Neonatal hematological and biochemical complications in TTTS and TAPS

Verbeek, L.I.

Chapter 9
General discussion and future perspectives

General discussion and future perspectives

Twin pregnancies, either dichorionic or monochorionic, are associated with higher morbidity and mortality rates compared to singletons due to the higher rate of premature delivery.[1-3] Monochorionic twin pregnancies carry a higher risk compared to dichorionic twins due to their unique placenta architecture. All monochorionic placentas have vascular anastomoses which can lead to inter-twin blood transfusion. When the inter-twin transfusion is unbalanced, severe disorders such as twin-twin transfusion syndrome (TTTS) and twin anemia-polycythemia sequence (TAPS) may occur.

The optimal treatment for TTTS is fetoscopic laser surgery to coagulate the vascular anastomoses.[4-6] Introduction of laser surgery in 1990 led to a strong decrease in perinatal mortality and neonatal morbidity. However, there is still room for improvement since incomplete laser treatment and residual anastomoses can lead to recurrent TTTS or post-laser TAPS.

The optimal treatment for TAPS is not yet found, since TAPS was only recently discovered in 2007. Different options have been described: expectant management, intrauterine transfusion in the donor twin with or without partial exchange transfusion in the recipient, fetoscopic laser coagulation of the vascular anastomoses or selective termination of pregnancy.[7-12] The only causal treatment is fetoscopic laser coagulation. A randomized controlled trial to determine the optimal treatment in TAPS is warranted. Given the rarity of TAPS, international collaboration is of paramount importance.

At birth, complicated monochorionic twins are at increased of neonatal morbidity, in particular cerebral injury such as severe intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (PVL) and porencephalic cysts and cardiovascular morbidity such as right ventricular outflow tract obstruction (RVOTO) and persistent pulmonary hypertension (PPHN).[13-19] In this thesis we focused primarily on the risk of hematological and biochemical disorders during the neonatal period in the various subgroups of complicated monochorionic twins.

Hematological disorders

A. Red blood cell disorders:

A.1. In *chronic TTTS*, hemoglobin differences are already present antenatally[20;21], but may also be encountered at birth. The presence of hemoglobin differences after delivery depends on the type of antenatal treatment. In TTTS twins treated with fetoscopic laser coagulation, no significant differences in hemoglobin levels between donor twins and recipient twins are found (chapter 2 and 5). On the other hand, in TTTS twins treated conservatively, donor twins have lower hemoglobin levels at birth compared to recipients. Donors may be severely anemic whereas recipients may suffer from severe hyperviscosity-polycythemia.

A.2. In *TAPS*, large inter-twin hemoglobin differences at birth are found. TAPS is based on chronic unbalanced inter-twin transfusion. Donor twins have chronic anemia requiring a blood transfusion at birth. Recipient twins may be severely polycythemic and may require a partial exchange transfusion.[22;23] Due to hyperviscosity, recipients may suffer from vascular limb necrosis or severe cerebral injury.[24;25] Donor twins with TAPS always have a highly increased reticulocyte count and the ratio of reticulocyte counts between donor and recipient is >1.7. Reticulocyte count should always be measured to distinguish between TAPS (high reticulocyte count ratio >1.7) and acute peripartum TTTS (low reticulocyte count ratio < 1.7). Examination of the placenta is also crucial to discriminate between the two disorders. One of the diagnostic criteria for TAPS is based on the detection of small anastomoses after careful placenta injection. However, placenta injection is not always easy and is only performed in a few specialized centers. Alternatively, examination of the maternal side of the placenta can help perinatologists, since in TAPS the placenta share of the recipient is much darker compared to the pale placenta share of the donor. [26] In our experience, no color difference is detected between the two placenta shares in acute peripartum TTTS (unpublished data).

A.3. In *acute peripartum TTTS*, large inter-twin hemoglobin differences are always present at birth due to acute transfusion through large superficial anastomoses. The donor suffers from acute blood loss which may lead to hypovolemic shock requiring an acute blood transfusion. Recipient twins on the other hand may need partial exchange transfusion in case of severe polycythemia-hyperviscosity.

The diagnostic criteria for acute peripartum TTTS are based on a large difference in hemoglobin levels of > 8 g/dL at birth in the absence of chronic TTTS or TAPS. Presence of oligo-polyhydramnios antenatally (criterion for chronic TTTS) or large reticulocyte count ratio and minuscule anastomoses (criterion for TAPS) should therefore be ruled out before reaching the diagnosis of acute peripartum TTTS. However, in most case reports reticulocyte count or placenta injection studies were not performed and TAPS could not be ruled out. We suspect that the majority of these reported cases were wrongly diagnosed and were probably TAPS cases. In our experience, TAPS occurs more frequently than acute peripartum TTTS. Given the rarity of acute peripartum TTTS, international multicenter studies are needed to increase our knowledge on the true incidence, hematological consequences and risk factors of acute peripartum TTTS.

Importantly, hemoglobin levels are often measured directly after birth, but in case of acute blood loss or transfusion, equilibration of hemoglobin levels occurs only several hours after the event. In case of suspected acute peripartum TTTS, hemoglobin level measurements should therefore be repeated approximately 4-6 hours after birth to determine the true hemoglobin levels.

A.4. Hemoglobin differences in *uncomplicated monochorionic twins* and dichorionic twins are often found when delivered vaginally, but not after cesarean delivery. Second-born twins delivered vaginally have higher hemoglobin levels compared to first-born twins (chapter 3 and 4). Since dichorionic twins have their own separate placenta without vascular anastomoses, hemoglobin differences in dichorionic twins cannot only be explained by inter-twin transfusion. We hypothesize that the hemoglobin differences are related to the

timing of cord clamping. Delayed cord clamping is associated with higher hemoglobin levels at birth due to increased placento-fetal transfusion.[27;28] We suspect that the umbilical cord of first-born twins is clamped relatively earlier than the cord of second-born twins, and that this could lead to the difference in hemoglobin levels. However, in our retrospective studies timing of cord clamping was not recorded, making it difficult to confirm our hypothesis. A prospective study on the timing of cord clamping in twins after vaginal delivery could give new insights. An alternative explanation for hemoglobin differences in uncomplicated monochorionic twins is unbalanced intra-partum transfusion. Due to differences in pressure gradients and uterine contractions relatively more blood might flow from twin 1 to twin 2 resulting in a higher hemoglobin level in twin 2. Another hypothesis is that after birth of twin 1, twin 2 might receive blood from both placenta shares through the anastomoses, resulting in a higher hemoglobin level. More research is needed to study various hypothesis leading to hemoglobin differences in uncomplicated monochorionic twins.

A.5. Hemoglobin differences in *monochorionic twins with selective intrauterine growth restrictions* (sIUGR)

sIUGR occurs in 10-25% of monochorionic twins and is defined by the presence growth restriction in one fetus (estimated fetal weight < 10th percentile).[29;30] A recent study from Stagnati et al. describes that third-trimester inter-twin middle cerebral arterial peak systolic velocity (MCA-PSV) discrepancy in uncomplicated MC is associated with selective intrauterine growth restriction (sIUGR) at birth and an inter-twin birth weight discrepancy of > 25%. The optimal cut-off point for MCA-PSV discrepancy was 0.30 multiples of median (MoM) (sensitivity of 70% and specifity of 69% for sIUGR). Hemoglobin levels at birth were however not reported in this study.[31] Nevertheless, given the good correlation between MCA-PSV measurements and hemoglobin levels, twins with sIUGR may have differences in hemoglobin levels at birth.[32] Growth restriction due to placental insufficiency is associated with chronic hypoxia and increased erythropoiesis which could in turn lead to higher hemoglobin levels. Further research on hemoglobin levels in monochorionic twins with sIUGR in a large cohort is required to confirm these preliminary findings.

B. Thrombocytopenia or leucopenia:

Not much is known on the occurrence of other hematological complications such as thrombocytopenia or leucopenia in TTTS survivors. Polycythemia is known to be associated with thrombocytopenia.[33] Therefore, polycythemic recipient twins may be at risk for thrombocytopenia at birth. Research on white blood cell disorders is also sparse. A small study from Koenig et al. showed neutropenia in each of five donor twins. Since no evidence of infection was observed and no left shift was seen (as in neutropenia of pregnancy-induced hypertension) they postulated that reduced neutrophil production was related to accelerated erythropoiesis.[34] Further investigations on the occurrence and associated complications of thrombocytopenia and leucopenia is warranted, particularly in TTTS not treated with laser surgery or after incomplete laser.

In TAPS, thrombocytopenia is often found (in 45% of cases) and occurs more often recipient twins compared to donor twins (63% versus 26%).[23] Recipient twins are per definition polycythemic and therefore at risk for thrombocytopenia. In donor twins thrombocytopenia could be related to IUGR or chronic hypoxia.[35-37] The white blood cell line is not yet investigated in TAPS twins.

The our best knowledge no studies reported on thrombocytes or the white blood cell rihanabocytopenia.[35-37] Research on the occurrence of thrombocytopenia and white blood cell disorders in twins with sIUGR is warranted.

Biochemical disorders

In both TTTS and TAPS, knowledge on biochemical values is scarce. We hypothesize that inter-twin blood transfusion through the vascular anastomoses in TTTS and TAPS allows not only inter-twin flow of red blood cells, but also inter-twin flow of nutrients and proteins and can lead to biochemical disorders. In addition, inter-twin circulatory and hemodynamic imbalance can lead to renal hypo-or hyperperfusion and eventually to renal dysfunction.

A. Hypoalbuminemia

In TTTS twins treated conservatively, we found that donor twins had significantly lower albumin levels compared to recipient twins. In TTTS twins treated with fetoscopic laser surgery, no inter-twin differences in albumin were detected (chapter 5). Our findings suggest that vascular anastomoses not only allow significant loss of hemoglobin, but also loss of albumin. Hypothetically, hypoalbuminemia in donor twins may also result from a decreased production in the liver due to a subordinate physical condition of these donor twins. However, we did not analyze other proteins or other parameters for the function of the liver such as the coagulation. Furthermore, since renal dysfunction occurs more often in donor twins treated conservatively (chapter 8), hypoalbuminemia in donor twins might also result from proteinuria and renal loss.

We found no differences in neonatal morbidity and mortality between donors and recipients. However, our retrospective study was not powered to detect such differences. In the 4 conservatively treated TTTS donors, 1 donor had skin edema.

In TAPS twins, albumin levels were also lower in donor twins (chapter 6). Hypoalbuminemia occurred more often in donor twins. In the 5 TAPS donors with hypoalbuminemia (< 20 g/L), skin edema was present in 2 donors of which one had severe respiratory and circulatory failure. Another donor suffered from hydrops fetalis. Although no significant differences in neonatal morbidity between donors and recipients were found, these data could suggest that in a larger cohort differences in morbidity may be detected.

To be able to compare TTTS and TAPS twins with uncomplicated monochorionic twins, we evaluated albumin levels in a control group of uncomplicated monochorionic twins as well. We compared the larger twin to the smaller twin and found no differences in albumin levels. The overall incidence of hypoalbuminemia was 1% (1/100).

In adults hypoalbuminemia is an independent risk factor for poor clinical outcomes.[38] As for most diseases, hypoalbuminemia in children is less studied. However, several studies in critically ill children concluded that it is a risk factor for morbidity and mortality.[39-41] Prognostic value of hypoalbuminemia in neonates is less investigated. Three studies showed that hypoalbuminemia in term and preterm neonates is associated with increased risk of mortality.[42-44] In addition, several studies in term and preterm neonates showed

that hypoalbuminemia is associated with increased risk of morbidity, including hydrops fetalis, edema, necrotizing enterocolitis, sepsis, respiratory distress syndrome, chronic lung disease, mechanical ventilation and longer hospital stays.[45-48] Albumin levels are also known to be correlated with gestational age [44;49-51] and normal ranges in preterm neonates are not well known. In our studies we defined hypoalbuminemia as albumin < 25 g/l and albumin < 20 g/l, whereas median gestational age was 30 weeks in TTTS twins and 32 weeks in TAPS twins (chapter 5 and 6).

B. Renal function

During pregnancy, donor twins with TTTS suffer from severe renal hypoperfusion resulting in hypovolemia, oliguria and oligohydramnios. Several studies in TTTS twins treated conservatively reported various renal complications in TTTS twins after birth.[52-57] Renal function in TTTS twins treated with laser surgery is less investigated.[58;59] In our retrospective study we evaluated creatinine levels in the first week after birth and urine output in TTTS twins treated with laser surgery compared to TTTS twins treated conservatively (chapter 8). We found that renal dysfunction (defined as creatinine level > 100 μmol/L) occurs less often in twins treated with laser surgery compared to twins treated conservatively (7.1% versus 37.9%). In the laser group, creatinine levels were higher in twins treated with incomplete laser compared with twins treated with complete laser. No differences in creatinine levels between donors and recipients were found. In TTTS twins treated conservatively, we found a high risk of oliguria in donors (> 90%) and lower blood pressure at birth.

Higher creatinine levels may reflect a state of chronic hypovolemia due to chronic blood loss (pre-renal hypothesis). Circulatory imbalance could reduce renal perfusion and glomerular perfusion pressure. This theory is supported by the lower blood pressure and lower urine output in conservatively treated TTTS donors. An alternative hypothesis may be that elevated creatinine levels could result from chronic hypoxia and anemia (renal hypothesis). Alternatively, hormonal dysfunction may also affect TTTS twins. Besides the concept of unbalanced inter-twin blood transfusion, there is also evidence for an adaptive response of the renal, endocrine and cardiovascular system to alter blood volume and causing twin oligo-polyhydramnios sequence (TOPS). Several studies have reported on highly abnormal values of hormones. In donor fetuses, plasma and amniotic vasopressin levels are higher compared to recipients. Oligohydramnios and higher creatinine levels in donors may therefore occur as a consequence of vasopressin mediated reduction in fetal urine output.[60] In autopsy studies in TTTS twins, overexpression of the renin protein and transcript with evidence of renin synthesis was observed in donor kidneys. In recipients, renin expression was virtually absent and probably down-regulated.[61-63] Fetal atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and endothelin levels are higher in recipient twins compared to donor twins.[64;65] Hypervolemia causes stretch of the cardiac atria and release of ANP and BNP which have natriuretic and vasodilatory properties resulting in polyuria and polyhydramnios.

Although these hormonal reactions seem to be sufficient; increased release of renin and vasopressin in hypotensive/hypovolemic donors and increased release of ANP and BNP in hypertensive/hypervolemic recipients, the placental anastomoses facilitate exchange of these hormones and cause paradoxic effects.[63]

In TAPS, donor twins do not have oligohydramnios reflecting a different antenatal situation compared to TTTS twins. However, we found that donor twins with TAPS have higher creatinine levels compared to recipients and renal dysfunction occurred more often in donor twins compared to recipients twins (26.0% versus 6.3%). Besides, donors had a lower blood pressure at birth and lower urine production. Our data suggest that chronic blood loss in donor twins may not only lead to anemia and hypoalbuminemia, but may also affect the short-term renal function. Our hypothesis is that chronic anemia in donor twins causes hypoxia and results in an increased risk for renal dysfunction.

We also evaluated renal function in uncomplicated monochorionic twins and compared larger twins to smaller twins. No differences between these twins were found. The overall incidence of short-term renal dysfunction in uncomplicated monochorionic twins was 7.7% (8/104).

The assessment of short-term renal function in our studies was only based on routine measurements at our neonatal nursery including urine production, creatinine and urea levels during the first week. More detailed information on renal function would require different assessments and a different study design. Whether renal dysfunction may also have long-term consequences such as impaired renal function in adult age requires further investigation. Beck et al. found in a small group of 18 children (TTTS twins treated with laser surgery) at median age 3 year no renal dysfunction.[66] However, accurate renal follow-up should take much longer. Due to the large reserve capacity of the kidney, serum creatinine could be normal for a long time. When children grow older and particularly during the growth spurt, renal insufficiency might become evident.

Renal injury which may occur in donor twins may have permanent effects up to adult age, warranting further long-term investigations. This is in analogy with the 'Brenner hypothesis' which states that retardation of renal development may give rise to increased postnatal risk for systemic hypertension as well as enhanced risk of expression of renal disease.[67] To conclude, complicated monochorionic twins are at increased risk for hematological and biochemical disorders in the neonatal period. Future research should focus on the long-term outcome. In TTTS, treatment with fetoscopic laser surgery has a protective effect. Whether in TAPS fetoscopic laser surgery is the optimal treatment and also protective against hematological and biochemical disorders, must be determined by further trials. Our studies focused on TTTS and TAPS, however other complications in monochorionic twins such as monoamniotic twinning, sIUGR and twin reversed arterial perfusion sequence (TRAP) are probably also at risk for biochemical and hematological complications in the neonatal period, warranting further investigations. Given the rarity of these diseases, close collaboration between obstetricians and neonatologists and multicenter participation is of paramount importance to improve our understanding of neonatal morbidity in complicated monochorionic twins.

References

1 Kiely JL: The epidemiology of perinatal mortality in multiple births. Bull N Y Acad Med 1990;66:618-637.

2 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.

3 Grothe W, Ruttgers H: Twin pregnancies: an 11-year review. Acta Genet Med Gemellol (Roma) 1985;34:49-58.

4 De Lia JE, Cruikshank DP, Keye WR, Jr.: Fetoscopic neodymium:YAG laser occlusion of placental vessels in severe twin-twin transfusion syndrome. Obstet Gynecol 1990;75:1046-1053.

5 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.

6 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.

7 Sananes N, Veujoz M, Severac F, Barthoulot M, Meyer N, Weingertner AS, Kohler M, Guerra F, Gaudineau A, Nisand I, Favre R: Evaluation of the Utility of in utero Treatment of Twin Anemia-Polycythemia Sequence. Fetal Diagn Ther 2015;38:170-178.

8 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.

9 Abdel-Sattar M, Platt LD, DeVore G, Porto M, Benirschke K, Chmait RH: Treatment of Complicated Spontaneous Twin Anemia-Polycythemia Sequence via Fetoscopic Laser Ablation of the Vascular Communications. Fetal Diagn Ther 2015;38:233-237.

10 Genova L, Slaghekke F, Klumper FJ, Middeldorp JM, Steggerda SJ, Oepkes D, Lopriore E: Management of twin anemia-polycythemia sequence using intrauterine blood transfusion for the donor and partial exchange transfusion for the recipient. Fetal Diagn Ther 2013;34:121-126.

11 Lopriore E, Hecher K, Vandenbussche FP, van den Wijngaard JP, Klumper FJ, Oepkes D: Fetoscopic laser treatment of twin-to-twin transfusion syndrome followed by severe twin anemia-polycythemia sequence with spontaneous resolution. Am J Obstet Gynecol 2008;198:e4-e7.

12 Guenot C, Robyr R, Jastrow N, Vial Y, Raio L, Baud D: Fetal Intra-Peritoneal Transfusion for the Management of Very Early Spontaneous Twin Anemia-Polycythemia Sequence in an Obese Patient With a Whole Anterior Placenta. Twin Res Hum Genet 2016;19:154-157.

13 Pruetz JD, Sklansky M, Detterich J, Korst LM, Llanes A, Chmait RH: Twin-twin transfusion syndrome treated with laser surgery: postnatal prevalence of congenital heart disease in surviving recipients and donors. Prenat Diagn 2011;31:973-977.

14 Michelfelder E, Tan X, Cnota J, Divanovic A, Statile C, Lim FY, Crombleholme T: Prevalence, Spectrum, and Outcome of Right Ventricular Outflow Tract Abnormalities in Twin-twin Transfusion Syndrome: A Large, Single-center Experience. Congenit Heart Dis 2015;10:209-218.

15 Eschbach SJ, Boons LS, van ZE, Middeldorp JM, Klumper FJ, Lopriore E, Teunissen AK, Rijlaarsdam ME, Oepkes D, Ten Harkel AD, Haak MC: Right ventricular outflow tract obstruction in complicated monochorionic twin pregnancies. Ultrasound Obstet Gynecol 2016.

16 Lopriore E, van Wezel-Meijler G, Middeldorp JM, Sueters M, Vandenbussche FP, Walther FJ: Incidence, origin, and character of cerebral injury in twin-to-twin transfusion syndrome treated with fetoscopic laser surgery. Am J Obstet Gynecol 2006;194:1215-1220.

17 Delsing B, Lopriore E, Blom N, Te Pas AB, Vandenbussche FP, Walther FJ: Risk of persistent pulmonary hypertension of the neonate in twin-to-twin transfusion syndrome. Neonatology 2007;92:134-138.

18 Takahashi H, Takahashi S, Tsukamoto K, Ito Y, Nakamura T, Hayashi S, Sago H: Persistent pulmonary hypertension of the newborn in twin-twin transfusion syndrome following fetoscopic laser surgery. J Matern Fetal Neonatal Med 2012;25:543-545.
19 van Klink JM, Koopman HM, van Zwet EW, Oepkes D, Walther FJ, Lopriore E: Cerebral injury and neurodevelopmental impairment after amnioreduction versus laser surgery in twin-twin transfusion syndrome: a systematic review and meta-analysis. Fetal Diagn Ther 2013;33:81-89.
20 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.
21 Denbow M, Fogliani R, Kyle P, Letsky E, Nicolini U, Fisk N: Haematological indices at fetal blood sampling in monochorionic pregnancies complicated by feto-fetal transfusion syndrome. Prenat Diagn 1998;18:941-946.
22 Ashwal E, Yinon Y, Fishel-Bartal M, Tsur A, Chayen B, Weisz B, Lipitz S: Twin Anemia-Polycythemia Sequence: Perinatal Management and Outcome. Fetal Diagn Ther 2016;40:28-34.
23 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.
24 Stranak Z, Korcek P, Hympanova L, Kyncl M, Krofta L: Prenatally Acquired Multiple Limb Ischemia in a Very Low Birth Weight Monochorionic Twin. Fetal Diagn Ther 2015.
25 Robyr R, Lewi L, Salomon LJ, Yamamoto M, Bernard JP, Deprest J, Ville Y: Prevalence and management of late fetal complications following successful selective laser coagulation of chorionic plate anastomoses in twin-to-twin transfusion syndrome. Am J Obstet Gynecol 2006;194:796-803.
26 Tollenaar LS, Zhao DP, Middeldorp JM, Slaghekke F, Oepkes D, Lopriore E: Color Difference in Placentas with Twin Anemia-Polycythemia Sequence: An Additional Diagnostic Criterion? Fetal Diagn Ther 2016;40:123-127.
27 Rabe H, Diaz-Rossello JL, Duley L, Dowswell T: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev 2012;CD003248.
28 McDonald SJ, Middleton P, Dowswell T, Morris PS: Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Evid Based Child Health 2014;9:303-397.
29 Lewi L, Gucciardo L, Huber A, Jani J, Van MT, Done E, Cannie M, Gratacos E, Diemert A, Hecher K, Lewi P, Deprest J: Clinical outcome and placental characteristics of monochorionic diamniotic twin pairs with early- and late-onset discordant growth. Am J Obstet Gynecol 2008;199:511-517.
30 Valsky DV, Eixarch E, Martinez JM, Crispi F, Gratacos E: Selective intrauterine growth restriction in monochorionic twins: pathophysiology, diagnostic approach and management dilemmas. Semin Fetal Neonatal Med 2010;15:342-348.
31 Stagnati V, Pagani G, Fichera A, Prefumo F: Intertwin discrepancy in middle cerebral artery peak systolic velocity and third-trimester fetal growth restriction in monochorionic-diamniotic twin pregnancy. Ultrasound Obstet Gynecol 2016;48:66-71.
32 Teixeira JM, Duncan K, Letsky E, Fisk NM: Middle cerebral artery peak systolic velocity in the prediction of fetal anemia. Ultrasound Obstet Gynecol 2000;15:205-208.
33 Sarkar S, Rosenkrantz TS: Neonatal polycythemia and hyperviscosity. Semin Fetal Neonatal Med 2008;13:248-255.
34 Koenig JM, Hunter DD, Christensen RD: Neutropenia in donor (anemic) twins involved in the twin-twin transfusion syndrome. J Perinatol 1991;11:355-358.
35 Eslami Z, Lookzadeh MH, Noorishadkam M, Hashemi A, Ghilian R, Pirdehghan A: Thrombocytopenia and Associated Factors in Neonates Admitted to NICU during Years 2010_2011. Iran J Ped Hematol Oncol 2013;3:205-215.

36 Gupta A, Mathai SS, Kanitkar M: Incidence of thrombocytopenia in the neonatal intensive care unit. Med J Armed Forces India 2011;67:234-236.
37 Maruyama H, Shinozuka M, Kondoh Y, Akahori Y, Matsuda M, Inoue S, Sumida Y, Morishima T: Thrombocytopenia in preterm infants with intrauterine growth restriction. Acta Med Okayama 2008;62:313-317.
38 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.
39 Horowitz IN, Tai K: Hypoalbuminemia in critically ill children. Arch Pediatr Adolesc Med 2007;161:1048-1052.
40 Leite HP, Fisberg M, de Carvalho WB, de Camargo Carvalho AC: Serum albumin and clinical outcome in pediatric cardiac surgery. Nutrition 2005;21:553-558.
41 Wong CS, Hingorani S, Gillen DL, Sherrard DJ, Watkins SL, Brandt JR, Ball A, Stehman-Breen CO: Hypoalbuminemia and risk of death in pediatric patients with end-stage renal disease. Kidney Int 2002;61:630-637.
42 Kenny SE, Pierro A, Isherwood D, Donnell SC, Van Saene HK, Lloyd DA: Hypoalbuminaemia in surgical neonates receiving parenteral nutrition. J Pediatr Surg 1995;30:454-457.
43 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.
44 Torer B, Hanta D, Yapakci E, Gokmen Z, Parlakgumus A, Gulcan H, Tarcan A: Association of Serum Albumin Level and Mortality in Premature Infants. J Clin Lab Anal 2016;30:867-872.
45 Atkinson SD, Tuggle DW, Tunell WP: Hypoalbuminemia may predispose infants to necrotizing enterocolitis. J Pediatr Surg 1989;24:674-676.
46 Yang CY, Li BY, Xu P, Yang YJ, Yang QZ: Correlation of serum albumin with the clinical features and prognosis of preterm neonates in the neonatal intensive care unit. Clin Exp Obstet Gynecol 2016;43:149-153.
47 Yang C, Liu Z, Tian M, Xu P, Li B, Yang Q, Yang Y: Relationship Between Serum Albumin Levels and Infections in Newborn Late Preterm Infants. Med Sci Monit 2016;22:92-98.
48 Jardine LA, Jenkins-Manning S, Davies MW: Albumin infusion for low serum albumin in preterm newborn infants. Cochrane Database Syst Rev 2004;CD004208.
49 Cartlidge PH, Rutter N: Serum albumin concentrations and oedema in the newborn. Arch Dis Child 1986;61:657-660.
50 Reading RF, Ellis R, Fleetwood A: Plasma albumin and total protein in preterm babies from birth to eight weeks. Early Hum Dev 1990;22:81-87.
51 Kensara OA, Azzeh FS: Nutritional status of low birth weight infants in Makkah region: Evaluation of anthropometric and biochemical parameters. J Pak Med Assoc 2016;66:414-417.
52 Oberg KC, Pestaner JP, Bielamowicz L, Hawkins EP: Renal tubular dysgenesis in twin-twin transfusion syndrome. Pediatr Dev Pathol 1999;2:25-32.
53 Barr M, Jr., Sedman AB, Heidelberger KP: Renal tubular dysgenesis in twins. Pediatr Nephrol 1998;12:408-413.
54 Chiang MC, Lien R, Chao AS, Chou YH, En Chen YJ: Clinical consequences of twin-to-twin transfusion. Eur J Pediatr 2003;162:68-71.
55 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.
56 Cincotta RB, Gray PH, Phythian G, Rogers YM, Chan FY: Long term outcome of twin-twin transfusion syndrome. Arch Dis Child Fetal Neonatal Ed 2000;83:F171-F176.
57 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.

58 Halvorsen CP, Ek S, Dellgren A, Grunewald C, Kublickas M, Westgren M, Norman M: Survival and neonatal outcome after fetoscopic guided laser occlusion (FLOC) of twin-to-twin transfusion syndrome (TTTS) in Sweden. J Perinat Med 2012;40:533-538.
59 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.
60 Bajoria R, Ward S, Sooranna SR: Influence of vasopressin in the pathogenesis of oligohydramnios-polyhydramnios in monochorionic twins. Eur J Obstet Gynecol Reprod Biol 2004;113:49-55.
61 Mahieu-Caputo D, Dommergues M, Delezoide AL, Lacoste M, Cai Y, Narcy F, Jolly D, Gonzales M, Dumez Y, Gubler MC: Twin-to-twin transfusion syndrome. Role of the fetal renin-angiotensin system. Am J Pathol 2000;156:629-636.
62 Kilby MD, Platt C, Whittle MJ, Oxley J, Lindop GB: Renin gene expression in fetal kidneys of pregnancies complicated by twin-twin transfusion syndrome. Pediatr Dev Pathol 2001;4:175-179.
63 Mahieu-Caputo D, Meulemans A, Martinovic J, Gubler MC, Delezoide AL, Muller F, Madelenat P, Fisk NM, Dommergues M: Paradoxic activation of the renin-angiotensin system in twin-twin transfusion syndrome: an explanation for cardiovascular disturbances in the recipient. Pediatr Res 2005;58:685-688.
64 Bajoria R, Ward S, Chatterjee R: Natriuretic peptides in the pathogenesis of cardiac dysfunction in the recipient fetus of twin-twin transfusion syndrome. Am J Obstet Gynecol 2002;186:121-127.
65 Bajoria R, Sullivan M, Fisk NM: Endothelin concentrations in monochorionic twins with severe twin-twin transfusion syndrome. Hum Reprod 1999;14:1614-1618.
66 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.
67 Brenner BM: The etiology of adult hypertension and progressive renal injury: an hypothesis. Bull Mem Acad R Med Belg 1994;149:121-125.