REVISTA CHILENA DE PEDIATRÍA
www.revistachilenadepediatria.cl
www.scielo.cl

Rev Chil Pediatr. 2019;90(1):36-43
DOI: 10.32641/rchped.v90i1.840

ORIGINAL ARTICLE

Growth restriction increases the risk of bronchopulmonary dysplasia, death, and sepsis in twins of 30 weeks or less of gestation

Restricción de crecimiento aumenta el riesgo de displasia broncopulmonar, muerte y sepsis en gemelos de 30 o menos semanas de gestación

Debora Sabatelli[a], Beatriz Milet[b], Patricia Mena[c,d], Angélica Domínguez[d], Red Neonatal Neocosur

[a]Hospital Juan A Fernández, Buenos Aires, Argentina
[b]Clínica Alemana, Santiago, Chile
[c]Hospital Sótero del Río, Santiago, Chile
[d]División de Pediatría, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile.

Received: 18-07-2018; Approved: 11-10-2018

Abstract

Introduction: Multiple factors influence the risk of morbidity and mortality of premature infants with intrauterine growth restriction (IUGR). The comparison of twins with different intrauterine growth allows evaluating the effect of the restriction, excluding maternal factors and prenatal management. Our objective was to assess the effect of IUGR on acute and chronic morbidity, and mortality of extreme preterm twins. **Patients and Method:** Twins weighing less than 1500 grams and gestation equal to or less than 30 weeks, of the Neocosur Network. Separate analyses were performed on concordant twin pairs, and on mild and severe discordant twins, evaluating the effect of IUGR on morbidity and mortality. A multivariate analysis was performed in order to establish the impact of this effect. **Results:** 459 twin pairs, 227 concordant twins, 110 of mild discordance, and 122 of severe discordance. Among the concordant ones, there was only a difference in oxygen uptake at 36 weeks. In those of mild discordance, the smaller twin presented a lower frequency of hyaline membrane disease and required fewer doses of surfactant, but had a higher risk of bronchopulmonary dysplasia (BPD) or death. In severe discordant twins, the smaller one presented higher mortality, sepsis, use and permanence in mechanical ventilation, despite the lower frequency of hyaline membrane disease. In multiple regression analysis, the combined risk of BPD or death was higher in the smaller twin and of severe discordance. **Conclusion:** In discordant twins, the acute respiratory pathology was more frequent in the larger one, although the risk of BPD or death was higher in the one with IUGR.

Keywords:
Discordant twins;
intrauterine growth restriction;
respiratory distress syndrome;
hyaline membrane disease;
bronchopulmonary dysplasia;
prematurity;
sepsis;
neonatal mortality

Correspondence:
Debora Sabatelli
debora.sabatelli@gmail.com

How to cite this article: Rev Chil Pediatr 2019;90(1):36-43. DOI: 10.32641/rchped.v90i1.840

Introduction

Intrauterine growth restriction (IUGR) is a risk factor for neonatal morbidity and mortality at all gestational ages but is critical in extreme prematurity. Generally, neonatal morbidity has an increased frequency and severity in the child with IUGR compared to the good growth of the same gestational age, describing a continuous decrease in morbidity as the weight percentile increases[1].

The risk of acute morbidities, such as hyaline membrane disease; or chronic, such as bronchopulmonary dysplasia, may differ in the presence of IUGR. In the case of hyaline membrane disease, discrepancies have been described in the risk conferred by IUGR[2,3], although with differences between children over and under 32 weeks of gestational age[4,5]. In addition, other factors, such as antenatal corticosteroid use, maternal morbidity, sex, mode of delivery, and peripartum events also influence risk.

The study of twins with discordant growth allows comparing the effect of intrauterine growth on neonatal outcomes under similar conditions of maternal morbidity, gestational age, and corticosteroid use. Our objective was to assess the effect of IUGR on acute and chronic morbidity, and mortality in twin pairs of gestational age less than or equal to 30 weeks and less than 1500 g of birthweight.

Patients and Method

The Neocosur Neonatal Network is a group of Neonatology Units from Argentina, Chile, Paraguay, Uruguay, and Peru, which gathers information on the evolution of children under 1500 g at birth, since 2001[6]. From this database, a retrospective descriptive study was carried out of cases and controls, of twins born between 2001 and 2010, establishing twin pairs, and those with gestational age less than or equal to 30 weeks were finally selected, avoiding that both had IUGR. In cases of multiple pregnancies of more than two twins, in order to maintain independence between two twins, one was randomly identified and, of each pair of quadruplets, two were randomly identified. A discordance was defined according to the formula:

[(Larger twin weight – Smaller twin weight) / Larger twin weight] x 100

The twin pairs with less than 10% discordance were considered concordant, between 10 and 20% were considered mild discordant, and over 20% were considered as severe discordant. Anthropometry, sex, gestational age, mortality, and morbidity were recorded such as early-onset sepsis, clinical sepsis (defined with clinical and laboratory elements, and antibiotic treatment for more than five days, even if blood cultures are negative), number of these, patent ductus arteriosus (PDA) diagnosed after 48 h, intraventricular hemorrhage (IVH) of grades III and IV, hyaline membrane disease (defined by altered radiography compatible with the diagnosis and/or surfactant use), respiratory distress syndrome (RDS, defined as altered respiratory rate, expiratory grunt , intercostal retraction during the first day of life), use of surfactant and number of doses, necrotizing enterocolitis (considering only those grade II or more), intestinal perforation, use and permanence in mechanical ventilation (MV) and continuous positive airway pressure (CPAP), air leak, days of oxygen therapy, bronchopulmonary dysplasia (BPD, defined as oxygen therapy at 36 weeks and discharge with supplemental oxygen).

Statistical Analysis: Separate analyses of concordant, mild and severe discordant twin pairs were performed. For each pair, the twin with the lowest (case) and the highest (control) weight was identified. Mixed models were used to identify the variables that differentiated between the larger and smaller twin, considering the non-independence between them. The twin pair identifier was used as an indicator of repeated measurement and, using a logistic link, regressions were performed to see the effect of the larger/smaller twin on the variables of interest. In addition, regressions were repeated by adjusting for sex. To see the effect of newborn (NB) characteristics on the outcome of BPD or death, a multivariate analysis was performed where all NB characteristics were included. The magnitude of the effect was quantified using OR and its confidence interval of 95%. A level of significance was set with a $p < 0.05$ value. Results are expressed as mean ± SD. The SPSS 17.0 software was used and, for logistic regressions, the "glmmML" methodology of the R software version 3.2.2 was used. The study was approved by the Ethics Committee of the South East Health Service in Santiago de Chile.

Results

We identified 1207 NB of multiple pregnancies, consisting of three pairs of quadruplets, 55 pairs of triplets, and 515 pairs of twins. Subsequently, those with 30 weeks or less of gestation were selected, resulting in 459 pairs of twins. They had a gestational age of 27.6 ± 2.03 weeks, and 227 pairs were concordant, 110 pairs were mild discordant, and 122 pairs were severe discordant.

In the concordant twins subgroup, the mean percentage difference in weight was 4.3% and height 0.9%. In the group with the highest weight, a significantly higher percentage was female (55.50 vs 46.70%, p = 0.012). There were no major differences in morbidity and mortality, except for a greater oxygen administration frequency at 36 weeks of corrected age in the smaller twin (22.5 vs 13.9% in the larger twin, p = 0.009) (Table 1).

In the mild discordant twins subgroup, the larger twin had 14.3% more weight and 3.6% more height than the smaller (both p = <0.0001), and a higher percentage were female (55.5 vs 41.8%, p = 0.02). The smaller twin had a lower frequency of hyaline membrane disease (77.6 vs 89.7%, p = 0.01) and required a lower number of surfactant doses (0.92 ± 0.98 vs 1.23 ± 1.01, p = 0.007), although the child had a higher combined risk of death and BPD (56.7 vs 50%, p = 0.04) (Table 2).

In the severe discordant twins subgroup, the average percentage difference in weight was 33.2% and height 9.6%. The smaller twin had less use and permanence in CPAP (57.3 vs 70.1%, p = 0.01, and 11.8 ± 11.8 vs 8.7 ± 11.3 days, p = 0.008), but greater use and permanence in mechanical ventilation (86.5 vs 76.6%, p = 0.027, and 11.4 ±15.5 vs 8.0 ± 13.0 days, p = 0.023), despite a lower frequency of hyaline membrane disease (82.9 vs 90.6%, p = 0.035). The child also had a higher number of clinical sepsis (1.18 ± 1.22 vs 0.82 ± 0.83, p = 0.014) and higher mortality (39.3 vs 26.2%, p = 0.01), without differences in BPD and other morbidities (Table 3).

In concordant twins, we found 2.5 times more risk that the smaller twin requires oxygen administration at 36 weeks of corrected age, persisting when adjusting for sex. In mild discordant twins, the smaller twin has 3.3 times less risk of hyaline membrane disease, increasing to 3.6 when adjusted for sex. In contrast, the larger NB had 0.08 times less combined risk of BPD or death. In severe discordant twins, the significant associations (and sense of these) found for mild discordant twins are maintained. In addition, being the larger twin was protective against death or severe IVH (OR = 0.26) and the need for MV (OR = 0.33), and had a higher risk of CPAP use (OR = 2.71) (Table 4).

Table 5 shows the multivariate analysis of the combined risk of BPD or death of the entire sample of twins, with an increased risk of the smaller twin, severe discordant, male sex, younger gestational age, and hyaline membrane disease.

Table 1. Comparison between larger twin and smaller twin in concordant pairs

	Larger Twin	Smaller Twin	P Value
Baseline Chracateristics			
Birthweigth (g)	1046.1 ± 270.2	1000.8 ± 260.3	< 0.001
Heigth (cm)	35.7 ± 3.3	35.4 ± 3.1	0.006
Mortality (%)	32.9	31.4	NS
Length of stay (n)	50.1 ± 45.7	50.4 ± 44.3	NS
Respiratory Morbilities			
Respiratory Distress Syndrome (%)	86.4	83.6	NS
Membrane Hyaline Disease (%)	84.4	83.9	NS
Surfactant doses (n)	1.29 ± 1.02	1.27 ± 0.98	0.347
Mechanical Ventilation (%)	78.9	76.5	NS
Days of Mechanical Ventilation (n)	7.8 ± 14.2	8.2 ± 15.1	NS
Continuos Positive Airway Pressure (%)	59.1	60.0	NS
Days of Continuos Positive Airway Pressure (n)	8.6 ± 8.7	8.3 ± 9.5	NS
Bronchopulmonary Dysplasia (%)	25.2	29.1	NS
BPD/ Death (%)	55.5	57.8	NS
Need for supplemental oxygen at 36 weeks (%)	13.9	22.5	0.009
Discharge with supplemental oxygen (%)	5.9	7.7	NS
Others Morbilities			
Early onset sepsis (%)	3.3	5.7	NS
Clinical Sepsis (%)	61.9	68.3	NS
Clinical Sepsis (n)	0.95 ± 1.1	0.98 ± 0.9	NS
Patent Ductus Arteriosus (%)	42.9	49.0	NS
Necrotizing enterocolitis (%)	11.3	15.1	NS
Intraventricular hemorrhage grade III or IV (%)	13.8	13.2	NS
Retinopathy of Prematurity (%)	23.5	26.1	NS

RDS: Respiratory distress Syndrome; MV: Mechanical Ventilation; CPAP: Continuos Positive Airway Pressure; BPD: Bronchopulmonary Dysplasia; PDA: Patent Ductus Arteriosus; NEC: Necrotizing enterocolitis; IVH III/IV: Intraventricular hemorrhage grade III or IV; ROP: Retinopathy of Prematurity; NS: not statistically significant.

Table 2. Comparison between larger twin and smaller twin in mild discordant pairs

	Larger Twin	Smaller Twin	P Value
Baseline Chracateristics			
Birthweigth (g)	1118.3 ± 268.9	958.5 ± 232.0	0.0001
Height (cm)	36.2 ± 3.4	34.9 ± 3.2	0.0001
Mortality (%)	22.2	27.3	NS
Length of stay (n)	56.4 ± 50.6	65.0 ± 74.1	NS
Respiratory Morbilities			
Respiratory Distress Syndrome (%)	84.9	77.4	NS
Membrane Hyaline Disease (%)	89.7	77.6	0.01
Surfactant doses (n)	1.23 ± 1.01	0.92 ± 0.98	0.007
Mechanical Ventilation (%)	71.0	73.0	NS
Days of Mechanical Ventilation (n)	9.9 ± 19.4	8.6 ± 14.2	NS
Continuos Positive Airway Pressure (%)	70.1	64.5	NS
Days of Continuos Positive Airway Pressure (n)	7.1 ± 7.1	8.7 ± 11.9	NS
Bronchopulmonary Dysplasia (%)	29.1	32.0	NS
BPD/ Death (%)	50.0	56.7	0.04
Need for supplemental oxygen at 36 weeks (%)	21.4	21.4	NS
Discharge with supplemental oxygen (%)	13.0	7.4	NS
Others Morbilities			
Early onset sepsis (%)	1.9	3.4	NS
Clinical Sepsis (%)	70.5	68.9	NS
Clinical Sepsis (n)	1.0 ± 0.9	1.2 ± 1.2	NS
Patent Ductus Arteriosus (%)	45.7	46.7	NS
Necrotizing enterocolitis (%)	10.3	15.0	NS
Intraventricular hemorrhage grade III or IV (%)	8.1	9.1	NS
Retinopathy of Prematurity (%)	23.8	32.5	NS

RDS: Respiratory distress Syndrome; MV: Mechanical Ventilation; CPAP: Continuos Positive Airway Pressure; BPD: Bronchopulmonary Dysplasia; PDA: Patent Ductus Arteriosus; NEC: Necrotizing enterocolitis; IVH III/IV: Intraventricular hemorrhage grade III or IV; ROP: Retinopathy of Prematurity; NS: not statistically significant.

Table 3. Comparison between larger twin and smaller twin in severe discordant pairs

	Larger Twin	Smaller Twin	P Value
Baseline Chracateristics			
Birthweigth (g)	1143.8 ± 206.7	764.4 ± 161.5	0.0001
Height (cm)	36.5 ± 2.3	32.9 ± 2.9	0.006
Mortality (%)	26.2	39.3	0
Length of stay (n)	56.0 ± 52.5	62.7 ± 62.8	NS
Respiratory Morbilities			
Respiratory Distress Syndrome (%)	91.5	85.5	NS
Membrane Hyaline Disease (%)	90.6	82.9	0.035
Surfactant doses (n)	1.40 ± 1.04	1.27 ± 0.99	NS
Mechanical Ventilation (%)	76.6	86.5	0.027
Days of Mechanical Ventilation (n)	8.0 ± 13.0	11.4 ± 15.5	0.023
Continuos Positive Airway Pressure (%)	70.1	57.3	0.01
Days of Continuos Positive Airway Pressure (n)	8.70 ± 11.3	11.8 ± 11.8	0.008
Bronchopulmonary Dysplasia (%)	31.0	34.5	NS
BPD/ Death (%)	53.5	66.7	0.06
Need for supplemental oxygen at 36 weeks (%)	22.5	27.5	NS
Discharge with supplemental oxygen (%)	8.5	10.3	NS
Others Morbilities			
Early onset sepsis (%)	1.8	1.8	NS
Clinical Sepsis (%)	58.2	68.7	NS
Clinical Sepsis (n)	0.82 ± 0.83	1.18 ± 1.22	0.014
Patent Ductus Arteriosus (%)	56.4	48.7	NS
Necrotizing enterocolitis (%)	8.5	16.2	NS
Intraventricular hemorrhage grade III or IV (%)	13.9	11.1	NS
Retinopathy of Prematurity (%)	33.8	40.3	NS

RDS: Respiratory distress Syndrome; MV: Mechanical Ventilation; CPAP: Continuos Positive Airway Pressure; BPD: Bronchopulmonary Dysplasia; PDA: Patent Ductus Arteriosus; NEC: Necrotizing enterocolitis; IVH III/IV: Intraventricular hemorrhage grade III or IV; ROP: Retinopathy of Prematurity; NS: not statistically significant.

Table 4. Logistics Regressions for twin pairs

Outcome	Crude OR (IC 95%)	Adjusted OR for sex (CI 95%)
Twin pairs concordant		
Need for supplemental oxygen at 36 weeks	0.40 (0.19 - 0.84)	0.36 (0.17 - 0.80)
Twin pairs mild discordant		
BPD/Death	0.08 (0.01 - 0.64)	0.006 (0.0002 - 0.19)
Hyaline membrane Disease	3.33 (1.26 - 8.85)	3.68 (1.34 - 10.15)
Twin pairs severe discordant		
Mortality	0.26 (0.11 - 0.65)	0.25 (0.10 - 0.62)
Hyaline membrane Disease	4.11 (1.15 - 14.66)	3.77 (1.06 - 13.34)
Mechanical Ventilation	0.33 (0.12 - 0.89)	0.29 (0.10 - 0.84)
High Frecuency Ventilation	0.10 (0.02 - 0.42)	0.10 (0.02 - 0.42)
CPAP	2.71 (1.22 - 6.03)	2.73 (1.22 - 6.10)
BPD/Death	0.29 (0.12 - 0.72)	0.27 (0.11 - 0.68)
Severe IVH or Death	0.32 (0.14 - 0.76)	0.31 (0.13 - 0.73)

CPAP: Continuos Positive Airway Pressure; BPD: Bronchopulmonary Dysplasia; IVH: Intraventricular hemorrhage; OR: odds ratio; CI 95%: Confidence intervals 95%.

Table 5. Multivariate analysis of the combined risk of BPD or death

Variable	OR (CI 95%)	P Value
Larger Twin Weight	**0.41 (0.25-0.67)**	**< 0.001**
Twin pair mild discordant	1.91 (0.70 - 5.21)	0.203
Twin pair severe discordant	**2.89 (1.12 - 7.46)**	**0.029**
Male	**2.84 (1.44 - 5.57)**	**0.003**
GA	**0.23 (0.16 - 0.33)**	**< 0.001**
Hyaline Membrane Desease	**4.97 (1.83 - 10.35)**	**0.002**

GA: Gestational Age; OR: odds ratios; CI 95%: Confidence intervals 95%.

Discussion

The main finding of this study of premature twins of less than 1500 g is that lower intrauterine growth is associated with an increased risk of death, BPD, and sepsis. In concordant twins, the smaller child has a higher risk of BPD, even if corrected by gestational age, sex, or having developed hyaline membrane disease. In both mild and severe discordant twins, there was greater acute morbidity in the larger twin, but greater chronic respiratory morbidity in the smaller twin, which is more marked in severe discordant twins. In the multivariate analysis of the total number of twins, the smaller one has 2.44 times more risk of BPD or death, adjusted for the degree of twin pair asymmetry, sex, gestational age, and hyaline membrane disease. The smaller twin who has had hyaline membrane disease has a much higher risk of BPD.

Studies of newborns of multiple pregnancies may have different outcomes depending on how the comparison is made. Much of the literature on discordant twins discusses the decision to terminate the pregnancy based on the degree of discordance and prematurity[8]. In this sense, the analysis is presented as products of pregnancies with or without discordance[9,10] or with small for gestational age[9], and only a minority analyzes the outcome of one twin with the other one[11]. Fetal mortality almost doubles that of neonates with discordance higher than 20% in twins of less than 32 weeks[11].

In relation to neonatal risk, it may vary according to definitions of discordance and assessments of zygosity, chorionicity, birth order, and fetal growth[8-10,12-17]. In the comparison of fetal growth, various definitions of discordance have been used, among which we prefer to classify them into mild and severe, in order to evaluate if the differences increased with the greater growth alteration.

In twin pregnancies, the risk of RDS has been associated with sex and birth order, where the male is the most susceptible, and the second twin has a higher risk of perinatal asphyxia and respiratory failure[9,18-20].

In our study, the BPD incidence increases in the smaller twins. When controlling by sex, the concordant and mild discordant twins were fewest women, but the distribution was similar in the severe discordant. Interestingly, it has been documented that in the presence of male and female twins, the first exerts a masculinizing effect on the risk of respiratory problems. Thus, male twins are at greater risk, which is similar to female twins of male-female pregnancies contrasting with female-female twins[21]. Also, there would be an effect of the twins sex on the birth weight. The presence of a male twin is associated with a higher birth weight of female twins than expected only by gender[22].

Regarding the RDS presentation, reports vary. Similian et al.[23] suggested that the RDS incidence and transient tachypnea in discordant preterm infants is higher than for concordant preterm infants. The gestational age of the compared groups clearly influences the results. In the older of 32 weeks, being small for gestational age (SGA) protects against the risk of RDS but is not evident in small twins[4,5]. In a retrospective study of 124 twin pairs, it was found that the need for O2 for four hours in twins younger than 28 weeks was strongly associated with being the largest twin (OR = 1.9 95% CI 1.03-3.46)[19]. The cause why the larger twin may develop more acute pulmonary morbidity may be given by the possibility that the smaller twin is more mature due to the chronic stress of IUGR, with endogenous corticosteroid production, which is greater at birth in the smaller discordant twin[24]. The IUGR has been associated with adverse effects on lung structure and function resulting in a persistent alteration in lung structure and impaired respiratory function in postnatal life (children, adolescents, and young adults)[2]. This explains why the smaller twin has more chronic respiratory pathology.

A recent analysis of twins in the Canadian prematurity network, by order of birth, shows a higher frequency of SGA in the second twin (which is repeated in other studies), but higher RDS[14]. The evolution according to the birth order is modified by the association between second twin and lower growth[25].

Few studies perform analysis by zygosity, but chorionicity and sex have been used as equivalent, although neither is enough, describing concordance between clinical assignment and genetic study of only 62.7% for monozygotic twins and 88.9% for dizygotic twins[13]. Zygosity is a very important intervening variable but it is not easy to include in the absence of genetic studies. Bhandari et al. studied zygosity, being able to show that there are associated genetic factors attributable to the possibility of developing BPD[12].

With respect to late sepsis, incidence analyses in relation to the genetic component are controversial, but it does not seem to be a clearly influential factor. Dizygotic twins show a higher risk of infection than the monozygotic ones[26]. In the case of late infection, it has been documented that genetic aspects are unlikely to be determinants of this risk, given the absence of differences between single or multiple products and the equal frequency between twins of the same and different sex[27]. In contrast, the effect of IUGR on the increased risk of sepsis has been documented in this and other studies[28]. Thus, IUGR increases the risk of infection. This is, in part, because children with IUGR have more requirement for central venous catheters, more time to reach full enteral feeding, more days and cycles of antibiotics than children of adequate weight, longer hospital stay, and mechanical ventilation. Even controlling for all these variables, IUGR is still a risk factor for infection[29]. Immune compromise has been documented in the SGA newborn for many years[30].

The main limitations of this study are not having chorionicity and birth order information since both factors modify the morbidity of the twins. Neither did we evaluate the growth compromise degree of the smaller twin, regarding intrauterine growth curves, the influence of the twin pairs sex, or the sepsis documented with positive blood culture, although it is possible that it had similar behavior to clinical sepsis.

Conclusions

There is a higher risk in twins with severe discordance, where the smaller twin has a lower risk of acute respiratory pathology but is more likely to die or have chronic lung disease, sepsis, and longer hospitalization.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors state that the information has been obtained anonymously from previous data, therefore, Research Ethics Committee, in its discretion, has exempted from obtaining an informed consent, which is recorded in the respective form

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

References

1. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth Weight in relation to morbidity and mortality among newborn infants. N Eng J Med 1999;340:1234-8.
2. Manzanares S, Sánchez-Gila M, Moreno-Martínez MD, Ramírez-Arredondo A, Pineda Perinatal outcomes in preterm growth-restricted twins: effects of gestational age and fetal condition. Twin Res Hum Genet. 2013;16(3):727-31.
3. Park CW, Park JS, Jun JK, Yoon BH. FGR in the setting of preterm sterile intra-uterine milieu is associated with a decrease in RDS. PediatrPulmonol. 2016;51(8):812-9.
4. Sharma P, McKay K, Rosenkrantz TS, et al. Comparisons of mortality and predischarge respiratory outcomes in small-for-gestational-age and appropriate-for-gestational-age premature infants. BMC Pediatr 2004; 4: 9.
5. Mena P, Smith J, Milet B, Toro C, Arredondo F, Llanos A. Incidencia y evolución de membrana hialina en menores de 35 semanas según crecimiento intrauterino. Rev Chil Pediatr 2011;82:395-401.
6. Grupo ColaborativoNeocosur. Very-low-birth-weight infant outcomes in 11 South American NICUs. JPerinatol. 2002;22(1):2-7.
7. Cerda J, Villarroel L. Evaluación de la concordancia inter-observador en investigación pediátrica: coeficiente de Kappa. Rev Chil Pediatr. 2008; 79 (1):54-8.
8. Patterson RM, Wood RC. What is twin birthweight discordance?Am J Perinat 1990;7:217-9.
9. Lopriore E, Sluimers C, Pasman SA, Middeldorp JM, Oepkes D, Walther FJ. Neonatal morbidity in growth-discordant monochorionic twins: comparison between the larger and the smaller twin. Twin Res Hum Genet. 2012;15(4):541-6.
10. Harper LM, Weis M, Odibo AO, Roehl KA, MaconesGA , Cahill, AG Significance of growth discordance in appropriately grown twins.Am J Obstet Gynecol. 2013;208(5):393.e1-5.
11. Wen SW, Fung KF, Huang L, et al. Fetal and Infant Health Group of the Canadian Perinatal Surveillance System. Fetal and neonatal mortality among twin gestations in a Canadian population: the effect of intrapair birthweight discordance. Am J Perinatol. 2005;22(5):279-86
12. Bhandari V, Bizzarro MJ, Shetty A, Zhong X, Page GP, Zhang H; Neonatal Genetics Study Group. Familial and genetic susceptibility to major neonatal morbidities in preterm twins. Pediatrics. 2006;117(6):1901-6.
13. Spiegler J, Härtel C, Schulz L, von Wurmb-Schwark N, Hoehn T, Kribs A; German Neonatal Network (GNN). Causes of delivery and outcomes of very preterm twins stratified to zygosity. Twin Res Hum Genet. 2012;15(4):532-6. .
14. Mei-Dan E, Shah J, Lee S, Shah PS, Murphy KE; Canadian NeonatalNetwork Investigators. The Effect of Birth Order on Neonatal Morbidity and Mortality in Very Preterm Twins.Am J Perinatol. 2017 Feb 23. doi: 10.1055/s-0037-1598255
15. Steingass KJ, Taylor HG, Wilson-Costello D, Minich N, Hack M. Discordance in neonatal risk factors and early childhood outcomes of very low birth weight (<1.5 kg) twins. J Perinatol. 2013;33(5):388-93
16. Frezza S, Gallini F, Puopolo M, De Carolis MP, D'Andrea V, Guidone PI, Luciano R,Zuppa AA, Romagnoli C. Is growth-discordance in twins a substantial risk factor in adverse neonatal outcomes? Twin Res Hum Genet. 2011;14(5):463-7.
17. Yinon Y, Mazkereth R, Rosentzweig N, Jarus-Hakak A, Schiff E, Simchen MJ. Growth restriction as a determinant of outcome in preterm discordant twins. Obstet Gynecol. 2005;105:80-4.
18. Steen EE, Källén K, Maršál K, Norman M, Hellström-WestasL.Impact of sex on perinatal mortality and morbidity in twins. J Perinat Med. 2014;42(2):225-31
19. Canpolat FE, Yurdakok M, Korkmaz A, Yigit S, Tekinalp G. Birthweight discordance in twins and the risk of being heavier for respiratory distress syndrome. Twin Research and Human Genetics. 2006;9:659-63.
20. Webb RD, Shaw NJ. Respiratory distress in heavier versus lighter twins. Journal of Perinatal Medicine 2001;29:60-3.
21. Shinwell ES, Reichman B, Lerner-Geva L, Boyko V, Blickstein I; Israel Neonatal Network. "Masculinizing" effect on respiratory morbidity in girls from unlike-sex preterm twins: a possible transchorionic paracrine effect. Pediatrics. 2007;120:e447-53.
22. Blumrosen E, Goldman RD, Blickstein I. Growth discordance and the effect of a male twin on birth weight of its female co-twin: a population-based study. J Perinat Med 2002; 30:510-3.
23. Smiljan Severinski N, Mamula O, Petrovic O. Neonatal outcome in discordant eutrophic twins: twin growth. Int J GynaecolObstet 2004;86:16-21.
24. Van Stralen G, vander Bos J, Lopriore E, Te Pas AB, Bloemenkamp. No short-termbenefits of antenatal corticosteroid treatment in severely preterm growth restricted fetuses: A case-control study. Early Human Develop. 2009;85:253-7.
25. Luo ZC, Ouyang F, Zhang J, Klebanoff M. Perinatal mortality in second- vs firstborn twins: a matter of birth size or birth order? Am J Obstet Gynecol. 2014;211(2):153.e1-8.
26. Härtel C, Schultz C, Herting E, Göpel W Genetic association studies in VLBW infants exemplifying susceptibility to sepsis-recent findings and implications for future research. Acta Paediatr. 2007;96(2):158-65.
27. Papiernik E, Zeitlin J, Delmas D, Blondel B, Künzel W, Cuttini M, MOSAIC Group. Differences in outcome between twins and singletons born very preterm: results from a population-based European cohort. Hum Reprod. 2010;25(4):1035-43.

28. Boghossian NS, Page GP, Bell EF, Stoll BJ, Murray JC, Cotten CM; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Late-onset sepsis in very low birth weight infants from singleton and multiple-gestation births. J Pediatr. 2013;162(6):1120-4.
29. Tröger B, Göpel W, Faust K, Müller T, Jorch G, Felderhoff-Müser U; German Neonatal Network. Risk for late-onset blood-culture proven sepsis in very-low-birth weight infants born small for gestational age: a large multicenter study from the German Neonatal Network. Pediatr Infect Dis J. 2014;33(3):238-43.
30. Chandra RK. Serum thymic hormone activity and cell-mediated immunity in healthy neonates, preterm infants, and small-for-gestational age infants. Pediatrics. 1981;67(3):407-11.