Long-term neurodevelopmental outcome after fetal therapy

Klink, Jeanine Monica Maria van

PART I

GENERAL INTRODUCTION

General Introduction

An increasing number of fetal diseases are being detected prior to birth due to major improvements in prenatal ultrasound examinations and the wide implementation of screening programs.[1] For various diseases, fetal therapy may be a life-saving option or an alternative to postnatal treatment, to prevent permanent organ damage including the developing fetal brain.
A major breakthrough in fetal therapy was the introduction of intrauterine blood transfusion (IUT) for severe fetal anemia. This intervention was first described in the early 1960s by Sir William Liley in New Zealand.[2] Since then, fetal therapy has gradually evolved and resulted in a dramatic increase in overall survival in several fetal diseases. Throughout the world, specialized fetal therapy centers were initiated and a new medical discipline commenced. In the Netherlands, fetal surgical interventions were concentrated in one center, The Leiden University Medical Center (LUMC). The LUMC is a tertiary medical center which serves as the national referral center for fetal therapy.

Intrauterine transfusion in fetal anemia
The technique of the first IUT was based on intraperitoneal blood transfusion. In the next decades, the technique evolved to an intravascular approach. The first intravascular IUTs in the Netherlands were performed in 1986. Indications for IUT mainly include fetal anemia due to hemolytic disease caused by Rhesus or Kell alloimmunization. Alloimmune hemolytic disease results from maternal alloimmunization to red cell antigens, for which mother and fetus are incompatible. Maternal antibodies pass the placenta into the fetal circulation and cause destruction of fetal red cells. The resulting progressive hemolysis leads, if left untreated, to severe fetal anemia, fetal hydrops and perinatal death.[3] Nowadays, perinatal survival rates after IUT for severe fetal anemia exceed 95% in experienced centers.[4] Other, non-immune, indications for IUT include parvovirus B19 infection or chronic or acute fetal maternal hemorrhage (FMT). Approximately 30 fetuses are treated annually with IUT at our center. With an average of 3 transfusions per fetus, up to a 100 transfusions are performed per year.

Fetoscopic laser surgery in monochorionic twin pregnancies
The other major intervention in fetal therapy, besides IUT, is related to fetal interventions in complicated monochorionic (MC) twin pregnancies. MC twins share their placenta and their blood circulation is connected by vascular anastomoses at the placental surface. Placental vascular anastomoses allow acute or chronic inter-twin blood transfusions between the circulation of the two fetuses. Imbalanced inter-twin blood flow can lead to severe complications such as twin-twin transfusion syndrome (TTTS).

In TTTS, imbalanced blood flow from one twin (the donor) to the other twin (the recipient), results in hypovolemia and oligohydramnios in the donor and hypervolemia and polyhydramnios in the recipient twin. The first treatment of choice in TTTS is fetoscopic laser coagulation of placental vascular anastomoses. In the Netherlands, the first fetoscopic laser surgery was performed at the LUMC in the year 2000. Nowadays, around 60 MC twin pregnancies are treated annually at our center with fetoscopic laser surgery, with an overall survival rate of 74%.[5] In a recently described complication in MC twins named twin anemia-polycythemia sequence (TAPS), several interventions can be considered including IUT or fetoscopic laser surgery. The optimal treatment of TAPS remains to be determined.

Fetoscopic surgical interventions in complicated MC twin pregnancies include, besides laser coagulation of placental vascular anastomoses, also selective feticide through umbilical cord coagulation or radiofrequency ablation (RFA). In specific complicated MC pregnancies, selective feticide via cord occlusion or RFA can be offered as an alternative management option. Indications include twin reversed arterial perfusion (TRAP) sequence, selective intrauterine growth restriction (sIUGR), monoamniotic twin pregnancies or severe discordant congenital anomalies. Perinatal survival rates following selective feticide vary between 65% and 92%, depending on indication and technique.[6]

Long-term neurodevelopmental outcome after fetal therapy

With an increasing number of children being born alive after fetal therapy, attention is shifting from short-term outcome and perinatal survival to long-term outcome and neurodevelopmental morbidity. However, data on long-term neurodevelopmental outcome after fetal therapy remain scarce. Long-term neurodevelopmental outcome studies are costly and difficult to perform and therefore hard to realize. In addition, follow-up studies after fetal therapy are hampered by the rarity of these fetal diseases. Nevertheless, long-term follow-up studies are of paramount importance to determine optimal fetal management. Follow-up studies may provide clinicians better insights into the long-term neurodevelopmental outcome and quality of survival in children after fetal therapy. Detailed and adequate information on long-term outcome is also required to improve the quality of antenatal parental counseling using evidence-based information.

Long-term follow-up studies with emphasis on child motor, cognitive and socio-emotional development are essential for conducting future randomized controlled trials in all fields of fetal therapy, in order to implement new or modified techniques. This requires cooperation between obstetricians, neonatologists, child psychologists and other experts in the field of early human development in order to look beyond perinatal survival as well as cooperation between international fetal therapy centers to

obtain reliable data with large enough case series with sufficient power. Large enough case series enable research on potential risk factors for adverse long-term outcome. It is important to continuously assess child development including formal psychological testing and standardized measures of well documented psychometric quality, with increasing reliability of results with increasing age of surviving children following fetal therapy.

The aim of this thesis is to improve our knowledge on the long-term neurodevelopmental outcome in children treated with fetal therapy and to identify potential risk factors for adverse long-term outcome.

Outline of this thesis

PART I: *General introduction*

PART II: *Intrauterine transfusions for fetal anemia*

Chapter 1 - Review of the literature on the long-term neurodevelopmental outcome in children treated with IUT for fetal anemia.

Chapter 2 - Study on the health-related quality of life and behavioral functioning in children treated with IUT for fetal hemolytic disease.

Chapter 3 - Study on the neurodevelopmental outcome in children included in a randomized controlled trial and treated with either neonatal intravenous immunoglobulins or placebo in Rhesus hemolytic disease.

PART III: *Fetoscopic laser surgery in twin-twin transfusion syndrome*

Chapter 4 - Review of the literature on the long-term neurodevelopmental outcome in MC twins after fetal therapy.

Chapter 5 - Systematic review of the literature on cerebral injury and neurodevelopmental impairment in children treated with either amnioreduction or fetoscopic laser surgery for TTTS.

Chapter 6 - Study on the long-term neurodevelopmental outcome in survivors of TTTS treated with laser surgery in the first six years (2000-2005) of the fetoscopic laser surgery program at the LUMC, compared to more recent years (2008-2010).

Chapter 7 - Study on the long-term outcome in children included in the Solomon randomized controlled trial and treated with either the Solomon or standard laser surgery technique for TTTS.

Chapter 8 - Study on the long-term neurodevelopmental outcome in TAPS after fetoscopic laser surgery for TTTS.

PART IV: *Specific complications in monochorionic pregnancies*

Chapter 9 - Systematic review on the neurological outcome in MC twins with sIUGR.

Chapter 10 - Study on the neurological outcome and incidence of severe cerebral injury in survivors after single fetal demise of the MC co-twin.

Chapter 11 - Study on the perinatal outcome of the surviving twin after selective feticide of the MC co-twin.

Chapter 12 - Study on the long-term neurodevelopmental and behavioral outcome in children following selective feticide of the MC co-twin.

PART V: *Discussion and summary*

Chapter 13 - General discussion concerning the results of these studies.

Chapter 14 - Future perspectives and proposals for future research on the long-term neurodevelopmental outcome after fetal therapy.

Chapter 15 - Summary.

References

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