Chapter 1

General introduction and outline of the thesis

General introduction

Intrauterine treatment of fetal anemia due to red cell alloimmunization by percutaneous intraperitoneal transfusion (IPT) was first introduced by Liley in the early 1960s [1]. Although survival rates improved, the outcome of especially hydropic and severely anemic fetuses in early gestation remained poor. Intravascular intrauterine transfusion (IUT) into the umbilical cord was first described by Rodeck et al in 1981, using guidance of the needle by fetoscopy [2]. IUT into the intrahepatic portion of the umbilical vein was first reported by Nicolini et al in 1990 [3] as a potentially safer alternative for umbilical cord transfusion, in particular in case of a posterior placenta [4]. IUT in the umbilical vein, either in the cord root or in the fetal liver, is nowadays considered to be a safe technique for fetal transfusion. Intravascular IUT is much more successful in resolving fetal hydrops and thus preventing fetal demise than IPT [5]. IUT is indicated to treat severe fetal anemia from a variety of causes. The main indication remains fetal anemia due to red cell alloimmunization. Other causes of fetal anemia are parvovirus B19 (B19V) infection and chronic fetomaternal hemorrhage (FMH). In addition, IUT is used in the management of inter-twin fetal transfusion due to twin anemia-polycythemia sequence (TAPS) or twin-to-twin transfusion syndrome (TTTS), inherited red cell disorders and fetal and placental tumors.

In red cell alloimmunization, fetal anemia results from maternal alloimmunization to red cell antigens, for which mother and fetus are incompatible. Maternal IgG antibodies pass the placenta into the fetal circulation and cause destruction of fetal red cells. The resulting progressive fetal anemia leads, when untreated, to fetal hydrops and may eventually result in perinatal death. The most prevalent anti-red cell antibodies causing fetal anemia are Rhesus D, Kell and Rhesus c. Universal use of postnatal and antenatal Rhesus D immunoglobulin prophylaxis programs has dramatically reduced the need for IUT [6].

In B19V infection, fetal anemia results from reduced red cell production. Human parvovirus B19 is a potent inhibitor of hematopoiesis. It causes bone marrow failure by affecting the erythroid-lineage cells, which are well-known target cells for B19V. These target cells are found on erythrocyte progenitor cells (erythroblasts and megakaryocytes) and also on erythrocytes, synovium, placental tissue, endothelial cells and fetal myocardium. Elimination of the erythroid lineage can cause fetal anemia, hydrops, and fetal death [7].

Nowadays, perinatal survival rates after IUT for red cell alloimmunization exceed 90% [8,9], which demonstrates the safety and efficacy of one of the most successful procedures in fetal

therapy. In B19V infection, perinatal survival after treatment with IUT is lower, ranging from 67% to 85% [10-12].

However, procedural complications do still occur, and affect outcome [4,13,14]. IUT in the early second trimester is associated with significant mortality which is believed to be related to more difficult access to the fetal circulation due to a smaller size of the blood vessels. Fetal hydrops is another known risk factor for perinatal loss. To further improve care for pregnancies complicated by fetal anemia, studies to evaluate current perinatal outcome and to elucidate contributing factors for perinatal loss after IUT are needed.

Without correction for individual learning processes and team experience, IUT is associated with a procedure-related fetal loss rate of 1.6% per procedure [4]. Increasing experience with this highly complex procedure may improve the invidual learning curve of fetal surgeons and thus further improve perinatal survival rates. However, there are no reliable data on the aspects of a learning curve for IUT. Therefore, studies to evaluate the use of a method for quality control of performing IUT are needed.

As perinatal survival after IUT is improving, one of the concerns is that this could lead to an increase in the number of children with long-term disabilities. The importance of long-term follow-up studies in fetal therapy lies in both the necessity of evaluation of antenatal management as well as in evidence-based preconceptional and prenatal counselling. Only a few studies with small patient numbers have reported on long-term neurodevelopmental outcome after IUT for fetal anemia due to red cell immunization and B19V infection [10,12,15-17]. Therefore, larger studies to determine the incidence and risk factors for adverse neurodevelopmental outcome are needed.

LUMC

In the Netherlands, the Leiden University Medical Center serves as the single national reference center for the management and treatment of fetal anemia in pregnancy. Intrauterine transfusion was introduced in Leiden in 1965 by Bennebroek Gravenhorst [18]. The intraperitoneal technique was replaced by the intravascular approach in 1987 by Kanhai [9]. In subsequent years, more indications for IUT were added; B19V infection, FMH, TTTS and TAPS. Yearly, around 70 IUTs are performed in fetuses with fetal anemia for these different indications.

Objectives of this thesis:

- to evaluate complications of IUT by indication
- to monitor the individual performance of operators carrying out IUT, and to assess learning curves for IUT
- to describe the incidence and risk factors for adverse perinatal and long-term outcome
- to evaluate the long-term outcome of surviving children after IUT treatment

Outline of the thesis

The objectives of this thesis are described in detail in the following chapters, and can be summarized as follows:

Chapter 2 - Review of the literature on the current indications and risks of the intrauterine blood transfusion (IUT).

Chapter 3 – Study to assess and compare the perinatal outcome after IUT performed before and after 20 weeks of gestation in a large cohort, and to analyse contributing factors.

Chapter 4 - Study to test the feasibility of CUSUM (CUmulative SUM) analysis for quality control of performing IUT.

Chapter 5 – Outline of the study protocol and the aims of the LOTUS study (LOng-Term outcome after intra-Uterine transfusionS).

Chapter 6 – Evaluation of the incidence and risk factors for adverse neurodevelopmental outcome after IUT treatment for alloimmune anemia (LOTUS study).

Chapter 7 – Evaluation of the long-term neurodevelopmental outcome of children treated with IUT for anemia, caused by parvovirus B19 infection.

Chapter 8 – Review on the long-term neurodevelopmental and cardiovascular outcome after IUT.

Chapter 9 – General discussion, summary and future perspectives concerning all studies of this thesis.

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