Summary and General discussion

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Summary

This thesis consists of a series of studies on a newly described complication in monochorionic twins, which we named twin anemia polycythemia sequence (TAPS). A review of the literature is given in part II. We studied the pathogenesis by placental injection studies in part III. In part IV diagnostic criteria were studied for antenatal and postnatal TAPS. We studied antenatal management and outcome including a randomized trial on the prevention of post-laser TAPS in part V. In part VI, studies on postnatal management and outcome including long-term neurodevelopmental follow-up are described.

Review

Chapter 1 opens with a review of the literature, and further comprises of our description of the TAPS staging system for antenatal and postnatal detected TAPS. The aim of this staging system is to reflect the increasing severity of anemia and polycythemia. The antenatal staging system is based on Doppler ultrasound measurements and signs of cardiac compromise due to severe anemia. Postnatal staging is based on the intertwin hemoglobin (Hb) difference, the larger the differences the higher the stage.

Pathogenesis

The pathogenesis of TAPS is based on its unique placenta angioarchitecture. TAPS placentas are characterized by the presence of only a few and very small (<1mm) arterio-venous (AV) anastomoses. TAPS placentas differ from uncomplicated monochorionic twin placentas. The latter are characterized by more and larger anastomoses and have AA anastomoses in up to 90% [1]. In TAPS placentas, AA-anastomoses are very rare. Studies described in Chapter 2 show that after fetoscopic laser for twin-twin transfusion syndrome (TTTS), most residual anastomoses are small and localized near the margin of the placenta. Almost half of the cases with residual anastomoses resulted in TAPS. Studies comparing placentas of spontaneous TAPS and post-laser TAPS cases in chapter 3 showed the presence of more anastomoses in spontaneous TAPS as compared with post-laser TAPS placentas. In both groups, most anastomoses were localized near the margins of the placenta. In contrast to a previous study by our group [1] we found AA anastomoses in both groups, although all AA-anastomoses in TAPS were very small (<1mm). In chapter 4 we report on our study on

AA-anastomoses in spontaneous TAPS cases compared with uncomplicated monochorionic twins. In TAPS cases, AA anastomoses were very small (all <1mm), much smaller than AA anastomoses in uncomplicated monochorionic twins. The placenta findings in these studies help us to understand the pathophysiology of TAPS. The presence of only a few and small anastomoses suggests that the transfusion process is slow and a hemodynamic compensation takes place resulting in an unchanged amount of amniotic fluid for both twins but with large Hb difference.

Diagnosis

Antenatal diagnosis

TAPS can be diagnosed antenatally or postnatally. Antenatal diagnosis is based on Doppler ultrasound abnormalities showing an increased peak systolic velocity in the middle cerebral artery (MCA-PSV) in the donor twin, >1.5 multiples of the mean (MoM), suggestive of fetal anemia. In the recipient twin decreased velocities in the MCA-PSV <1.0 MoM are seen, without signs of the oligo-polyhydramnios sequence as in TTTS, as reported in chapter one. MCA-PSV measurement, a non-invasive test, has become the standard test for the prediction of fetal anemia in singletons in a variety of fetal diseases [2]. In chapter 5 we showed the diagnostic accuracy of MCA-PSV measurements to predict abnormal fetal hemoglobin levels in TAPS. We found high sensitivities and specificities of MCA-PSV both for anemia and for polycythemia, confirming the clinical usefulness of this noninvasive test. Our results also strengthen our previous findings and proposal to use 1.0 MoM as cut-off level for the TAPS recipient, as described in chapter one. With the use of the previously suggested cut-off level of 0.8 MoM, a significant number of cases of severe polycythemia would be missed [3].

Postnatal diagnosis

In chapter 6 we proposed to use a fixed cut-off level of Hb difference ≥ 8g/dL to define TAPS based on a case-control study where we compared hematologic values in TAPS compared with uncomplicated monochorionic twins. We found that all TAPS cases had an intertwin difference of at least 8.0 g/dL. In addition to the Hb difference, an essential part of the postnatal definition is an increased reticulocyte count measured in the TAPS donor resulting from chronic anemia. An intertwin reticulocyte count >1.7 was pathognomonic for TAPS. An additional criterion for postnatal TAPS is the presence of small (residual) anastomoses at the placental surface. These two criteria enable us to distinguish between chronic feto-fetal transfusion as it occurs in TAPS, and the acute form of transfusion as in acute TTTS [4]. Acute TTTS is also characterized by the large Hb differences but is based on large amount

of feto-fetal transfusion through large anastomoses, whereas TAPS is a chronic form of transfusion through small anastomoses.

Antenatal management and outcome

Solomon trial; prevention of post-laser TAPS

For the prevention of post-laser TAPS we compared in chapter 7, in a randomized controlled trial, two laser techniques for the treatment of TTTS. Post-laser TAPS is caused by residual anastomoses at the placental surface after fetoscopic laser surgery for TTTS. In order to reduce the number of residual anastomoses, a new technique named the Solomon technique was introduced. With the standard technique all visible anastomoses are coagulated. With the Solomon technique, after identifying and coagulating the individual anastomoses, a line is drawn with the laser from one placenta margin to the other. In this randomized trial we showed a significant reduction of the primary outcome, which was a composite outcome of TAPS, recurrent TTTS, perinatal mortality or severe neonatal morbidity, of 49% in the standard group versus 34% in the Solomon group. A significant reduction of post-laser TAPS of 16% in the standard group to 3% in the Solomon group was seen. In addition, a reduction of recurrent TTTS was seen of 7% in the standard group to 1% in the Solomon group. With the Solomon technique we showed an important improvement for the prevention of post-laser TAPS and recurrent TTTS. The Solomon technique did not appear to be associated with an increase in any identifiable adverse outcome or complication.

Secondary analysis Solomon trial, residual anastomoses

In chapter 8 we performed a secondary analysis of the Solomon trial. All placentas that were injected with color dye were analyzed. After using the standard technique, residual anastomoses were seen in 34% of the placentas, which is in line with a previous published incidence of residual anastomoses (32%) in chapter two. Using the Solomon technique an almost 50% reduction to 19% was seen. In a subgroup analysis where the surgeon stated that the procedure had been complete, a reduction to 12% was seen. The presence of residual anastomoses was associated with a 58% risk of developing TAPS or recurrent TTTS, a similar risk as was described in chapter two. The main reason for residual anastomoses in the Solomon group was the fact that the laser-line along the vascular equator was not complete. In conclusion, the Solomon technique reduces the incidence of residual anastomoses and their clinical complications such as TAPS and recurrent TTTS, but does not guarantee a complete dichorionization of the placenta. Therefore, careful follow-up with serial Doppler

ultrasound measurements of the middle cerebral artery peak systolic velocity and of amniotic fluid volumes of both twins remains of crucial importance, even after a laser intervention using the Solomon technique.

Management antenatal detected TAPS

The optimal management for TAPS is not clear. Options include fetoscopic laser surgery, intrauterine blood transfusions (IUT) in the donor, with or without combination of partial exchange transfusion (PET) in the recipient, expectant management or selective feticide. The rationale for intrauterine treatment is to prevent or treat severe fetal anemia or polycythemia. In chapter 9 we applied a computational model simulation to illustrate the mechanism of IUT with and without PET in TAPS occurring after laser surgery for TTTS. Model simulations were performed with the representative anastomotic pattern as observed during laser intervention, and after placental dye injection. In this model simulation we showed that the addition of PET to IUT reduces the severity of polycythemia in the recipient. PET may thus be important to prevent complications of hyperviscosity, such as limb necrosis and severe cerebral injury. However, IUT with or without PET remains a symptomatic treatment for TAPS, it does not solve the underlying problem, which are the small (residual) anastomoses. Laser coagulation of the vascular anastomoses is the only causal treatment for TAPS.

In chapter 10 we compared fetoscopic laser therapy with intrauterine transfusion and expectant management for the treatment of antenatal detected TAPS. The results of this retrospective cohort suggest that laser treatment for TAPS may improve survival and neonatal outcome by prolonging the pregnancy, compared to treatment with intrauterine transfusion or expectant management. Prolonging the pregnancy is known to be of paramount importance for neonatal outcome. Low gestational age at birth is independently associated with increased risk for severe neonatal morbidity [5;6], severe cerebral lesions [7] and impaired neurodevelopmental outcome [8]. We cannot firmly conclude that the improved outcome after laser reflects a true benefit of laser treatment. To determine the optimal management and to evaluate possible benefits of laser surgery for TAPS, adequately powered, prospective studies are needed.

Postnatal management and outcome

In chapter 11 we evaluated differences in biochemical variables in TAPS and showed that donor twins have significantly lower levels of albumin and total protein levels at birth compared to recipients, in addition to lower hemoglobin levels. Lower albumin levels and total protein levels in donors compared to recipients is also seen in TTTS [9-11]. The findings of this study suggest that placental vascular anastomoses in TAPS allow intertwin transfusion

not only of hemoglobin but also of albumin and other proteins. Another explanation could be that the production of albumin in donors is reduced. An additional finding in this study was that in the control group (uncomplicated monochorionic twins) the smaller twin had a significantly lower placental share. In contrast the donors in the TAPS group had lower birth weight but larger placental shares. This finding was also reported by Lewi et al. [12]. Lower levels of albumin and total protein may play a role in the reduced growth of the donors despite the larger placental share.

In chapter 12 we report a case of spontaneous TAPS with severe cerebral injury resulting in neonatal death due to severe polycythemia-hyperviscosity syndrome in the recipient twin. This case-report shows that complications of TAPS are not only limited to hematological complications and may be severe. The risk of severe polycythemia-hyperviscosity syndrome is substantial, and our findings support our computed model (chapter 9) where we suggest adding partial exchange transfusion to reduce the severity of polycythemia and hyperviscosity. Chapter 13 is the first study evaluating long-term neurodevelopmental outcome in post-laser TAPS. Neurodevelopmental impairment (NDI) was detected in 9%, with no difference between donors and recipients. Our results suggest that impairment in post-laser TAPS cases is frequent, but is within the range of the incidence of NDI reported in case series of TTTS treated with laser (range 6% to 18%) [13-15]. In a univariate risk factor analysis on cognitive scores, we found that low gestational age and low birth weight were important risk factors for cognitive delay. Low gestational age at birth and low birth weight are known to be independently associated with increased risk for severe cerebral lesions [7] and impaired neurodevelopmental outcome [8]. In a subgroup analysis on antenatally detected and managed TAPS cases, we found that the TAPS subgroup treated with IUT had a lower median cognitive score compared to the other subgroups. A possible explanation for the low cognitive scores could be that these cases were born at a lower gestational age due to induced labor or planned caesarean for severe anemia or polycythemia. Larger studies are needed to reliably investigate long-term neurodevelopmental outcome and evaluate risk factors for adverse outcome.

In summary, in this thesis we describe that TAPS is a form of chronic feto-fetal transfusion based on a small amount of blood transfusion through very small anastomoses. For the antenatal diagnosis of TAPS, MCA-PSV Doppler measurements appear to be an accurate predictor for anemia and polycythemia. If antenatally detected, fetoscopic laser therapy might improve pregnancy outcome by treating the cause, and thereby prolonging the pregnancy. Another very important finding for the prevention of post-laser TAPS is that by using the Solomon technique for the treatment of TTTS the incidence of post-laser TAPS is

reduced. If laser is not feasible and IUT is the preferred treatment option, we suggest adding PET to prevent severe polycythemia and possible complications as limb necrosis and severe cerebral injury. Long-term neurodevelopmental outcome in post-laser TAPS is 9% and seems comparable with long-term outcome after treated TTTS.

In conclusion, with this thesis we increased our knowledge on the pathophysiology, the diagnostic tools, management options, short and long-term outcome. However management of TAPS remains a challenging problem and more research is necessary to improve treatment and outcome.

Discussion

Pathogenesis

Based on the placental injection studies we showed that TAPS has its own unique placental angio-architecture. Interestingly TAPS donors tend to have a bigger placental share but a lower birth weight compared to TAPS recipients. Future research should focus on the placental territory and birth weight ratio in TAPS pregnancies. Another interesting study on placentas would be to analyze the type, size and localization of residual anastomoses after using the Solomon technique. After using the Solomon technique we showed a reduction of residual anastomoses, however in most cases with residual anastomoses it was due to a discontinuous laser line. For the optimal laser effect, a careful balance should be sought between avoiding excessive tissue damage due to too much laser energy, and insufficient tissue damage (and possible residual anastomoses) due to reduced laser energy. Future research should be aimed at optimizing the laser energy use, for which numerous in vitro and in vivo experiments are likely needed. Some are currently carried out in our Medical Delta collaboration with the Technical University Delft and the Erasmus Medical Center, Rotterdam.

Diagnosis

In this thesis we showed that MCA-PSV Doppler is a powerful tool for the prediction of fetal anemia and polycythemia in selected pregnancies with an increased risk for TAPS. Whether MCA-PSV Doppler is also a good predictor of anemia and polycythemia in uncomplicated monochorionic twins needs to be established. For postnatal diagnosis, fixed Hb concentration cut-of levels have been abandoned and an intertwin Hb difference is used. Whether delta MoM of MCA-PSV would be a more accurate tool in predicting TAPS compared to fixed cut-off levels, and whether the prenatal staging system predicts the stage of postnatal

TAPS should be studied in future. In addition to these studies, MCA-PSV values in all monochorionic twins close to delivery could be compared with postnatal Hb levels to test the accuracy of MCA-PSV measurement in relation to Hb levels. Apart from abnormal Doppler measurements, distinct differences in placenta echodensity and thickness (an increased and hydropic placental part of the TAPS donor and a normal part of the TAPS recipient) [16;17], and a starry sky aspect of the liver in the TAPS recipient suggestive for polycythemia have been reported in TAPS [18]. Future studies should address the sensitivity, specificity and reproducibility of these additional ultrasound findings.

Prenatal management and outcome

Recent retrospective studies [19-21] on the Solomon technique showed a reduction of TAPS and recurrent TTTS and an improvement in survival. However our study was not powered to detect such differences. The effect of the Solomon technique on survival, and the effect of post-laser TAPS and recurrent TTTS on neonatal morbidity need to be studied prospectively in sufficiently large cohorts.

We compared the different treatment options for TAPS in a retrospective cohort, and found that laser seemed to improve pregnancy outcome. We cannot yet firmly conclude that the improved outcome reflects a true benefit of laser treatment. More studies (ideally using a randomized controlled design, including long term follow-up) are needed to determine the optimal management and to evaluate the possible benefits of laser therapy for the treatment of TAPS. In the meantime, a prospective evaluation of the management in TAPS cases worldwide may further improve our understanding in this complex and rare disease. To facilitate this evaluation, we recently set up a web-based TAPS registry: www.TAPSregistry.org.

Postnatal management and outcome

Future long-term follow-up studies are of utmost important to increase our knowledge on the neurodevelopmental outcome of TAPS pregnancies. By comparing the reported neurodevelopmental impairment of 9% with a control group of treated TTTS cases the influence of post-laser TAPS on treated TTTS twins will be studied. In addition, evaluation of long-term neurodevelopment in survivors after spontaneous TAPS and in relation to the different treatment modalities for TAPS requires further study.

Since disease-free survival is the most important outcome in fetal therapy we will also assess the long-term neurodevelopmental outcome in all surviving twins at the age of 2 in the Solomon trial.