Neonatal hematological and biochemical complications in TTTS and TAPS

Verbeek, L.I.

General introduction

Over the past decades the incidence of monozygotic and dizygotic twin pregnancies has increased, largely as a result of assisted reproductive technologies.[1] The number of spontaneously conceived twins has increased as well due to increased maternal age in pregnant women.[2] Dizygotic twins are more common than monozygotic twins, 70 percent of twins is dizygotic and 30 percent is monozygotic.[3] Monozygotic twinning occurs in 3.5-4 per 1000 births across the world.[4] However, the incidence of dizygotic twinning variates among countries.[5] In the United States the twin birth rate was 33.9 twins per 1000 births in 2014.[6] In low and middle income countries the average twinning rate is approximately 13.1 per 1000 births.[5]

Dizygotic twins occur from fertilization of two oocytes, resulting in two embryos with each their own placenta and their own amniotic sac, named therefore dichorionic diamniotic twinning. Monozygotic twins are identical since these twins result from fertilization of a single oocyte. The type of placentation in monozygotic twins varies and depends on the timing of cleavage of the monozygotic blastomere. Cleavage during the first three days after fertilization results in two placentas, two chorions and two amnions, thus dichorionic diamniotic twinning (such as in dizygotic twins). When cleavage occurs between the fourth to the eighth day after fertilization, monozygotic twins will share their placenta and have one chorion and two amnions, henced called monochorionic diamniotic twinning. Cleavage between the ninth till twelfth day after fertilization results in a monochorionic monoamniotic twin, where fetuses share not only their placenta but also their amniotic sac. Cleavage after the twelfth day results in conjoined twins.[4;7] Approximately 75% of monozygotic twins are monochorionic, with an overall incidence of one in 400 pregnancies.[8] Twin pregnancies are at a higher risk of perinatal and neonatal morbidity and mortality compared to singleton pregnancies.[9-11] This is partly due to the fact that twins are more likely to be born prematurely and small for gestational age.[12-15] In addition, one of the most important risk factors for the increased rate of perinatal complications in twins is due to the type of placentation. Monochorionic twins (which occur only after monozygoc twinning) are at increased risk of complications compared to dichorionic twins due to the differences in placentas. Nearly all monochorionic twins (99%) have placental vascular anastomoses connecting the blood circulation of both twins[16;17] whereas dichorionic twins have always two separate placentas without vascular connections. Only a few rare cases of dichorionic twins with placental anastomoses have been described.[18;19]

Vascular anastomoses lead to inter-twin blood transfusion, which is 'balanced' in uncomplicated monochorionic twins during pregnancy. However, vascular anastomoses play may also lead to unbalanced inter-twin transfusion and play a key role in the development of severe complications such as twin-twin transfusion syndrome (TTTS) and twin anemia-polycythemia (TAPS).

TTTS occurs in approximately 9-15% of monochorionic pregnancies.[20;21] TTTS is diagnosed prenatally based on the presence of twin oligo-polyhydramnios sequence (TOPS). Oligohydramnios in the donor is defined as a cut-off at a deepest vertical pocket of amniotic fluid ≤ 2 cm and polyhydramnios in the recipient as ≥ 8 cm within the first 20 weeks of

gestation or, according to the Eurofoetus criteria, ≥ 10 cm after 20 weeks of gestation.[22;23] In 1999, Quintero et al. defined a classification which consists of 5 stages. Staging depends on bladder filling, abnormal Doppler studies, hydrops fetalis and fetal demise.[23] TTTS is associated with a high fetal and neonatal mortality rate of 73-100% if left untreated.[24] The best treatment for TTTS is fetoscopic laser coagulation of the anastomoses during pregnancy.[25]
Another complication in monochorionic twins is TAPS, first described by our research group in 2007.[26] TAPS may occur spontaneously in 3-5% of monochorionic twins or in 2-16% after laser surgery in TTTS ('post-laser TAPS').[27-31] TAPS is characterized by slow inter-twin blood transfusion resulting in large inter-twin hemoglobin differences at birth, without signs of TOPS during pregnancy. The pathogenesis is based on the presence of minuscule (<1 mm) vascular anastomoses. TAPS can be diagnosed prenatally or postnatally. Prenatal diagnosis of TAPS is based on Doppler ultrasound measurements with an increased middle cerebral artery-peak systolic velocity (MCA-PSV) > 1.5 multiples of median (MoM) in the donor, suggestive for fetal anemia and a decreased MCA-PSV (MoM < 1.0) in the recipient suggestive for polycythemia.[32] In 40-63% of cases, TAPS is diagnosed after birth.[32] Postnatal diagnosis is based on inter-twin hemoglobin difference of ≥ 8 g/dL (i.e. ≥ 5 mmol/L). In addition, to distinguish from acute peripartum TTTS, at least one of the following criteria are required: reticulocyte count ratio > 1.7 or minuscule placental anastomoses.[33]

Outline of the thesis

The Leiden University Medical Center (LUMC) is a tertiary care center and the national referral center for the treatment of complicated monochorionic twins with TTTS and TAPS. Improved antenatal management in TTTS and TAPS has led to an increase in perinatal survival. Attention is now shifting towards postnatal complications in survivors. The aim of this thesis is to evaluate the hematological and biochemical complications in twins affected by TTTS or TAPS.

A. Hematological complications: Most previous studies reported on differences in hemoglobin values in *complicated* monochorionic twins. To compare the hematological values with *uncomplicated* twins, we analyzed hemoglobin levels in dichorionic twins and monochorionic twins without TTTS or TAPS. Since hemoglobin differences may be due to a multitude of factors, we studied the impact of various risk factors including birth order, mode of delivery and delivery time interval between the first-born and second-born twin.
B. Biochemical complications: Only a few small studies in TTTS reported on inter-twin biochemical differences.[34;35] Knowledge on biochemical abnormalities in twins with TAPS is also sparse. We hypothesized that inter-twin blood flow through the placental anastomoses not only lead to transfer of red blood cells from one twin to the other, but also allow inter-twin transfer from nutrients and proteins, and focused mainly on differences in albumin and total protein, and renal function. Hypoalbuminemia is an independent risk factor for morbidity and mortality in neonates.[36;37] In addition, inter-twin blood flow may have an important impact on renal function due to impaired renal perfusion. To date, only a few small studies on renal function have been performed, mainly in TTTS treated with amniocentesis.[38-41]

The following chapters describe the objectives in more detail:

Chapter 2 – Literature review on hematological disorders in twins with TTTS, TAPS, acute peripartum TTTS, acute perimortem TTTS and uncomplicated monochorionic twins.

Chapter 3 – Study on hemoglobin differences in a large cohort of uncomplicated monochorionic twins in relation to birth order, mode of delivery and delivery time interval between the first-born and second-born twin.

Chapter 4 – Study on hemoglobin levels in a large cohort of dichorionic twins compared to uncomplicated monochorionic twins and in relation to birth order and mode of delivery.

Chapter 5 – Study on albumin levels in donor and recipient twins with TTTS treated conservatively or with fetoscopic laser surgery.

Chapter 6 – Study on albumin levels in donor and recipient twins with TAPS compared to a matched group of uncomplicated monochorionic twins.

Chapter 7– Evaluation of short-term renal function in neonates with TAPS admitted to three European centers.

Chapter 8 – Study on short-term renal function in twins with TTTS treated with fetoscopic laser surgery or conservative treatment.

Chapter 9 – General discussion concerning the results of these studies and future perspectives and proposals for future studies.

Chapter 10 – Summary of the thesis.

Chapter 11 - Appendices.

References

1 Derom C, Vlietinck R, Derom R, Van den Berghe H, Thiery M: Increased monozygotic twinning rate after ovulation induction. Lancet 1987;1:1236-1238.
2 Martin JA, Park MM: Trends in twin and triplet births: 1980-97. Natl Vital Stat Rep 1999;47:1-16.
3 Cameron AH, Edwards JH, Derom R, Thiery M, Boelaert R: The value of twin surveys in the study of malformations. Eur J Obstet Gynecol Reprod Biol 1983;14:347-356.
4 Hall JG: Twinning. Lancet 2003;362:735-743.
5 Smits J, Monden C: Twinning across the Developing World. PLoS One 2011;6:e25239.
6 Hamilton BE, Martin JA, Osterman MJ, Curtin SC, Matthews TJ: Births: Final Data for 2014. Natl Vital Stat Rep 2015;64:1-64.
7 McNamara HC, Kane SC, Craig JM, Short RV, Umstad MP: A review of the mechanisms and evidence for typical and atypical twinning. Am J Obstet Gynecol 2016;214:172-191.
8 Lewi L, Van SD, Gratacos E, Witters I, Timmerman D, Deprest J: Monochorionic diamniotic twins: complications and management options. Curr Opin Obstet Gynecol 2003;15:177-194.
9 Kiely JL: The epidemiology of perinatal mortality in multiple births. Bull N Y Acad Med 1990;66:618-637.
10 McCarthy BJ, Sachs BP, Layde PM, Burton A, Terry JS, Rochat R: The epidemiology of neonatal death in twins. Am J Obstet Gynecol 1981;141:252-256.
11 Grothe W, Ruttgers H: Twin pregnancies: an 11-year review. Acta Genet Med Gemellol (Roma) 1985;34:49-58.
12 Rode L, Tabor A: Prevention of preterm delivery in twin pregnancy. Best Pract Res Clin Obstet Gynaecol 2014;28:273-283.
13 Biggio JR, Anderson S: Spontaneous Preterm Birth in Multiples. Clin Obstet Gynecol 2015;58:654-667.
14 Ananth CV, Vintzileos AM, Shen-Schwarz S, Smulian JC, Lai YL: Standards of birth weight in twin gestations stratified by placental chorionicity. Obstet Gynecol 1998;91:917-924.
15 Lewi L, Devlieger R, De CL, Deprest J: Growth discordance. Best Pract Res Clin Obstet Gynaecol 2014;28:295-303.
16 Denbow ML, Cox P, Taylor M, Hammal DM, Fisk NM: Placental angioarchitecture in monochorionic twin pregnancies: relationship to fetal growth, fetofetal transfusion syndrome, and pregnancy outcome. Am J Obstet Gynecol 2000;182:417-426.
17 Zhao D, Lipa M, Wielgos M, Cohen D, Middeldorp JM, Oepkes D, Lopriore E: Comparison Between Monochorionic and Dichorionic Placentas With Special Attention to Vascular Anastomoses and Placental Share. Twin Res Hum Genet 2016;19:191-196.
18 Biran V, Bornes M, Aboura A, Masmoudi S, Drunat S, Baumann C, Osimani S, Dalle JH, Sterkers G, Verloes A, Farnoux C, Maury L, Schmitz T, Khung S, Baud O: A long-term competent chimeric immune system in a dizygotic dichorionic twin. Pediatrics 2011;128:e458-e463.
19 Lage JM, Vanmarter LJ, Mikhail E: Vascular anastomoses in fused, dichorionic twin placentas resulting in twin transfusion syndrome. Placenta 1989;10:55-59.
20 Lutfi S, Allen VM, Fahey J, O'Connell CM, Vincer MJ: Twin-twin transfusion syndrome: a population-based study. Obstet Gynecol 2004;104:1289-1297.
21 Baschat A, Chmait RH, Deprest J, Gratacos E, Hecher K, Kontopoulos E, Quintero R, Skupski DW, Valsky DV, Ville Y: Twin-to-twin transfusion syndrome (TTTS). J Perinat Med 2011;39:107-112.
22 Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y: Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. N Engl J Med 2004;351:136-144.

23 Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M: Staging of twin-twin transfusion syndrome. J Perinatol 1999;19:550-555.
24 Berghella V, Kaufmann M: Natural history of twin-twin transfusion syndrome. J Reprod Med 2001;46:480-484.
25 Slaghekke F, Lopriore E, Lewi L, Middeldorp JM, van Zwet EW, Weingertner AS, Klumper FJ, DeKoninck P, Devlieger R, Kilby MD, Rustico MA, Deprest J, Favre R, Oepkes D: Fetoscopic laser coagulation of the vascular equator versus selective coagulation for twin-to-twin transfusion syndrome: an open-label randomised controlled trial. Lancet 2014;383:2144-2151.
26 Lopriore E, Middeldorp JM, Oepkes D, Kanhai HH, Walther FJ, Vandenbussche FP: Twin anemia-polycythemia sequence in two monochorionic twin pairs without oligo-polyhydramnios sequence. Placenta 2007;28:47-51.
27 Casanova J, Paiva C, Carvalho C, Cunha AC: Twin anemia polycythemia sequence: a report of three cases. J Reprod Med 2014;59:596-598.
28 Habli M, Bombrys A, Lewis D, Lim FY, Polzin W, Maxwell R, Crombleholme T: Incidence of complications in twin-twin transfusion syndrome after selective fetoscopic laser photocoagulation: a single-center experience. Am J Obstet Gynecol 2009;201:417.
29 Lopriore E, Slaghekke F, Middeldorp JM, Klumper FJ, Oepkes D, Vandenbussche FP: Residual anastomoses in twin-to-twin transfusion syndrome treated with selective fetoscopic laser surgery: localization, size, and consequences. Am J Obstet Gynecol 2009;201:66-4.
30 Lewi L, Jani J, Blickstein I, Huber A, Gucciardo L, Van MT, Done E, Boes AS, Hecher K, Gratacos E, Lewi P, Deprest J: The outcome of monochorionic diamniotic twin gestations in the era of invasive fetal therapy: a prospective cohort study. Am J Obstet Gynecol 2008;199:514-518.
31 Gucciardo L, Lewi L, Vaast P, Debska M, De CL, Van MT, Done E, Devlieger R, Deprest J: Twin anemia polycythemia sequence from a prenatal perspective. Prenat Diagn 2010;30:438-442.
32 Slaghekke F, Kist WJ, Oepkes D, Pasman SA, Middeldorp JM, Klumper FJ, Walther FJ, Vandenbussche FP, Lopriore E: Twin anemia-polycythemia sequence: diagnostic criteria, classification, perinatal management and outcome. Fetal Diagn Ther 2010;27:181-190.
33 Lopriore E, Slaghekke F, Oepkes D, Middeldorp JM, Vandenbussche FP, Walther FJ: Hematological characteristics in neonates with twin anemia-polycythemia sequence (TAPS). Prenat Diagn 2010;30:251-255.
34 Berry SM, Puder KS, Bottoms SF, Uckele JE, Romero R, Cotton DB: Comparison of intrauterine hematologic and biochemical values between twin pairs with and without stuck twin syndrome. Am J Obstet Gynecol 1995;172:1403-1410.
35 Okamura K, Murotsuki J, Kosuge S, Tanigawara S, Yajima A: Diagnostic use of cordocentesis in twin pregnancy. Fetal Diagn Ther 1994;9:385-390.
36 Vincent JL, Dubois MJ, Navickis RJ, Wilkes MM: Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg 2003;237:319-334.
37 Morris I, McCallion N, El-Khuffash A, Molloy EJ: Serum albumin and mortality in very low birth weight infants. Arch Dis Child Fetal Neonatal Ed 2008;93:F310-F312.
38 Lenclen R, Paupe A, Ciarlo G, Couderc S, Castela F, Ortqvist L, Ville Y: Neonatal outcome in preterm monochorionic twins with twin-to-twin transfusion syndrome after intrauterine treatment with amnioreduction or fetoscopic laser surgery: comparison with dichorionic twins. Am J Obstet Gynecol 2007;196:450-457.
39 Beck M, Graf C, Ellenrieder B, Bokenkamp A, Huber A, Hecher K, Bartmann P: Long-term outcome of kidney function after twin-twin transfusion syndrome treated by intrauterine laser coagulation. Pediatr Nephrol 2005;20:1657-1659.
40 De Paepe ME, Stopa E, Huang C, Hansen K, Luks FI: Renal tubular apoptosis in twin-to-twin transfusion

syndrome. Pediatr Dev Pathol 2003;6:215-225.
41 Lopriore E, Nagel HT, Vandenbussche FP, Walther FJ: Long-term neurodevelopmental outcome in twin-to-twin transfusion syndrome. Am J Obstet Gynecol 2003;189:1314-1319.