (14.3)	40 (27.2)	**0.01**	11 (10.8)	4 (19.1)	0.28	39 (20.8)	30 (37.9)	**0.004**	13 (12.6)	6 (22.2)	0.21
Newborns	DC (n=1043)	MC (n=357)	P value	DC (n=267)	MC (n=59)	P value	DC (n=484)	MC (n=211)	P value	DC (n=292)	MC (n=87)	P value
BW, g (+/-SD)	1376 (±459)	1386 (±484)	0.80	839 (±167)	822 (±188)	0.71	1355 (±275)	1306 (±274)	0.06	1902 (±313)	1962 (±329)	0.21
BW z-score EPOPe	-0.80 (±1.15)	-1.06 (±1.25)	0.92	-0.50 (±1.20)	-0.75 (±1.46)	0.30	-0.87 (±1.20)	-1.26 (±1.32)	**0.001**	-0.97 (±1.11)	-0.77 (±1.16)	0.21
BW <10ème p EPOPe	313 (33.3)	126 (28.5)	0.24	60 (23.2)	18 (31.5)	0.24	149 (30.7)	89 (42.1)	**0.008**	104 (35.6)	19 (21.8)	**0.03**
BW <3^{éme} p EPOPe	172 (19.2)	84 (19.8)	0.86	35 (13.7)	11 (19.5)	0.32	75 (15.5)	59 (27.9)	**<0.001**	62 (21.2)	14 (16.0)	0.35
Death in NICU among all fetuses	86 (3.5)	28 (3.2)	0.75	68 (23.9)	21 (32.9)	0.16	16 (3.3)	7 (3.3)	0.99	2 (0.6)	0 (0)	0.44
Severe neonatal morbidity or death	202 (10.6)	67 (11.5)	0.67	144 (53.6)	37 (61.3)	0.36	53 (11.6)	28 (13.9)	0.46	5 (2.2)	2 (3.0)	0.71
Survival at discharge without severe morbidity	690 (84.0)	242 (83.6)	0.90	108 (43.7)	20 (37.1)	0.42	378 (83.0)	161 (80.1)	0.41	204 (91.8)	61 (92.4)	0.90

Abbreviations: Weeks: weeks' gestational age; SD: standard deviation; DC: dichorionic; MC: monochorionic, ACS: antenatal corticosteroids TTTS: twin twin transfusion syndrome; FGR: fetal growth restriction, p: percentile, Severe neonatal morbidity: neonatal morbidity (defined by IVH ≥ grade 3 and/or cPLV and/or DBP and/or ROP ≥ stage 3 and/or NEC ≥ stage 2) or death.
Data are presented as n (%) unless stated differently. Percentages and p-values are weighted according to gestational age**.**

Table 3: Comparison of the outcome at 2 years of children born <32 weeks, alive at discharge and followed up at 2 years, according to the chorionicity.

	Newborn from BC N=630 (%)	Newborn from MC N=225 (%)	P value	aOR* after multivariate analysis	P value	aOR* after multiple imputation	P value
Cerebral palsy at 2 years	19 (3.0)	8 (3.6)	0.69	1.59 [0.48-5.30]	0.44	2.48 [0.81-7.53]	0.11
Blindness at 2 years	0 (0)	0 (0)	-	-	-	-	-
Deafness at 2 years	3 (0.4)	1 (0.5)	0.30	-	-	-	-
Survival with neurosensory impairment	21 (3.3)	8 (3.5)	0.84	1.48 [0.44-5.04]	0.52	2.19 [0.75-6.40]	0.15
ASQ pathology at 2 years	233 (42.4)	83 (42.6)	0.98	1.00 [0.53-1.89]	0.99	1.04 [0.69-1.56]	0.86

SD: Standard deviation; ASQ: Age and stage questionnaire.

*Multivariate analysis with variables: sex, gestational age, birth weight <10th percentile, level maternal education, socio-economic level of the household, and assisted reproductive therapy, death of cotwin, twin-twin transfusion syndrome, birth weight discordance and the cause of preterm

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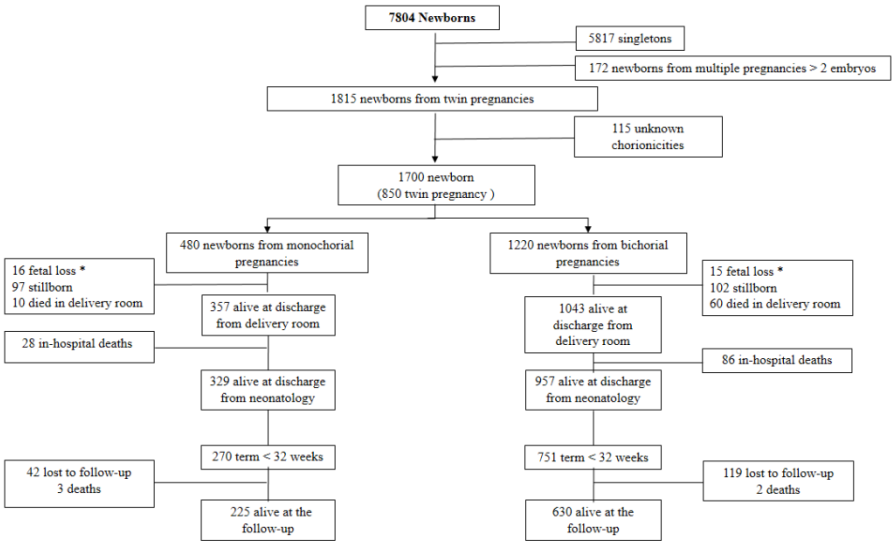
Table 4: Comparison of the outcome at 2 years of children born <32 weeks, alive at discharge and followed up at 2 years, according to the chorionicity (without TTTS in the group of children born from monochorial pregnancies).

	Newborn from BC N=630 (%)	Newborn from MC N=158 (%)	P value	aOR* after multivariate analysis	P value	aOR* after multiple imputation	P value
Cerebral palsy at 2 years	19 (3.0)	3 (1.9)	0.45	0.55 [0.13-2.43]	0.43	1.23 [0.29-5.24]	0.77
Blindness at 2 years	0 (0)	0 (0)	-	-	-	-	-
Deafness at 2 years	3 (0.4)	0 (0)	-	-	-	-	-
Survival with neurosensory impairment	21 (0.33)	8 (3.5)	0.36	0.47 [0.10-2.24]	0.34	1.06 [0.26-4.39]	0.93
ASQ pathology at 2 years	233 (42.4)	59 (43.4)	0.87	0.92 [0.45-1.89]	0.82	1.16 [0.75-1.80]	0.51

TTTS: twin-twin transfusion syndrome; SD: Standard deviation; ASQ: Age and stage questionnaire.

*Multivariate analysis with variables: sex, gestational age, birth weight <10th percentile, level maternal education, socio-economic level of the household, assisted reproductive therapy, cotwin death, birth weight discordance and the cause of preterm.



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