

A RETROSPECTIVE STUDY OF DISCORDANT TWIN GROWTH IN DICHORIONIC TWIN PREGNANCIES AND RISK OF PRETERM DELIVERY AT SPLIT UNIVERSITY HOSPITAL CENTRE: THREE-YEAR EXPERIENCE

Marko Vulić¹, Lara Lalić², Luka Vulić³, Damir Roje¹, Zdeslav Benzon¹ and Zoran Meštrović¹

¹Department of Gynecology and Obstetrics, Split University Hospital Centre, School of Medicine, University of Split, Split, Croatia; ²Split University Hospital Centre, Split, Croatia; ³School of Medicine, University of Split, Split, Croatia

SUMMARY – The aim was to determine whether discordant twin growth has an impact on preterm birth in dichorionic pregnancies. This retrospective study included dichorionic twin pregnancies in the period from January 1, 2013 to December 31, 2015. The following variables were investigated: maternal age (years), parity, body mass index (kg/m²), week ($\leq 36^{6/7}$ and ≥ 37) and mode of delivery (vaginal and cesarean section), birth weight (grams) and Apgar score (≤ 7 , 8-10). Discordant twin growth in dichorionic pregnancies was found to be associated with preterm birth ($\chi^2=4.74$; $p=0.03$) but had no impact on the mode of delivery ($\chi^2=0.119$; $p=0.73$). There was a statistically significant difference in the rate of small for gestational age (SGA) neonates ($\chi^2=16.4556$; $p=0.000267$) and Apgar score ($\chi^2=7.9931$; $p<0.05$) between the study groups. Mode of conception in dichorionic pregnancies was not a risk factor for preterm delivery ($\chi^2=1.417$; $p=0.23$). In conclusion, discordant twin growth in dichorionic pregnancies is a risk factor for preterm delivery and has no impact on the mode of delivery but has an impact on the rate of SGA and Apgar score.

Key words: Premature birth; Pregnancy; Retrospective studies; Twins, dizygotic; Croatia

Introduction

The rate of twin pregnancy has risen by 70% since 1980. Twins now account for 3% of all births, largely due to the increased use of assisted reproductive technologies (ART)^{1,2}. Multiple gestations contribute nearly 20% to the overall perinatal mortality and morbidity rates^{1,3}. Twin gestations are at an increased risk of preterm delivery, hypertensive disorders of pregnancy, intrauterine growth restriction, and structural

anomalies. Discordant twin growth is most often defined as >20% difference in birth weight between twins². The percentage is calculated with the (A-B)/A formula, where A stands for larger and B for smaller twin. It may be attributed to differences in genetic potential between co-twins, placental dysfunction confined to one placenta only, or one placental territory within a shared placenta²⁻⁴. Discordant growth is recognized as an independent risk factor for adverse perinatal outcome including mortality, respiratory distress syndrome, hypoxic-ischemic encephalopathy, periventricular leukomalacia, necrotizing enterocolitis, or sepsis^{2,4}. This study aimed at determining whether discordant twin growth in dichorionic pregnancies has an impact on preterm birth.

Correspondence to: Prof. Marko Vulić, MD, PhD, Department of Gynecology and Obstetrics, Split University Hospital Centre, School of Medicine, University of Split, Spinčićeva 1, HR-21000 Split, Croatia

E-mail: marko.vulic1@st.t-com.hr

Received March 24, 2017, accepted July 4, 2017

Table 1. Demographic data in twin pregnancies with discordant and concordant twin growth

	Discordant fetal growth, n	Concordant fetal growth, n	p value
Age (yrs)	31.4±5.6	30.93±4.83	NS*
Primiparae	37	102	**p=0.56493
Multiparae	18	60	$\chi^2=0.3312$
BMI (kg/m ²):			
18.5-24.9	10	22	**p=0.516427
25-29.9	11	43	$\chi^2=1.3216$
≥30	34	97	

*Student's t-test; ** χ^2 -test; NS = nonsignificant; BMI = body mass index

Materials and Methods

We conducted a retrospective study that included dichorionic twin pregnancies in the period from January 1, 2013 to December 31, 2015. The following variables were investigated: maternal age (years), parity, body mass index (BMI, kg/m²), week ($\leq 36^{6/7}$ and ≥ 37) and mode (vaginal and cesarean section) of delivery, birth weight (grams) and Apgar score (≤ 7 , 8-10). Stillbirths, aneuploidy and pregnancies with one or both twins with congenital anomaly were excluded from the study. Small for gestational age (SGA) babies were calculated from the tables of birth weights for singletons which were adjusted for local specificity⁵. Chorionicity was determined by ultrasonography during first trimester or by histopathologic study. Gestational age at birth was calculated by first day of last menstrual period, adding 14 days to the day of ovum pick-up as the week of amenorrhea for the *in vitro* fertilization (IVF) group and by adding 14 days to the presumed day of ovulation for the ovulation induction group. Statistical analysis was performed with Statistica SPSS version 14.0 (SPSS, Chicago, IL, USA) using Student's t-test and χ^2 -test. The values of $p < 0.05$ were considered statistically significant.

Results

During the three-year period, 217 twin pregnancies met the inclusion criteria. The mean age of women with discordant growth twins was 31.4±5.6

Table 2. Perinatal outcome in twin pregnancies with discordant and concordant growth

	Discordant fetal growth, n (%)	Concordant fetal growth, n (%)	p value
≥37 Weeks	24 (43.64)	98 (60.49)	*p=0.02954
≤36 ^{6/7} Weeks	31 (56.36)	64 (39.51)	$\chi^2=4.74$
Cesarean section	44 (80)	126 (77.78)	0.73**
Vaginal delivery	11 (20)	36 (22.22)	
SGA	13 (11.82)	8 (2.47)	*p=0.000267
AGA	69 (62.73)	240 (74.07)	$\chi^2=16.4556$
LGA	28 (25.45)	76 (23.46)	
Spontaneously conceived	46 (27.22)	123 (72.78)	*p=0.23
ART	9 (18.75)	39 (81.25)	$\chi^2=1.417$
Apgar score ≤7	29 (26.36)	47 (14.51)	*p=0.004696
Apgar score 8-10	81 (73.64)	277 (85.49)	$\chi^2=7.9931$

* χ^2 -test; **Student's t-test; ART = assisted reproductive technologies; SGA = small for gestational age; AGA = appropriate for gestational age; LGA = large for gestational age

years, whereas in concordant pregnancy group it was 30.93±4.8 years. Difference in the mean age was not statistically significant. There was no significance in terms of parity ($\chi^2=0.3312$; $p=0.56493$) and BMI ($p=0.516427$; $\chi^2=1.3216$) between the study groups.

In the groups with discordant and concordant twin pregnancy, there were 31 and 64 preterm births, respectively. This difference was statistically significant ($\chi^2=4.74$; $p=0.03$). Cesarean section was performed in 44 discordant group women and 126 control group women. Statistical analysis showed no difference in the mode of delivery rates ($\chi^2=0.119$; $p=0.73$).

In the discordant pregnancy group, 13 out of 110 babies were SGA, while in control group eight out of 324 babies were SGA. This difference was statistically significant ($\chi^2=16.4556$; $p=0.000267$). Apgar scores also yielded between-group differences ($\chi^2=7.9931$; $p < 0.05$). Mode of conception was not a risk factor for preterm delivery in discordant dichorionic pregnancies ($\chi^2=1.417$; $p=0.23$).

Discussion

Our study demonstrated discordant twin growth (by definition, we accepted -20%) to be a risk factor for preterm delivery and lower Apgar score. Due to the lack of reliable information from our medical documentation, we are not able to make conclusion on the possible differences in the subgroups of preterm delivery (spontaneous, preterm premature rupture of membranes and iatrogenic). Current understanding of the etiology of preterm birth is that it is a multifactorial syndrome^{6,7}. Some of the triggers that activate the common pathway of parturition are intra-amniotic infection, decidual senescence, vascular disorders, maternal stress, cervical disease, decline in progesterone action, and breakdown of maternal-fetal tolerance^{3,6}. Uterine overdistention in multiple gestations (and in polyhydramnios) has been implicated in preterm birth^{3,6}. It is well known that stretching of human myometrium results in proinflammatory cytokine expression⁸. In the case of preterm delivery, the common pathway of labor is activated prematurely by one or more of several triggers mentioned above. Recently, a concept that cell free fetal DNA is involved in maternal/fetal dialogue is discovered⁹. It is intriguing to speculate that disruption of maternal/fetal tolerance in dichorionic discordant pregnancies is a trigger that activates the common pathway of labor. Altered intraplacental (anastomoses) blood flow in discordant twin pregnancies could also contribute to the activation of this process. However, more studies are needed to confirm this hypothesis.

Results on differences in Apgar score were expected and reflected hostile intrauterine environment for one or both twins in these high-risk pregnancies.

Our study showed that there was no difference in the mode of delivery between discordant and concordant twins. In fact, 80% of all twin pregnancies are delivered by cesarean section irrespective of discordant twin growth. Based on the retrospective data available, twin discordance does not represent a contraindication for vaginal trial of labor, even if the larger twin is the nonpresenting twin. Weak evidence may support consideration of elective cesarean section in cases with extreme discordance in order to avoid combined delivery, particularly when the nonpresenting twin is 40% larger than the second twin¹⁰. From the practical standpoint, this may apply when the second twin is approx-

imately 40% larger than the presenting co-twin. However, even in cases of extreme discordance, the overall contribution of discordant twins to the outcome of combined delivery is minimal^{10,11}.

With regard to the choice of mode of delivery (elective cesarean delivery *versus* vaginal delivery), some recommendations can be made to contemporary obstetrician practice. The mode of twin delivery should be considered on the individual basis. This pregnancy specification should include twin presentations, gestational age, estimated birth weights, mother comorbidity, availability of expertise in the management of vaginal twin birth, and the woman's preference¹⁰. From the authors' point of view, vaginal delivery is indicated as long as the obstetrician is comfortable with and skilled in vaginal breech delivery. Most probably, explanation for the results of this study is the fact that modern obstetricians are more comfortable in delivering twins by cesarean section than vaginally. By doing that, they are 'protected' from law suits because they did what was 'the best for the mother and the child'.

The incidence of SGA in twins is usually over 20%^{12,13}. This is a much higher incidence than in our investigation. We also showed that there was difference in the SGA incidence between the groups. One of the possible explanations is that we used the birth weight chart specific for twins⁵. Unfortunately, twin-specific growth centiles have not been incorporated into routine practice in most centers due to the assumption that the genetic growth potential of twins should not differ significantly from that of a singleton¹⁴. It could be recommended that each department use birth weight chart specific for singletons and twins from local subpopulation.

Pregnancy with one or both twins with congenital anomaly was an exclusion criterion. So far, it has been documented that twin pregnancies complicated by one anomalous fetus are not at an increased risk of preterm delivery compared to twin pregnancies where both fetuses are normal^{14,15}. Stillbirth was also an exclusion criterion because twin pregnancies complicated by single intrauterine demise regardless of chorionicity, have a significantly higher risk of preterm birth. Reliable data on chorionicity were the most important advantage of our study. There are some data stating that there is no difference in preterm delivery rate between mono- and dichorionic pregnancies after ART^{16,17}. Most of the authors report opposite results. According to chorion-

icity, the mean gestational age at delivery is lower in monochorionic compared to dichorionic pregnancies. The proportion of twins born before 32 weeks (extreme preterm) is 2.5 times higher among monochorionic than dichorionic twins (30% *vs.* 13%)¹⁸⁻²⁰.

Our investigation confirmed that the mode of conception of twin pregnancy was not a risk factor for preterm delivery in discordant twin growth. This result is in concordance with previously published literature^{14,21,22}.

Fetal growth in pregnancies is under influence of genetic, maternal and uteroplacental factors. In twin pregnancies, it can be additionally influenced by different genetic potentials in dizygotic twins, by intraplacental anastomoses that result in unequal blood supply, or by abnormalities in the placental umbilical cord insertion site². Growth discordance is also one of the key defining features of the twin-to-twin transfusion syndrome (TTTS), a condition which confers a high risk of twin mortality and severe perinatal morbidity. To our knowledge, this is the first study of perinatal outcome in discordant twins regardless of the way of conceiving, performed at our Department, so we find it very important for our daily practice.

Conclusion

Usually, birth weight discordance is a risk factor for adverse perinatal outcomes. Discordant growth is influenced by gestational age at delivery, actual birth weight, gender discordance, chorionicity, growth restriction, TTTS, and birth order. In monochorionic twins, birth weight discordance is most often attributed to TTTS, inequalities in distribution of placental mass between the two fetuses, and abnormalities in cord insertion site. In dichorionic twins, there might be a difference in the genetic growth potential in some cases, but frequently growth discordance is a consequence of placental insufficiency, e.g., defective trophoblast invasion or impaired development of uteroplacental circulation. Twin discordance does not represent a contraindication to a vaginal trial of labor, even if the larger twin is the nonpresenting twin. From practical standpoint, when the second twin is approximately 40% bigger, elective cesarean section should be performed. Discordant growth twins, regardless of chorionicity, may benefit from increased antenatal surveillance.

References

- Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S. Births: final data for 2004. *Natl Vital Stat Rep.* 2006;55(1):1-101.
- Breathnach FM, Malone FD. Fetal growth disorders in twin gestations. *Semin Perinatol.* 2012;36(3):175-81. doi: 10.1053/j.semperi.2012.02.002
- Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet.* 2008;371(9606):75-84. doi: 10.1016/S0140-6736(08)60074-4
- Breathnach FM, McAuliffe FM, Geary M, Daly S, Higgins JR, Dornan J, *et al.* Definition of intertwin birth weight discordance. *Obstet Gynecol.* 2011;118(1):94-103. doi: 10.1097/AOG.0b013e31821fd208
- Roje D, Tadin I, Vućinović M, Vulić M, *et al.* Porodne težine i duljine novorođenčadi u Splitu, opravdanost razvijanja vlastitih referentnih vrijednosti za ocjenjivanje fetalnog rasta. *Gynaecol Perinatol.* 2005;14: 66-74. (in Croatian)
- Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. *Science.* 2014;345(6198):760-5. doi: 10.1126/science.1251816
- Morgan TK. Role of the placenta in preterm birth: a review. *Am J Perinatol.* 2016;33(3):258-66. doi: 10.1055/s-0035-1570379
- Shynlova OP, Oldenhof AD, Liu M, Langille L, Lye SJ. Regulation of c-fos expression by static stretch in rat myometrial smooth muscle cells. *Am J Obstet Gynecol.* 2002;186(6):1358-65.
- Jakobsen TR, Clausen FB, Rode L, Dziegiel MH, Tabor A. High levels of fetal DNA are associated with increased risk of spontaneous preterm delivery. *Prenat Diagn.* 2012;32(9):840-5. doi: 10.1002/pd.3917
- Christopher D, Robinson BK, Peaceman AM. An evidence-based approach to determining route of delivery for twin gestations. *Rev Obstet Gynecol.* 2011;4(3-4):109-16.
- Kontopoulos EV, Ananth CV, Smulian JC, Vintzileos AM. The influence of mode of delivery on twin neonatal mortality in the US: variance by birth weight discordance. *Am J Obstet Gynecol.* 2005;192(1):252-6.
- Fox NS, Rebarber A, Klauser CK, Roman AS, Saltzman DH. Intrauterine growth restriction in twin pregnancies: incidence and associated risk factors. *Am J Perinatol.* 2011;28(4):267-72. doi: 10.1055/s-0030-1270116
- Puccio G, Giuffrè M, Piccione M, Piro E, Malerba V, Corsello G. Intrauterine growth pattern and birthweight discordance in twin pregnancies: a retrospective study. *Ital J Pediatr.* 2014; 40:43. doi: 10.1186/1824-7288-40-43
- Jauniaux E, Ben-Ami I, Maymon R. Do assisted-reproduction twin pregnancies require additional antenatal care? *Reprod Biomed Online.* 2013;26(2):107-19. doi: 10.1016/j.rbmo.2012.11.008
- Harper LM, Odibo AO, Roehl KA, Longman RE, Macones GA, Cahill AG. Risk of preterm delivery and growth restriction in twins discordant for structural anomalies. *Am J Obstet Gynecol.* 2012;206(1):70-5. doi: 10.1016/j.ajog.2011.07.025

16. Mascarenhas M, Kamath MS, Muthukumar K, Mangalaraj AM, Chandy A, Aleyamma T. Obstetric outcomes of monochorionic pregnancies conceived following assisted reproductive technology: a retrospective study. *J Hum Reprod Sci.* 2014;7(2):119-24.
17. Trojner BA, Blickstein I, Verdenik I, Lucovnik M, Tul N. Outcome of monochorionic-biamniotic twins conceived by assisted reproduction: a population-based study. *J Perinat Med.* 2016;44(8):881-5.
18. Hack KE, Derks JB, Elias SG, Franx A, Roos EJ, Voerman SK, *et al.* Increased perinatal mortality and morbidity in monochorionic *versus* dichorionic twin pregnancies: clinical implications of a large Dutch cohort study. *BJOG.* 2008;115(1):58-67.
19. Hack KE, Derks JB, de Visser VL, Elias SG, Visser GH. The natural course of monochorionic and dichorionic twin pregnancies: a historical cohort. *Twin Res Hum Genet.* 2006;9(3):450-5.
20. Assuncao RA, Liao AW, Brizot ML, Krebs VL, Zugaib M. Perinatal outcome of twin pregnancies delivered in a teaching hospital. *Rev Assoc Med Bras.* 2010;56(4):447-51.
21. Geisler ME, O'Mahony A, Meaney S, Waterstone JJ, O'Donoghue K. Obstetric and perinatal outcomes of twin pregnancies conceived following IVF/ICSI treatment compared with spontaneously conceived twin pregnancies. *Eur J Obstet Gynecol Reprod Biol.* 2014;181:78-83. doi: 10.1016/j.ejogrb.2014.07.033
22. Zadori J, Kozinszky Z, Orvos H, Katona M, Kaali SG, Pal A. Birth weight discordance in spontaneous *versus* induced twins: impact on perinatal outcome. *J Assist Reprod Genet.* 2004;21(3):85-8.

Sažetak

DISKORDANTNI RAST U DIKORIONSKIH BLIZANACA I RIZIK PRIJEVREMENOG POROĐAJA

M. Vulić, L. Lalić, L. Vulić, D. Roje, Z. Benzon i Z. Meštrović

Cilj istraživanja je bio ustanoviti ima li diskordantni rast blizanaca u dikorionskim blizanačkim trudnoćama utjecaja na pojavnost prijevremenog porođaja. U studiju su uključene dikorionske blizanačke trudnoće u razdoblju od 1. siječnja 2013. do 31. prosinca 2015. Istraživane varijable su bile majčinska dob (godine), paritet, indeks tjelesne mase (kg/m²), način porođaja (vaginalno i carski rez), porođajna masa (grami) i zbroj APGAR (≤ 7 , 8-10). U blizanačkim trudnoćama s diskordantnim rastom bila je veća učestalost prijevremenog porođaja ($\chi^2=4,74$; $p=0,03$), ali nije bilo razlike u načinu dovršetka trudnoće između istraživanih skupina ($\chi^2=0,119$; $p=0,73$). Utvrđena je statistički značajna razlika u pojavnosti hipotrofične djece ($\chi^2=16,4556$; $p=0,000267$) i zbroju APGAR ($\chi^2=7,9931$; $p<0,05$) između istraživanih skupina. Način zanošenja u dikorionskim trudnoćama nije bio činitelj rizika za prijevremeni porođaj u istraživanim skupinama ($\chi^2=1,417$; $p=0,23$). Zaključno, diskordantni rast blizanaca u dikorionskim trudnoćama predstavlja činitelj rizika za prijevremeni porođaj, hipotrofiju novorođenčadi i niži zbroj APGAR, ali nema utjecaja na način dovršetka trudnoće.

Ključne riječi: *Prijevremeni porođaj; Trudnoća; Retrospektivne studije; Blizanci, dvojajčani; Hrvatska*