CHAPTER 1

General introduction
The fetus in prenatal medicine

According to Medline definitions, a conceptus is an embryo until a postconceptional age of 8 weeks (or a gestational age of 10 weeks) and will then be a fetus until birth. If born viable, the person then becomes an infant. The fetus is a unique patient for several reasons. First, there is a unique relationship between the mother and her unborn child. Although the fetus has its own rights, he or she can only be treated via the mother. Therefore the purported rights of the fetus can never take precedence over that of the mother. Second, despite advances in medical care there is striking little knowledge about fetal life. Questions such as does the fetus experience pain, does it have a memory, are still unanswered. Third, the accessibility of the fetus as a patient is limited. Finally, the ill fetus often displays a paucity of symptoms.

The introduction of real-time ultrasound and molecular biology in medicine, in the second part of the last century, has ushered a new era in prenatal medicine. Both diagnostic and therapeutic tools became available. Fetal medicine has evolved from interventions aimed at short term care in normal developing individuals towards interventions aimed at improving the starting-point for long-term postnatal therapy.

When asking about the prognosis of their fetus, parents are thinking of a future that lays twenty, thirty years ahead of us, and are wishing their children to be independent individuals having their own family. They know but not always realize that prenatal diagnosis may lead in some cases to the initiation of therapy and in other cases to the abstinence of further diagnostic or therapeutic interventions or even to feticide or termination of pregnancy. In order to provide effective counseling, centers for fetal medicine have an obligation to include long-term follow-up of the children that were the subject of fetal interventions for diagnosis and/or therapy. After all, there is a danger of overenthusiastic doctors that value every improvement that fetal medicine does accomplish and forget about the parents that have to care for a handicapped child. Such "dedicated" care will greatly influence the rest of their lives and that of other members of their family.

Brief history of prenatal medicine

In 1822, Jaques-Alexandre Lejumeau de Kergaradem was the first to describe the detection of the fetal heart beat by auscultation, in 1906 Cremer first described the fetal electrocardiogram from the abdominal surface of a pregnant woman. By 1920, the first successful fetal operations on guinea pig fetuses had been performed. In the 1930s and 1940s, experimental fetal observations were done by performing operations on fetal lambs while still in utero. This experimental fetal
observations changed in the 1950s into studying the causality of fetal malformations (i.e. by interrupting the mesenteric blood supply, intestinal atresia occurred) and in the 1960s and 1970s into performing fetal surgery to simulate a variety of human congenital anomalies (congenital diaphragmatic hernia in the lamb, congenital hydronephrosis in the rabbit and lamb). In the 1950s, Smyth described invasive electrocardiographic monitoring with an intra-amniotic electrode. From the 1960s onward amniocentesis, fetoscopy, and ultrasonography, and consequently the possibility of examining the fetus clinically, genetically and biochemically were introduced. Analysis of the contents of amniotic fluid made possible the prenatal diagnosis of many inherited metabolic and chromosomal disorders and permitted assessment of fetal pulmonary maturity and the severity of fetal hemolytic disease. The era of fetal medicine had really begun.

Second trimester amniocentesis is traditionally performed around 16 weeks' gestation. Observational data from the 1970s suggested that, at this gestation, relatively large amounts of amniotic fluid (up to 20 ml) could be aspirated without significant technical difficulties. This amount of amniotic fluid was needed to yield a sufficient number of viable fetal cells to minimize the risk of laboratory failure. A major disadvantage of second trimester amniocentesis is that a final result is usually available only after 18 weeks' gestation. Such a long waiting period for a diagnosis can be very distressing for couples. Alternatively, earlier options include chorionic villus sampling and early amniocentesis. Chorionic villus sampling was first introduced in 1975. It involves aspiration of placental tissue rather than amniotic fluid. Ultrasound guided aspiration can be performed using either percutaneous transabdominal or the transvaginal/transcervical approach. Currently the choice of approach and the choice of instruments tend to be based on the operator's personal preference. There is an understandable desire to perform chorionic villus sampling as early as possible. Technically, this can be done successfully as early as 6 weeks' gestation. However, a few clusters of limb reduction defects have been reported following chorionic villus sampling with a trend toward an increased incidence of these defects when chorionic villus sampling was done before 9 weeks' gestation. Although large epidemiological follow-up studies failed to confirm this association, most clinicians delay this procedure until after 10 weeks' gestation. Early amniocentesis (9-14 weeks' gestation), introduced in the late 1980s, is technically the same as a 'late' procedure except that less amniotic fluid is removed. Ultrasound needle guidance is considered to be an essential part of the procedure because of the relatively small target area. The presence of two separate membranes (amnion and chorion) until 15 weeks' gestation creates an additional technical difficulty. Only the amniotic (inner) sac should be aspirated, because the outer sac does not contain sufficient numbers of living fetal cells.

The British Professor Ian Donald (1910-1987) was the pioneer for the
utilization of ultrasound in obstetrics. Before the discovery of ultrasound, X-ray was used for fetal diagnosis. Plain X-rays yielded little information. The introduction of lipophylic/hydrophylic radiopaque materials into the amniotic fluid (amniogram) facilitated intraperitoneal transfusions but was not suitable for fetal diagnosis.

In the Netherlands, obstetric ultrasound was first developed and introduced in the early 1970s in the Leiden and Utrecht University Women’s Hospitals. Important for fetal diagnosis and therapy was the introduction of real-time ultrasound in the early 1980s. A milestone in prenatal medicine was achieved by William Liley. He demonstrated that severe red cell immunization, infusion of red cells in the intra-peritoneal cavity of the fetus ameliorated severe hydrops.

During the 1960s two clinical methods were developed to record fetal heartbeat pattern, one based on fetal electrocardiogram (internal registration) and the other based on ultrasound (external registration). In both methods, uterine contractions were recorded simultaneously. During the 1970s, the use of cardiotocography became common practice in Western labor wards. In 1961, Erich Saling introduced the concept of blood pH measurements to fetal scalp blood sampled during labor for fetal surveillance. Three years later, Saling published normal values for fetal pH and blood gas during labor and at birth. Blood pH is presently accepted by many as the biochemical gold standard in fetal monitoring during labor.

The advent of echocardiography, and especially M-mode and pulsed wave Doppler ushered the field of fetal arrhythmia detection and differentiation. Robinson and Shaw-Dunn detailed the use of M-mode in the evaluation of fetal arrhythmias during the early 1970s. As ultrasound technology expanded to include two-dimensional and both spectral and color Doppler modes, additional echocardiographic techniques for the identification and differentiation of fetal arrhythmias were described.

The intravascular intrauterine fetal transfusion performed by the use of fetoscopy was introduced by Rodeck in 1981. Daffos et al. described fetal bloodsampling by ultrasound-guided percutaneous cordocentesis. This method was used also for fetal intravascular transfusions and later for administering medication by cordocentesis. In the Netherlands, intraperitoneal fetal transfusion guided by X-rays started in 1965, and sonographic-guided intravascular fetal transfusion started in 1987. In 1988, Nicolini first described fetal blood sampling from the intrahepatic portion of the umbilical vein in the fetus, as an alternative procedure in cases where cord needling was unsuccessful.

By the 1980s, fetal surgeons were ready for the next step, which is the correction of fetal anatomic defects.
Prenatal medicine at the Leiden University Hospital

Leiden is the national referral center for invasive fetal therapy (intravascular fetal transfusion of red cells or platelets, fetoscopy and laser treatment in complicated monochorionic twin pregnancies). In the recent years, however, indications for treatment have been expanded and now also include non-immune fetal hydrops (caused by hydrothorax, congenital cystic adenomatoid malformations of the lung, parvo B19 infections, tachyarrhythmia) and more experimental forms of fetal treatment. Clinical research at the LUMC include minimally invasive intrauterine treatment and fetal patho-physiology in case of anemia, alloimmune thrombocytopenia and twin-to-twin transfusion syndrome.

In 1965, the first intrauterine transfusion of red cells was given to the fetus intraperitoneally because of severe red cell immunization. In 1987 the first intrauterine intravascular transfusion of red cells for anemia in alloimmunized pregnancies was performed. Intravascular transfusion of platelets in the fetus with neonatal alloimmune thrombocytopenia (NAITP) was introduced in 1989. From 1994 onwards serial fetal platelet transfusions therapy was gradually replaced by the maternal administration of high dose immunoglobulins. Severe fetal anemia induced by Parvovirus B19 infection was corrected by intravascular transfusion of red cells and platelets since 1997.

In 2000, the first fetoscopic lasercoagulation of the intraplacental anastomoses in twin to twin transfusion syndrome in monochorionic twins was performed in Leiden. Intrauterine fetal shunting for lower urinary tract obstruction or congenital cystic adenomatoid malformation (CCAM) was introduced in 2002.

Counselling and guiding the parents is an important part of fetal medicine. Parents should obtain information on risks and benefits of prenatal medicine and possible alternatives. The long-term prognosis of children treated antenataly is an important part of counseling. This thesis describes the follow-up studies after prenatal diagnosis and therapy. The aim of this research is to evaluate our management in order to generate data for realistic counselling of parents.
Outline of this thesis

We describe the results of 7 studies on the outcome of children after diagnostic or therapeutic interventions during fetal life.

Section A presents follow-up studies after prenatal diagnosis.

Chapter two provides an overview of invasive prenatal diagnosis in the Netherlands during the period 1991-2000 and analyses trends. In the Netherlands, invasive prenatal diagnostic procedures have to meet Section 2 of the Special Medical Procedures Act. That act requires that each licensed center provide an annual report following a standardized format. We combined and described the annual results from all 13 centers for invasive prenatal diagnosis, with particular emphasis on indications, abnormal results, number and type of invasive procedures and terminations of pregnancy.

Chapter three presents a semi-randomized controlled trial comparing transabdominal chorionic villus sampling with amniocentesis, both performed before 14 weeks of pregnancy. It is a follow-up study on fetal morbidity and mortality and infant morbidity. First trimester amniocentesis was introduced in the late 1980s because it was thought to combine the advantage of chorionic villus sampling, namely early diagnosis, with that of mid-trimester amniocentesis, namely accuracy and safety.

In chapter four the outcome of pregnancies with a prenatally diagnosed central nervous system malformation is presented. The aim of this study was to evaluate the accuracy of ultrasound examination in our center, to describe the outcome of these pregnancies, and to provide information for clinicians in counseling future parents. Central nervous system malformations were most frequently detected after 24 weeks’ gestation. This was a consequence of the fact that prenatal ultrasound screening for abnormalities was not routinely performed in The Netherlands.

In chapter five we discuss our follow-up study with neurodevelopmental assessment of children born with an umbilical artery blood pH < 7. Umbilical blood pH provides good means for retrospective evaluation of obstetric efforts in preserving fetal health during birth. Normal values at birth are above 7.09 (Saling 1961) and less than 1% of children are born with a blood pH below 7.

Section B presents follow-up studies after prenatal therapy.

Chapter six describes the long-term neurodevelopmental outcome in children after twin-to-twin transfusion syndrome. Monochorionic twinning predisposes to cerebral damage due to complications caused by twin-to-twin transfusion.
Twin-to-twin transfusion syndrome occurs in approximately 15% of monochorionic pregnancies and results from shunting of blood from one twin, the donor, to the other twin, the recipient, through placental vascular anastomoses. Untreated, twin-to-twin transfusion syndrome is associated with high perinatal mortality and morbidity. Maternal and neonatal medical records of all twin-to-twin transfusion syndrome cases admitted to our center between 1990 and 1998 were reviewed. Amniodrainage had been performed in more than half of these pregnancies. Neurological and mental development at school age was assessed during a home visit in all twin-to-twin transfusion syndrome-survivors.

Chapter seven aims at evaluating long-term neurodevelopmental outcome and general health status after Parvovirus B19-induced fetal hydrops treated with intrauterine transfusion. We performed a detailed standardized general and neurological examination and age specific neurodevelopmental tests in the surviving children.

In chapter eight we describe the perinatal mortality and morbidity, as well as long-term neuropsychologic and cardiologic outcome of 44 fetuses with severe brady- or tachyarrhythmia. Fetal cardiac arrhythmias are diagnosed in at least 2% of pregnancies. In less than 10% of cases it concerns prolonged or incessant episodes of brady- or tachycardia. These prolonged periods of tachyarrhythmia or continuous bradyarrhythmia can lead to congestive heart failure, non-immune hydrops, and fetal or neonatal death. Episodes of heart failure may lead to permanent damage, or not. We performed a detailed standardized general, cardiac and neurological examination and age specific neurodevelopmental tests in the surviving children.

Chapter nine presents a general discussion and reflection on future perspectives.

Chapter ten summarizes the results of the presented studies.
CHAPTER 1

References

REFERENCES
