
Fetal therapy

Update on the current level of knowledge

Horizon scanning report





To the Minister of Health, Welfare and Sport

Subject : Submission of a horizon scanning report from the MTA committee
Fetal therapy

Your reference:

Our reference : U-5228/WD/tvdk/589-G3

Enclosures : 1

Date : May 27, 2008

Dear Minister,

Please find enclosed a horizon scanning report produced by the Health Council's Committee on Medical Technology Assessment (MTA). It is an update on the current level of knowledge in the field of fetal therapy. The Health Council last produced an advisory report on this subject in 1990. In the more than fifteen years that have passed since then, significant new developments have taken place, particularly with regard to minimally invasive surgery and drug therapy, where certain drugs can be administered to the fetus via the mother. The horizon scanning report contains a summary of the forms of fetal therapy currently in use in the Netherlands, specifying in each case whether the treatment in question is accepted or experimental and how strong the scientific evidence is. It also provides information about research currently being undertaken in other countries, such as into fetal therapy for spina bifida, and on possible future developments in the field of fetal stem cell therapy and gene therapy.

Since the introduction of red cell alloimmunisation in 1965, fetal therapy in the Netherlands has been concentrated at the Academisch Ziekenhuis in Leiden [Leiden University Hospital], now known as the Leids Universitair Medisch Centrum (LUMC) [Leiden University Medical Centre]. Unlike the situation in some centres abroad, the doctors involved have always been more cautious with regard to high-risk innovations. No problems in the quality of care have arisen as a result. The procedures in question are rare and require scarce expertise and a good infrastructure. As rightly pointed out in the horizon scanning report, it is important for the quality of this care to be assured into the future. Concentration, as has already taken place in practice, can make a further contribution to this. I also support the plea for a quality standard and the rationale behind this request: the field is a sensitive one, where transparency and justification of medical interventions is all the more important.

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The developments described in this horizon scanning report also give rise to ethical and legal questions that are relevant to policy. The Health Council will address these questions in more detail in a separate horizon scanning report to be published later this year by the Centrum voor Ethiek en Gezondheid [Centre for Ethics and Health] (CEG).

Yours faithfully,
(signed)
Prof. dr. J.A. Knottnerus

Fetal therapy

Update on the current level of knowledge

Horizon scanning report

Committee on Medical Technology Assessment

Prepared by
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to:

the Minister of Health, Welfare and Sport

No. 2008/10E, The Hague, May 27, 2008

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, Agriculture, Nature & Food Quality, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.



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INAHTA

The Health Council of the Netherlands is a member of the International Network of Agencies for Health Technology Assessment (INAHTA), an international collaboration of organisations engaged with *health technology assessment*.

This report can be downloaded from www.healthcouncil.nl.

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Executive summary

The use of ultrasound scans during pregnancy can detect numerous fetal abnormalities. Some fetal diseases can even be treated before birth. The Health Council published an advisory report on these developments in 1990. This horizon scanning report gives an update on the current level of knowledge in the Netherlands and beyond. It aims to contribute to the debate on how to safe-guard high quality care in the field of fetal therapy in the future.

The most commonly performed invasive fetal treatments are intra-uterine blood transfusion for severe fetal anaemia and the fetoscopic laser coagulation of blood vessels in the placenta of twins with twin-to-twin transfusion syndrome. The number of such procedures carried out in the Netherlands each year are 100 and 45 respectively.

Non-invasive treatment of the fetus by the administration of medications to the mother can be used for conditions such as cardiac arrhythmias, thyroid abnormalities and the production of anti-platelet antibodies. Each of these disorders involves five to ten pregnancies per year. Each year, a few fetuses are treated by using a large-gauge hypodermic needle to insert a shunt (drainage tube) into their thoracic cavity or bladder. Open fetal surgery, in which the mother's abdomen and uterus are opened and then closed-up again once the operation on the fetus is complete, is not carried out in the Netherlands.

Those fetal treatments which are carried out in the Netherlands are either non-invasive or only marginally so. Such treatments pose only a very slight risk to the pregnant mothers themselves. The decision to proceed with fetal treatment

is usually only taken in cases where delaying treatment until after birth is virtually certain to lead to an adverse outcome. Furthermore, most of the children who successfully undergo fetal treatments in the Netherlands have a good chance of being completely healthy. One promising new application is the pre-natal treatment of rare metabolic diseases. This involves keeping pregnant mothers on a special diet or giving them food supplements.

Research is currently being conducted abroad into treating fetuses for diaphragmatic hernias, spina bifida and heart valve stenosis. However, the results of this work will not be available for another three to five years. Should these studies produce favourable results, then the Netherlands will also experience increasing demand for these procedures. Stem cell therapy and gene therapy are still in the laboratory stages, but it seems sensible to assume that these techniques too will eventually be applied to the treatment of human fetuses.

Given the complexity of fetal therapy (and of invasive fetal therapy) and the small numbers involved, the preconditions for such treatment would be concentration in a small number of centres, complete and transparent reporting, sound scientific research, and cooperation at national and international level. Any proper assessment of the pros and cons of fetal therapy requires that the children receiving treatment be monitored for many years and that they be tested from time to time as they grow up.

Introduction

1.1 Background

Most newborn children are healthy. However, in about five per cent of pregnancies (10,000 a year) the fetus suffers from an illness or abnormality acquired in the early stages of pregnancy. The conditions in question vary considerably and include infections, anatomical deviations of organs, genetic syndromes and chromosomal abnormalities. Some are harmless or self-resolving, but others cause serious handicaps or are life-threatening. This group accounts for a high proportion of perinatal mortality (19 to 27 per cent).^{1,2}

Echoscopic examinations allow most congenital abnormalities to be diagnosed at a relatively early stage of pregnancy. Beneficial therapeutic intervention can be offered for some fetal diseases and abnormalities prior to birth. This is the topic covered by this horizon scanning report.

1.2 Previous Health Council advice

In its advisory report published in 1990, *The unborn child as a patient*, the Health Council mapped the state of scientific knowledge regarding fetal therapy at that time.³ By then, improvements in echoscopy had led to more rapid developments in this field. The council advised a cautious approach. Open surgery (in which the womb is opened) was rejected as being far too risky (at the time), and requiring further investigation in the form of animal trials. It was recommended

that further research first be conducted into less risky procedures involving closed surgery or drug therapy. The only treatment regarded as having been proved to be worthwhile was the treatment of blood group immunisation.

1.3 The purpose of this report

The aim of this report is to provide an update on the state of scientific knowledge. It covers developments in the field of fetal therapy in the Netherlands and other countries since the publication of the Health Council's report. It also aims to contribute to the vital debate on the issue of how high-quality care in this field can continue to be assured in the years to come.

The developments in this field give rise to ethical and legal questions. What is the significance of the fact that fetuses can increasingly also be regarded as patients? How does this relate to the abortion debate? What are doctors responsible for in this area, and what lies outside their responsibility? And what about pregnant women in this regard? What regulations apply, and are they adequate? The Health Council will address these normative aspects in more detail in a separate report to be produced by the Centre for Ethics and Health (CEG).

1.4 Authorship

This report was produced by the Health Council's Medical Technology Assessment (MTA) committee (see annex A for a list of members). The text was prepared by Dr. D. Oepkes, a gynaecologist/perinatologist working at Leiden University Medical Centre (LUMC). Written comments on a previous version were submitted by

- Dr. G.C.M.L. Page-Christiaens, gynaecologist, Utrecht University Medical Centre;
- Dr. F.P.H.A. Vandenbussche, gynaecologist, Leiden University Medical Centre;
- Dr. T.J. de Koning, paediatrician specialising in metabolic conditions, Utrecht University Medical Centre.

This horizon scanning report was reviewed by the Standing Committee on Genetics and the Standing Committee on Medicine.

1.5 Structure of the study

The history of fetal therapy is described in chapter 2. The treatments currently available in the Netherlands and other countries are discussed in chapters 3 and 4 respectively. Chapter 5 contains a brief description of new experimental treatments, such as fetal stem cell and gene therapy. Finally, chapter 6 underlines a number of aspects that are important to the maintenance and improvement of the quality of this care, such as centralisation, scientific research and transparency.

Where a chapter deals with a specific intervention, the level of evidence for the intervention is stated, using the U.S. Preventive Services Task Force classification. An explanation of the grading system is given in annex B.

History of fetal therapy

The history of fetal therapy is closely associated with the development of technology used to produce images of the fetus. Until the 1960s, the pregnant womb was unknown territory. It was sometimes possible to ascertain that a woman might be carrying twins or have too much amniotic fluid by performing external palpation. However, in most cases the fact that a child had abnormalities was not detected until after birth.

But within twenty years the invisible existence of the fetus was transformed into visible life, and it became clear that many diseases and conditions could be detected before birth. Enthusiasm at the new diagnostic opportunities was rapidly followed by doctors and pregnant women asking whether some diseases could perhaps be treated prior to birth. Over a few decades obstetrics changed into perinatology (care during the perinatal period) or maternal-fetal medicine. Thanks to imaging technology, the fetus became a visible 'human being in miniature', and the sick fetus a tiny patient.

2.1 Important developments

2.1.1 The 1960s: X-rays

The first imaging technology was based on X-rays. A simple photograph of the entire abdomen provided information on multiple fetuses, positioning and fetal skeletal abnormalities.

Better information was obtained by first injecting contrast media into the amniotic fluid. The fetus drank a water-soluble contrast medium, so that its gastrointestinal system could be displayed. Fat-soluble contrast media adhered to the skin of the fetus, showing an image of its contours. Applications of this included the diagnosis of hydrops foetalis in cases of blood group immunisation and placenta location in cases of suspected placenta praevia.

Working in New Zealand in the early 1960s, Liley developed a method of treating red cell alloimmunization prior to birth. This disease, which leads to severe progressive fetal anaemia, was at the time still one of the main causes of perinatal death. Severe neurological damage caused by nuclear icterus (severe jaundice) was common in affected children who survived. Liley used X-ray amniography to insert a needle into the fetal abdominal cavity and give blood to the fetus through this needle. This first successful fetal therapy, along with developments in diagnosis and neonatology, caused a sharp decline in perinatal death due to red cell alloimmunization.

During the same period experiments took place in the US in which the womb was partially opened, one of the fetus's legs was extracted and blood was introduced into a blood vessel in the leg via a catheter in order to treat anaemia. This first application of 'open fetal surgery' had poor outcomes and considerable drawbacks for the mother. This approach was therefore rapidly abandoned in favour of Liley's much safer and more elegant method.

In 1965 Bennebroek Gravenhorst, later Professor of Obstetrics at Leiden University, was trained by Liley and learned the technique, which he introduced on his return to the Netherlands.

2.1.2 *The 1970s: the arrival of ultrasound*

Obstetric ultrasound was introduced in the 1970s, allowing multiple births to be diagnosed, the placenta to be located and fetal growth to be measured without the problem of potentially dangerous radiation (as with the use of X-rays). Despite the very mediocre quality of the images by modern standards, the procedure allowed fetal structural abnormalities including neural tube defects such as anencephaly and spina bifida, and congenital renal agenesis to be diagnosed. Routine ultrasound was introduced in Germany in 1980. Every pregnant woman underwent two (later on three) ultrasound scans during pregnancy. In the early stages of pregnancy to estimate the delivery date, detect multiple births and gross structural abnormalities; in the third trimester to determine any growth problems.

In the first 25 years of increasing use of obstetric ultrasound, considerable attention and research was devoted to the possible harmful effects of ultrasound

on the fetus. International guidelines and limits built into the equipment have led to the present consensus that in normal diagnostic use ultrasound presents no risks to the fetus.

2.1.3 *The 1970s and 1980s: fetoscopy*

In 1974, Hobbins from the USA was the first person to insert an endoscope into the uterus in order to be able to visualise the fetus.⁴ In the early 1980s, Rodeck in London performed umbilical cord punctures under direct vision. A lens a few millimetres thick, fitted with a light source, was inserted into the uterus under local anaesthetic. This method is called fetoscopy. The most important application was relatively safe needle insertion into the umbilical cord for blood tests and blood transfusion.

2.1.4 *The 1980s and 1990s: high-resolution ultrasound*

The quality of ultrasound images improved very quickly, and soon made fetoscopy redundant. Daffos in Paris, and Bang in Copenhagen, introduced ultrasound-guided needle insertion into the umbilical cord for fetal blood tests and blood transfusions.

The high resolution of ultrasound equipment allowed practically all fetal structural abnormalities to be 'seen', often at an early stage in pregnancy. A large number of publications dealing with early detection of fetal conditions subsequently appeared. Ever-improved diagnostic opportunities led to the question of whether interventions carried out on the fetus, i.e. while it was still in the womb, could improve the outcome for the child in the case of some diseases.

Both obstetricians (in Europe) and paediatricians (in the US) were searching for ways of treating the sick fetus. They initially looked for treatments from paediatric surgery that it might be possible to carry out on the fetus. Two important examples are open fetal surgery for hiatus hernia (a hernia in the diaphragm) and the insertion of a drainage tube (shunt) to remove various forms of fetal fluid accumulation. The history of these procedures is summarised at the end of this chapter.

2.1.5 *The 1990s: fetoscopy revisited*

Twin-to-twin transfusion syndrome (TTS) is a serious complication of pregnancy that occurs only in the case of monovular twins. In this condition, both fetuses share a placenta, and placental vascular anastomoses allow blood to flow from

one fetus to the other. Chronic blood transfusion from one fetus (the donor) to the other (the recipient) takes place in 15 per cent of monovular twins with a shared placenta (monochorial twins). This leads to increased blood volume of the recipient, which responds by secreting abnormally large amounts of urine (and so excess amniotic fluid), and decreased blood volume of the donor, leading to decreased urinary output. This condition also puts too much strain on both fetal hearts.

If no action is taken, the excess amniotic fluid produced by one fetus causes severe distension of the womb, contractions and premature delivery, or the death of one or both fetuses as a result of excess cardiac strain. Diagnosis can be established by ultrasound, but until recently the only treatment available was repeated removal of the excess amniotic fluid surrounding one of the fetuses (serial amniodrainage). This control of the symptoms sometimes postponed premature delivery, but the outcome of these pregnancies was still often poor.

In 1990 DeLia reported on a treatment for TTS that addressed the cause. He used a fetoscopic technique, first extensively tested in sheep and Rhesus monkeys, to image the vascular anastomoses on the surface of the placenta and then used a laser wire passed through an operating channel of the same instrument to seal the blood vessels. This technique was refined by Nicolaides and Ville in London, and they described good results in 1995. On the basis of these successes many centres for fetal medicine, mainly in Europe (London, Hamburg, Leuven and Paris), started to perform the same treatment. This laser therapy for TTS was introduced in Leiden in 2001. A large, randomised multi-centre trial (the 'Eurofetus trial') was published in 2004. It compared fetoscopic laser treatment with the 'traditional' method of repeated drainage of excess amniotic fluid.⁵ The laser treatment was found to be better than serial amniodrainage. Apart from the higher survival rate, the main advantage was a much smaller number of children with neurological damage in the laser group.

The Eurofetus group, the group of European centres pioneering endoscopic TTS treatment, also contributed to the creation of a register of other fetoscopic interventions (see chapter 3). One of the people behind the initiative to set up this group, Deprest from Leuven, has performed much fundamental and animal research into fetal endoscopic surgery in all its facets, concentrating on what is still the major problem of amniotic fluid leakage or ruptured membranes following fetoscopy.

In addition to the treatment of TTS, his main focus of interest is fetoscopic intervention in fetuses suffering from the most serious form of diaphragmatic hernia. His method consists of temporarily blocking the fetal windpipe (trachea), causing the lungs to fill with fluid and as a result pushing the intestines back into

the abdominal cavity. He has experimented on this technique with gravid sheep for some years, and it is now also being applied in humans in the context of a study (see chapter 3).

2.1.6 *The late 1990s to the present day: fetal MRI*

Ultrafast MRI is a recent development in imaging. MRI (magnetic resonance imaging) uses magnetic fields and the phenomenon of nuclear spin to produce detailed images of human tissues. The MRI technique has existed for a considerable time, but fetal movements made it impossible to produce clear images unless drugs were administered to ‘immobilise’ the fetus. Powerful computers are now able to capture and process the images very quickly, and the images can be assessed from multiple planes via calculations. The images of fetal brains produced by MRI in particular are much better than those produced by ultrasound. Recent improvements in other imaging techniques, especially 3D ultrasound, might however reduce the superiority of MRI.

Although few long-term studies have been conducted so far, it is assumed that the use of (1.5 Tesla) MRI in the second and third trimesters of pregnancy is safe.^{6,7}

In addition to the fetal therapies referred to above, many experiments have been carried out in the past forty years, sometimes only in the (animal) laboratory and sometimes on human fetuses. Most of these experiments were abandoned for various reasons. Two important examples are discussed below from a historical point of view and because, in contrast to many other procedures, these procedures were performed on large numbers of pregnant women.

2.2 **Examples of treatments**

2.2.1 *1980-2004: rise and ‘decline’ of fetal diaphragmatic hernia surgery*

Congenital hiatus hernia is a relatively common condition (1 in 5,000 births). In this condition, the stomach, intestines and sometimes part of the liver migrate from the abdominal cavity into the chest cavity, compressing the heart and lungs.

This impedes lung development, and the infant may die shortly after birth because it is unable to breathe properly. An operation performed shortly after birth can be life-saving, provided that the lungs are not too seriously underdeveloped. This involves opening the chest cavity, returning the intestines to the abdominal cavity, and closing the hole in the diaphragm.

However, no treatment is available for lungs that have not developed sufficiently (pulmonary hypoplasia). In the 1980s 50 to 70 per cent of neonates with this condition died. Then it was discovered that the condition could be detected by ultrasound prior to birth, and the San Francisco paediatric surgeon Harrison came up with the idea that the operation which he often had to perform as an emergency on neonates with severely impaired respiration might be possible before birth. He hoped that this could prevent pulmonary hypoplasia.

His group conducted extensive preliminary research, laboratory tests and experiments on animals before performing the procedure on human fetuses.⁸ The technique involved performing a modified Caesarean section; after the uterus and membranes were opened, one of the fetus's arms was brought outside the uterus (for monitoring) and part of the fetal chest was exposed. The operation was performed in the same way as on a newborn infant. Then the membranes and the uterus were closed, amniotic fluid is added and medication is administered to inhibit contractions.

The research team devoted a great deal of effort to minimising complications such as amniotic fluid leakage, membrane rupture and premature delivery, which occurred frequently. It was found that the membranes which were opened during the procedure could not knit back together. Amniotic fluid leakage leads to a high risk of infection rising from the vagina, causing infection of the fetus and triggerinlabour. The consequences for the fetus depend mainly on the stage of pregnancy at which this happens. All pregnant women undergoing this operation ('open fetal surgery') were kept in hospital until they gave birth. They were put on a prolonged course of antibiotics and drugs to inhibit contractions. Because of the scar in the uterus, delivery and all future deliveries by these patients required a planned Caesarean section. These drawbacks for the pregnant woman herself caused most European doctors to decide not to perform such operations; in addition to disappointing conclusions as to the benefits of the procedure.

A prospective study found 75 per cent survival in the group undergoing prenatal surgery. However, survival was 86 per cent in the control group of infants who were operated on shortly after birth. Over the course of the study, neonatal surgery, ventilation and intensive care had improved to such an extent that there appeared to be no real reason to continue performing prenatal surgery, particularly open fetal surgery.⁹

A major technical advance was achieved when open surgery was replaced by an endoscopic technique in which the fetal trachea was temporarily blocked. As a result, fluid produced by the lungs could not drain away into the amniotic fluid but caused the lungs to swell. This pushed the intestines back from the chest cavity into the abdomen. Extensive research was also conducted into better selection

of fetuses with a poor prognosis, which could benefit from prenatal surgery. Following preparatory investigations, a randomised study into this method was sponsored by the National Institute of Health (NIH). Once again the same phenomenon occurred: the outcome of the group undergoing prenatal surgery appeared to be good (73 per cent survival), but the survival figure for the control group was 77 per cent.¹⁰ After 25 years of research, this seemed to signal the end of the road for fetal therapy for congenital hiatus hernia. However, a small subgroup of fetuses with congenital hiatus hernia, those with very small lungs and a large proportion of the liver in the chest, still have an extremely poor prognosis. Work on prenatal interventions for this group is being carried out mainly in Europe (Deprest, Leuven), involving even less invasive endoscopic techniques (see chapter 3).

2.2.2 *1982-present day: fetal shunt therapy: from enthusiastic introduction to careful and limited determination of its role*

Fetal conditions in which large amounts of fluid are in abnormal locations can easily be detected by ultrasound. Examples of this include severe overdistention of the bladder (megabladder) where the bladder outlet is obstructed, fluid on the brain (hydrocephalus) and accumulation of fluid in the pleural cavity (hydrothorax). The extreme pressure that these conditions often cause can damage organs (kidneys, brain, lungs) or endanger cardiac function. Fetal or neonatal death, or life-long handicaps, can be the result. A paediatrician or paediatric surgeon can insert a drain or shunt (a small plastic tube) into infants born with such conditions in order to remove the fluid.

In the 1980s Rodeck developed a shunt that could be guided via ultrasound into an overdistended fetal bladder using a thick needle.¹¹ This silicon tube, two millimetres thick, has a double pigtail (one at each end) and a 'memory' for this shape. The tube is rolled out inside the insertion needle once the needle has penetrated the pregnant woman's skin and passed through the wall of the womb to reach the fetal bladder. The tube is pushed until the first pigtail is inside the bladder and the needle is then withdrawn so that the second pigtail comes to rest outside the fetus, in the amniotic fluid. The open-ended connection allows the excess fluid to drain away.

The same technique was applied in abnormal fluid accumulation in the fetal chest cavity and brain. Members of the *International Fetal Medicine and Surgery Society* (IFMSS) founded by Harrison in 1982 kept records of these procedures. It soon became obvious that it was not a good option for treating hydrocephalus.

Children with hydrocephalus routinely undergo surgery to insert a shunt after birth, but performing the procedure prior to birth appeared to involve too many complications and no demonstrable benefit to the child. Shunt treatment is however still performed in cases of bladder obstruction and fluid in the chest cavity. Where the technique is still carried out nowadays, this is done in conjunction with a thorough scientific assessment of the (long-term) outcomes (see chapter 3).

2.3 Developments in neonatology: consequences for fetal therapy

2.3.1 Successful treatment of increasingly younger and lighter babies

The term neonatology was introduced in the 1960s. At that time, a baby weighing 1,000 grammes had a five per cent chance of survival. This figure is now 95 per cent.¹² Improved support of cardiac and pulmonary function, and the ability to feed these infants via an infusion drip, have brought the viability threshold down to 24 weeks, 500 grammes, or even lower. Most research has been and is still focused on improving methods in order to prevent or treat the many complications of prematurity. Some of the most significant developments in neonatology are described below.

2.3.2 Progress in neonatal care: the most significant examples

Newborn infants who are detached from the placenta too soon must breathe, drink, and regulate their temperature. Incubators and intravenous feeding were major steps forward in neonatal care. The many developments in supporting respiration have been crucial to increasing the survival chances of very premature babies. Continuous positive pressure ventilation and the administration of surfactant to keep the pulmonary alveoli open have been routine parts of neonatal intensive care for years. Sophisticated techniques such as high-frequency oscillation, liquid respiration, nitrogen monoxide and extracorporeal membrane oxygenation (ECMO, heart-lung machine) can often keep infants with very poor lung function alive.

More cautious ventilation, with higher carbon dioxide levels in the infant's blood accepted (gentle ventilation), causes fewer complications, is less likely to require the use of ECMO, and is associated with better survival rates, especially in neonates with congenital hiatus hernia.¹³

Persistent high blood pressure in the pulmonary vessels is a serious consequence of lung damage caused by premature birth or excessively small lungs.

New drugs such as sildenafil now offer better treatment opportunities for this condition.

The outcomes of cardiac surgery performed on neonates are improving all the time. This is helped by progress in many areas.¹⁴ An increasing number of procedures can be performed via a catheter which travels along the blood vessels to the heart.¹⁵ This technique can entirely or partially replace open heart surgery. Better heart/lung machines, filters and drugs to control inflammatory reactions and better protection of the heart muscle and the brain during surgery all play a part. Under-development of the left ventricle of the heart was regarded as an almost inevitably fatal congenital heart abnormality until the 1980s. One Dutch centre achieved survival rates of 74 per cent between 1999 and 2005. The survival trend is still rising thanks to technical improvements such as the Sano shunt.¹⁶ The ventilation developments referred to above have also had a beneficial impact on the outcome of heart surgery.

Minimally invasive surgery with endoscopic techniques have taken off dramatically not only for adults and fetuses, but are increasingly being used in neonatal surgery as well.¹⁷ The improvements in perioperative care also go hand in hand with surgery being performed on ever younger and smaller premature babies. Successful operations such as surgery for fistulas between the oesophagus and the windpipe have already been described in children under 1,000 grammes.¹⁸

Genetic and gene-environment interaction studies constitute a whole new direction of research from which much is expected.¹⁹ Fields such as genomics, proteomics and metabolomics can provide entirely new insights into causes of diseases, consequences of prematurity and their treatment.²⁰

2.3.3 *Neonatal versus fetal therapy*

The better care and outcomes for prematurely born infants are also influencing the debate on fetal therapy. The decision whether it is better to treat a sick fetus while it is still in the womb or to wait for its premature birth and then give treatment depends on the effects of the premature birth, the risk of a prenatal intervention to the expectant mother, and the difference in prognosis after fetal and neonatal treatment. Another factor is that improvements in many areas are also making operations in the early neonatal phase safer all the time.

If there is any possibility of treating a full-term infant after birth with a reasonable prognosis, preference should always be given to this rather than fetal treatment with the associated risks of premature delivery and drawbacks for the pregnant woman.

In centres for fetal therapy, multidisciplinary consultation and treatment by a team of specialists is the norm. However, there is a difference between the situation in Europe and that in the United States. In Europe it is the gynaecologist who both diagnoses the fetus and performs any treatment. He or she is also the primary practitioner and coordinator of multidisciplinary management. In the US, imaging is carried out by the radiologist and treatment to the fetus is given by the paediatric surgeon. The paediatric surgeon is also often the coordinator in the US. The recent creation of the North American Fetal Therapy Network (NAFT-NET), an initiative taken by gynaecologists, looks to be changing this situation. The European emphasis on the primary responsibility of the gynaecologist gives expression to the view that the interests of the expectant mother must always take precedence. This distinction is probably one of the reasons why experiments with open fetal surgery have hardly ever been carried out in Europe.

Close cooperation between all specialists, including those who will be involved in the care of the child in question after it is born, is a condition for optimum care. The team can only provide considered advice to the parents with regard to the options for their sick fetus if its members are fully aware of the latest insights in both prenatal and neonatal treatment.

New opportunities in both forms of treatment, fetal and neonatal, mean that more children survive than used to be the case. Some of these children will not be healthy, but will have to cope with permanent damage throughout their lives. Sometimes this damage is regarded by medical practitioners, parents or society as so severe that doubts have arisen as to whether it would not have been better to refrain from treatment. Close monitoring and recording of the health and development of all children who undergo treatment is vital to this debate, and important in assessing both fetal and neonatal treatments.²¹

Situation in the Netherlands

This chapter contains a brief summary of options currently available in the Netherlands for prenatal, intra-uterine treatment of fetal diseases. So far, fetal treatments carried out in the Netherlands have been limited to non-invasive and minimally invasive interventions. The paragraphs below discuss both types of interventions in turn.

'Non-invasive' here means administering drugs to the mother which reach the fetus via the placenta. 'Minimally invasive' refers to treatment involving the insertion of a needle or thin (< 5 mm in diameter) tubular instrument into the uterus. The inconvenience and risk to the pregnant woman herself are regarded as minimal.

Most of the aforementioned treatments are carried out only in university medical centres. Fetal treatment is preceded by multidisciplinary consultation with neonatologists, geneticists and other specialists (paediatric cardiologists, paediatric neurologists, etc.) depending on the condition involved. Careful consideration is given to whether fetal treatment is better than the alternatives. These alternatives are generally: delaying treatment until after birth if possible, inducing premature delivery of the child and then giving treatment after birth, and termination of pregnancy if this is legally possible. These options and their likely consequences are discussed in the team and with the expectant parents. Psycho-social support, often provided by a social worker, is also usually provided. There is (as yet) no specific registration of fetal treatments in the Netherlands. Recommendations in this respect are described in chapter 6.

3.1 Non-invasive fetal treatment: fetal pharmacotherapy

'Non-invasive fetal treatment refers those forms of intervention in which medication, administered to the mother, passes through the placenta to reach the fetus. This medication can sometimes be given orally, but it usually has to be administered to the pregnant woman by intramuscular or intravenous routes. Strictly speaking, these two latter options are also somewhat invasive, but in this context the accepted international definition of 'invasive' is a technique in which a needle or larger instrument is inserted into the uterus. Pregnant women are also sometimes given drugs or dietary advice to prevent fetal diseases, such as folic acid around the time of conception to reduce the likelihood of a neural tube defect or antibiotic treatment during pregnancy or delivery to prevent fetal or neonatal infections. This report does not address this type of preventive treatment.

The risks to the pregnant woman herself, in addition to the possibility of an allergic reaction which may occur with any drug, depend on the primary action and side-effects of the drugs. The Canadian pharmacologist Koren *et al.* have published a summary analysing the scientific evidence for particular drugs and dosages.²² They argue for well-controlled studies, with randomised placebo-controlled trials. International cooperation is necessary in view of the rarity of most of the conditions.

3.1.1 Administration of corticosteroids

Indication I: threat of premature delivery between 25 and 34 weeks.

- Administration: two injections of betamethasone into the pregnant woman's buttock or thigh at 24-hour intervals.
 - Effect: accelerated fetal lung development and protective effect on other organs in the event of premature birth within ten days after administration.
 - Status: this treatment has been widely accepted and proven to be beneficial since the 1970s. It is listed in guideline 3 of the Netherlands Association for Obstetrics and Gynaecology (NVOG).
 - Risk to the pregnant woman: temporary disregulation of sugar balance, possibility of fluid behind the lungs in certain high-risk groups and when combined with other substances.
 - Level of evidence: level I.
 - Number of pregnant women treated in the Netherlands each year: estimated at 2,000-4,000.
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Indication 2: corticosteroids in the form of dexamethasone are also used in pregnancies where there is a risk of congenital adrenal hyperplasia, also referred to as adrenogenital syndrome. The incidence of this inherited disease is one in 15,000 to 18,000 births. It is an autosomal recessive inherited disease; this means that if both parents are carriers, they have a one in four chance of having a child with this condition. An enzyme defect in the production of the adrenal cortex hormones causes the adrenal cortex to be constantly stimulated, leading to enlargement of the adrenal gland, a deficiency in cortisol (stress hormone) and aldosterone, and excess male hormones (androgens). Girls undergo 'masculinisation', or virilisation of the external sex organs during fetal development. This means that a female infant may be mistaken for a boy at birth. The high androgen content also causes functional disorders in the developing brain.

Dexamethasone can counteract virilisation. If the disease is known in the family – usually because a previous child was found to be affected – treatment can be given in a subsequent pregnancy. The medication is given as early as possible in pregnancy, before the sex of the fetus is known. The sex of the fetus can be determined by testing the mother's plasma from seven weeks into pregnancy, which is a non-invasive procedure. If the fetus is found to be male, the medication is stopped. If the fetus is female, a CVS test is carried out to determine whether it is affected (25 per cent chance); if it is not, the medication is stopped.

- Administration: oral.
- Effect: prevention of virilisation of the female fetus.
- Status: accepted treatment, usually coordinated by clinical geneticists.
- Risk to the pregnant woman: the high doses of steroids used can sometimes cause serious side-effects to the pregnant woman if they are administered for prolonged periods, such as Cushing's syndrome, hypertension and disregulated sugar balance. Treatment is started early in pregnancy, often before the sex of the fetus is known. The medication is stopped once it is clear that the fetus is a boy or an unaffected girl, but in more than 80 per cent of cases the woman takes the drugs 'for nothing' for a few weeks.
- Level of evidence: level II-2.
- Number of pregnant women treated in the Netherlands: estimated at 10-20 a year.

3.1.2 *Administration of anti-arrhythmic drugs (drugs which return an abnormal heart rhythm to normal: digoxin, flecainide, sotalol, amiodarone, betasympaticomimetics)*

Indication: life-threatening fetal cardiac arrhythmia.

- Administration: orally or by intravenous administration to the pregnant woman.
- Effect: improves fetal heart rhythm.
- Status 1: This treatment has passed the experimental stage in the case of supraventricular tachycardia (continuous excessively rapid heartbeat) with the threat of or evident heart failure and a gestational age at which planned premature delivery followed by neonatal treatment has a poor prognosis (<32 weeks).

The risks to the mother are very low if the proper precautions are taken. Oudijk *et al.* recently described the clinical aspects of this fetal treatment, including long-term follow-up studies.²³ Each university hospital carries out this procedure and has a protocol for it.

- Status 2: Beta-sympathomimetic drugs are used experimentally a few times a year to treat fetal bradycardia (excessively slow heartbeat) where the heart rate is below 55 beats per minute, leading to heart failure. This drug causes a slight, but in some cases just sufficient, increase in the fetal heart rate. It can gain time until the fetus is sufficiently 'mature' to be delivered and fitted with a pacemaker. These drugs have been used for several decades in obstetric medicine in order to inhibit contractions, with known minor side-effects to the mother (cardiac palpitations, headache). The success rate is low, and depends mainly on the underlying cause of the bradycardia. It should be considered as a last resort in cases of heart failure, with clear information on the mediocre prognosis being given. Infants who survive will depend on a pacemaker.
- Risk to the pregnant woman: any anti-arrhythmic drug can itself trigger rhythm disorders. The drugs referred to above are also used on adult patients with rhythm disorders, and the spectrum of adverse events for each drug is well known. They can include nausea, vomiting, abdominal pain, headache, fatigue, depression, sight disorders and cardiac rhythm disorders. It is important that the pregnant woman be checked for concentrations of the drug and effects on her heart, and she should also undergo prior testing for cardiac disease. A cardiologist must therefore be involved in the treatment.
- Level of evidence: level II-3.
- Number of pregnant women treated in the Netherlands each year: 10-20.

3.1.3 *Intravenous administration of immunoglobulin (IVIg)*

- Indication: fetal and neonatal alloimmune thrombocytopenia (FNAIT).
- Administration: once a week by intravenous administration to the pregnant woman in the second half of pregnancy until birth.
- Effect: prevention of perinatal cerebral haemorrhage. The disease is characterised by an excessively low platelet count (thrombocytopenia), caused by antibodies to fetal platelets in the pregnant woman. The antibodies are formed in pregnant women who are negative for a platelet antigen following contact (pregnancy) with blood of the fetus that is positive for this antigen. The fetus inherits this property from the father. The mechanism of the disease is similar to that involved in red cell alloimmunisation. In FNAIT, the antibodies often cause serious symptoms in the first pregnancy. Fetal or neonatal cerebral haemorrhages often lead to lasting damage and handicap. FNAIT occurs in one in 2,000 births. There is (as yet) no screening programme for the condition. This means that treatment during pregnancy is almost always given after a woman has already given birth to an affected child, or to the sisters or daughters of women who have had an affected child.
- Treatment with IVIG is effective. A recent study of 98 pregnancies found no cases of cerebral haemorrhage.²⁴
- Status: Internationally accepted treatment since 1988, a routine procedure for this condition. Patients are treated at LUMC or in other hospitals in close consultation with and coordination by LUMC. Clinical and laboratory studies have been taking place for several years, in a joint venture organised by the obstetrics department of LUMC, Sanquin Leiden and Sanquin Amsterdam. The scientific evaluation has been described in theses by C.M. Radder²⁵ and E.S.A. van den Akker.²⁶
- Risk to the pregnant woman: IVIG is a human multi-donor (>1,000 donors) blood plasma product, but is regarded as safe. The clinical signs that may occur in connection with the first administration are slight headache and nausea. Pregnant women undergo treatment in the form of intravenous infusion once a week for six to ten weeks, or sometimes 20 weeks in the most serious cases, and each session takes a few hours. The procedure costs €2,500 to €3,000 a week at the current standard dose of 1 g per kg maternal weight.
- Level of evidence: level II-3.
- Number of pregnant women treated in the Netherlands each year: 5-10.

3.1.4 Administration of antiviral or antiparasitic drugs

Indication: proven viral or parasitic infection of the pregnant woman, with a high probability that the fetus will be infected, or proven fetal infection.

- Effect: It may be important for the health of a pregnant woman who contracts an infection for her to have it treated by drugs, as is done in the case of syphilis. The therapy is then targeted not primarily at the fetus, but one of the additional benefits is that the likelihood of transmission via the placenta is reduced. Perinatal death from congenital syphilis is much lower in women treated with penicillin in good time (first half of pregnancy). The percentage of infants with infection in the cerebral fluid is much higher in those born to women with syphilis who have not been treated compared to those who have been treated. In the Netherlands, all pregnant women are screened for syphilis and those found to be infected are treated with penicillin as rapidly as possible. There is not really any debate on the issue of co-treatment of the fetus in this case. The current recommendation for treating pregnant women with early-stage syphilis is 2.4 million IU of benzathine benzylpenicillin on days one, eight and fifteen, as a single treatment may lead to a poorer outcome for the infant. There were six reported cases of congenital syphilis in the Netherlands in 1990, and none in 1995 (the condition has not been notifiable since 1999). The National Institute for Public Health and the Environment (RIVM) receives nought to three requests for congenital syphilis testing a year.
- In the case of viral infections that do not require treatment for the benefit of the pregnant woman herself, such as Parvovirus B19, chickenpox or cytomegaly, antiviral therapy or immunoglobulins have not yet been shown to be useful in improving fetal outcomes.
- Toxoplasmosis infection during pregnancy is a complex subject. Around 65 per cent of young women in the Netherlands are seronegative (have never been infected) and therefore vulnerable.²⁷ Hygiene and lifestyle advice are routinely provided. The infection can cause miscarriage, growth retardation or serious damage to the nervous system, deafness and blindness. The chance of passing on the infection to the fetus (transmission) ranges from 20 to 80 per cent. It is less likely early in pregnancy, but the consequences then are more severe.²⁸ The TIP study carried out in the Zuid-Holland region in the late 1980s found the incidence of congenital infections in seronegative pregnant women to be eight in 10,000.²⁹ The conclusion of this study was that screening would not be useful.

It appears from the data from PALGA (the pathology database) that there

were fourteen stillborn infants with toxoplasmosis between 1996 and 2006. The average incidence of toxoplasmosis is 1.2 reports per 1,000 reported stillbirths. However, most infants infected prior to birth have no symptoms at birth. The eye inflammation (chorioretinitis) that does often occur can lead to serious sight problems later in life.

The RIVM conducted a unique study in 2007 to obtain more information about the incidence of congenital toxoplasmosis among infants born alive. For the purposes of the study, heel-prick blood samples taken in 2006 from 10,000 babies born alive selected at random were tested for specific IgM antibodies against *Toxoplasma*. The results of this study are due for publication in 2008.³⁰ Diagnosing a suspected case of *Toxoplasma* infection is not a simple matter, as all of the tests have uncertainties. Several immunoglobulins need to be measured, and the measurements often need to be repeated after three weeks. In the absence of ultrasound abnormalities such as hydrocephalus or cerebral calcification, fetal toxoplasmosis can only be ascertained by amniotic puncture and a PCR test for *Toxoplasma*. This is commonly practised in France, where toxoplasmosis occurs more frequently. American investigators have calculated that each fetal treatment following diagnosis by amniotic puncture in pregnant women with signs of toxoplasmosis is associated with 18.5 miscarriages due to the puncture.³¹

Spiramycin is routinely prescribed for pregnant women with an active infection, either in isolation or in combination with sulfonamides. Treatment is continued until delivery because the placenta can continue to act as a source of infection. It has not been established whether sufficient amounts of spiramycin reach the fetus, but the drug does appear to reduce the likelihood of damage due to fetal infection.³² Pyrimethamine is not prescribed during pregnancy in the Netherlands because of possible teratogenic effects. It is prescribed in other European countries, but only in cases of proven fetal infection where the pregnancy has passed the 16-week stage.³⁰

- Administration: depending on the type of infection, penicillin via intramuscular injection for syphilis, while spiramycin is available in tablet form for toxoplasmosis.
 - Status: The RIVM routinely recommends treatment of pregnant women with syphilis or toxoplasmosis.
 - Risk to the pregnant woman: treatment is also important for the woman herself in the case of syphilis. Clear explanations, and emphasis of the often favourable outcomes in the absence of ultrasound abnormalities, are important when treating women with toxoplasmosis. Tests for toxoplasmosis during pregnancy are associated with significant problems. They can involve
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multiple amniotic punctures, which are of limited predictive utility and can cause miscarriage. Pregnant women may request termination of pregnancy because of an unjustified strong fear of having a child with abnormalities.³³

- Level of evidence: level II-2.
- Number of pregnant women treated in the Netherlands each year: unknown, estimated at < 10.

3.1.5 Administration of thionamides: propylthiouracil (PTU)

Indication: fetal hyperthyroidism (thyroid gland working too fast), usually in pregnant women who have the thyroid conditions Grave's disease or Hashimoto's disease and where the maternal thyroid-stimulating antibodies (TSI) are affecting the fetal thyroid gland. Fetal thyreotoxicosis (acute intoxication caused by excess thyroid hormone) has a reported mortality rate of 16 per cent and can cause growth problems, struma (enlarged thyroid, also called goitre), and skeletal abnormalities.³⁴ Clinicians may pick up on this condition by noticing an accelerated fetal heart rate. Fetal struma can cause problems in swallowing, leading to an increase in quantities of amniotic fluid. Struma can also in rare instances be caused by fetal hypothyroidism (thyroid gland working too slowly). This is sometimes due to PTU treatment of pregnant women with Grave's disease. For this reason, the lowest possible dose is recommended. There have been a few case reports of successful treatment of this condition by weekly injections of levothyroxine into the amniotic fluid.³⁵

- Administration: orally, 100-600 mg per day. Alternative: carbimazole.
- Effect: normalises fetal thyroid function. The effect can easily be assessed by measuring the fetal heart rate. Umbilical cord punctures to measure thyroid hormone levels are not necessary, and in view of the risks not recommended. There are many case reports of successful treatment.³⁵
- Status: in view of the severity of the disease for the fetus, and the minor side-effects for the pregnant woman, an accepted treatment when carried out in cooperation with an internal medicine specialist/endocrinologist.
- Risk to the pregnant woman: PTU can slow down the functioning of the pregnant woman's thyroid gland, and thyroid hormones must be given to treat this. Other adverse events include pruritis and skin rash, sometimes fever, nausea and vomiting, and in rare cases a fall in the white blood cell count.
- Level of evidence: level II-3.
- Number of pregnant women treated in the Netherlands each year: unknown, estimated at 1 to 3.

3.1.6 *Substitution or restriction diet in inherited fetal metabolic diseases*

Indication: there are many inherited metabolic diseases in which a genetic defect results in the absence of an enzyme, impeding the process of making or breaking down certain proteins. This leads to a deficiency or actually a surplus of the protein in question, which often has serious consequences for the health of the fetus or child. These diseases are often recessive or dominant hereditary diseases, which implies a high chance of recurrence (25 or 50 per cent). Pregnant women who are known to have a specific disease in their family can undergo a CVS test to have it diagnosed in their fetus.

In the Netherlands, women who are found to be carrying a fetus with a condition of this kind often choose to terminate their pregnancy once this is known, but in the case of some diseases prenatal therapy can be given to minimise the consequences for the fetus or to prevent the condition. Examples of metabolic disorders for which prenatal treatment is successful are: methylmalonic acidemia (MMA) (treated with vitamin B12), carboxylase deficiencies (treated with biotin), 3-phosphoglycerate-dehydrogenase (3-PGDH) deficiency (treated with L-serine).³⁶ The number of metabolic diseases that can be detected prior to birth is expected to increase dramatically over the coming years. It is expected that prenatal intervention may be beneficial for some of these conditions.

- Administration and effect: depending on the disease, restricting or actually increasing the intake of certain proteins or vitamins, i.e. altering the pregnant woman's diet, is one way of attempting to normalise the abnormal concentrations of the substance in question in the fetus.
 - Status: the literature contains only case reports, in which selection bias (only successful outcomes are reported) plays a part. Families known to suffer from metabolic disorders of this kind in the Netherlands are almost always known to a clinical geneticist, who can be assumed to be familiar with any developments in diagnosis and treatment. This is still an experimental treatment, which requires considerable care and multidisciplinary consultation on a case-by-case basis, including consideration of the medical ethics aspects. There is one important development, which should also be considered in the light of the expected increase in abnormalities that can be detected prior to birth. The Health Council has recently argued for the introduction of pre-conception advice including testing for carrier status of genetic conditions; such a policy might contribute to this increase.
 - At present, infants born in the Netherlands undergo neonatal screening for 16 rare metabolic diseases. This is done so that dietary or other treatment can be
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initiated as soon as possible once the disease is diagnosed, so as to prevent irreparable harm due to the disease.

These diseases usually involve the absence of an enzyme, or the failure of an enzyme to work properly, leading to the accumulation of harmful substances. During pregnancy the fetus is often protected from the consequences because the mother produces the substance in question, or the harmful substance is removed via the placenta. One of the diseases for which infants are screened is galactosemia. Affected children cannot metabolise galactose (lactic sugar) properly. Accumulation of galactose can cause severe jaundice, neurological damage, cataracts and fertility problems. These consequences can largely be avoided by a low-galactose diet. However, there are indications that the disease can cause damage at the fetal stage to organs including the ovaries and the lens of the eye.^{35,37} Galactose restriction during pregnancy may be beneficial to a fetus with galactosemia. This suggests that screening for galactosemia, and theoretically for other comparable conditions as well, could be brought forward from after birth to early in pregnancy or even before.

- Risk to the pregnant woman: the proteins or vitamins in question are usually not harmful to the pregnant woman herself. Dosages are normally set in practice, and as each condition is rare in itself it would be hard to conduct research into the best treatment. This is at the same time the major problem with this form of fetal therapy: checking the effect of the treatment and estimating the likelihood of complete or partial success is very difficult. Accurate records, follow-up and, in view of the rarity of the conditions, international cooperation are important here.
- Level of evidence: level III.
- Number of pregnant women treated in the Netherlands each year: 0-1.

3.2 Minimally invasive fetal treatment via needle insertion

Minimally invasive fetal treatment via needle insertion is a phrase used to describe a category of interventions that involve inserting a thin needle (0.7 to 1.1 mm in diameter) into the uterus. The risks of this technique to the pregnant woman herself are comparable to those associated with amniotic puncture, a well-known procedure. The chance of complications, mainly a miscarriage brought about by the procedure, is estimated at 0.5 per cent in the Netherlands. About 8,000 amniotic punctures a year are performed with this type of needle in the Netherlands for the purposes of prenatal diagnosis. The risks to the mother are regarded as minimal. They are carried out in an out-patient clinic under local anaesthetic applied to the skin, and usually take 15 to 30 minutes.

3.2.1 *Intra-uterine blood transfusion*

Indications: erythrocyte immunisation, Parvovirus B19 infection, severe fetomaternal transfusion.

- These conditions cause severe fetal anaemia via a number of mechanisms.³⁸ In the case of erythrocyte immunisation, the pregnant woman has formed antibodies to the fetus's red blood cells. These pass through the placenta and break down the red blood cells, causing severe anaemia. Parvovirus B19 infection, also known as fifth disease, is a very common childhood illness that usually disappears by itself. If a pregnant woman is infected, the virus can reach the fetus. The virus has a preference for rapidly-dividing cells such as those found in the bone marrow of the fetus. It interferes with the process of blood production which takes place there, leading to anaemia. Acute or chronic placental haemorrhage is another cause of fetal anaemia. Fetal blood ends up in the mother's bloodstream. This can be shown using the Kleihauer test which can distinguish between adult blood cells and fetal blood cells. If the fetus loses too much blood to the mother's circulation (fetomaternal transfusion), this can lead to severe fetal anaemia and death. If the condition is not treated, severe anaemia will cause a decline in cardiac function, as a consequence of which the fetus will accumulate fluid (hydrops) and may die. This is the final common pathway of all the causes described above. Inducing premature delivery of the fetus with a view to performing the blood transfusion after birth is an alternative. Before 32 to 34 weeks into pregnancy, intra-uterine treatment produces better results. This treatment is regarded as the classic example of successful fetal therapy. The survival rate of fetuses treated in good time stands at well over 90 per cent. 'In good time', means before severe hydrops sets in.³⁹ A number of researchers who have investigated cases of erythrocyte immunisation have found that the long-term development of these children is the same as that of healthy children.^{40,41} The combination of a very poor prognosis if no action is taken and the high likelihood of having a healthy child in the case of erythrocyte immunisation is the reason why this procedure has become a standard form of care.³⁹
 - Effect: symptomatic treatment in cases of severe fetal anaemia.
 - Side-effects/drawbacks: a large study has calculated the risk of complications for the fetus caused by the procedure at 1.6 per cent per intervention.⁴² There is currently no alternative. The prognosis for cases of severe immunisation is very poor if action is delayed.
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- There are two long-term follow-up studies on children who contracted Parvovirus B19 infection as fetuses and were treated with intra-uterine transfusions. One study found good outcomes for all surviving children.⁴³ Recent research has found neurological abnormalities in five of the 16 surviving children, two of whom suffered severe abnormalities.⁴⁴ Brain abnormalities have also recently been observed in Canada and in Utrecht in some surviving children who underwent intra-uterine treatment for Parvovirus infection (Ryan and Pistorius, personal communication).
- Status: accepted standard treatment for erythrocyte immunisation, included in the NVOG's guideline 50. Introduced in the Netherlands in 1965 (see chapter 2), and performed in its modern form at LUMC approximately 1,500 times since 1987. Recent scientific assessment performed by I.L. van Kamp.³⁹
- Risk to the pregnant woman: as described above, the risk of puncture is practically zero. The expectant mother may form additional antibodies that could cause problems if she herself needs a blood transfusion subsequently.
- Level of evidence: level II-3.
- Also internationally accepted as treatment for fetal anaemia caused by Parvovirus B19.^{45,46} Recorded as such in the Netherlands Health Care Inspectorate's new national guidelines on infectious diseases during pregnancy. Recent scientific assessment performed by T.R. de Haan.⁴⁷
- Number of pregnant women treated in the Netherlands each year: for erythrocyte immunisation 40, for Parvovirus B19 infection 3-12 (in years of epidemics, >10), for fetomaternal transfusion 1-3.

3.2.2 *Intra-uterine thrombocyte transfusion*

Indications: alloimmune thrombocytopenia (FNAIT), Parvovirus B19 infection.

- Effect: prevention of (cerebral) haemorrhage in fetuses with a low platelet count (<50 x 10⁹/L).
 - Side-effects/drawbacks: possibility of bleeding in cases of umbilical cord puncture if thrombocytes cannot be administered in good time. For this reason thrombocyte transfusion is hardly ever performed in cases of FNAIT nowadays, as non-invasive therapy involving IVIG (see 3.1.3 above) appears to produce very good results. In cases of Parvovirus B19 infection, low platelet count is often also found in addition to severe anaemia. Thrombocyte transfusion is administered here only in combination with blood transfusion.
 - Status: this procedure is performed less often for FNAIT than used to be the case, as the results of non-invasive therapy are just as good if not better
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(safer).^{24,48,49}

When a blood transfusion is being carried out to treat Parvovirus B19 infection, the thrombocytes are kept to hand during the blood transfusion procedure but not administered unless the fetus has severe thrombopenia as well as anaemia. In a recent study, de Haan *et al.* speculated that it might be better to refrain from this thrombocyte transfusion.⁴⁷

- Risk to the pregnant woman: as described above, the risk of puncture is practically zero. The expectant mother may form additional antibodies that could cause problems if she herself needs a blood transfusion subsequently.
- Level of evidence: level III.
- Number of pregnant women treated in the Netherlands each year: 5-10.

3.2.3 *Direct intravascular fetal anti-arrhythmic administration (via umbilical cord puncture)*

Indications: failure of trans-placenta treatment (see 3.1.2) and imminent fetal death in pregnancies under 32 weeks.⁵⁰

- Effect: as above. The drugs used are amiodarone and adenosine.
- Side-effects/drawbacks: a 1-2 per cent risk of complications of umbilical cord puncture. The probability of short- and long-term success is still insufficiently clear due to the absence of large-scale studies.
- Status: has a place as 'salvage' therapy: a last resort if the other options have not worked and the fetus is at risk of death from heart failure.
- Risk to the pregnant woman: the risk of puncture to the pregnant woman is practically zero, as described above.
- Level of evidence: level III.
- Number of pregnant women treated in the Netherlands each year: 0-3.

3.2.4 *Interstitial laser coagulation*

Indication: to interrupt the flow of blood to a life-threatening tumour, used mainly in cases of acardiac twins (also known as twin reversed arterial perfusion (TRAP) sequence). This is a particular type of monovular twins, where one fetus starts to develop abnormally at an early stage of pregnancy. The bloodstream in the umbilical cord of this fetus runs in the wrong direction, and its heart and upper body are underdeveloped. This 'fetus' has no chance of life. It is referred to as *acardiac* because it does not have a beating heart. The heart of the other fetus also has to maintain the flow of blood to the other fetus, and may come under excessive strain as a result.

Large tumours of fetal tissues or of the placenta that have a good supply of blood can cause the same kind of strain to the fetal heart.

- Effect: laser coagulation can be applied to seal the blood vessel where the heart is at risk of overload, or to counter the mechanical effects of a tumour fed by a large blood vessel. In the case of an acardiac twin, the chance of survival of the normal fetus is estimated at 50 per cent if no treatment is given, rising to 70-80 per cent following treatment.^{51,52} The only publications describing treatment of rare fetal or placental tumours are isolated case reports, and are not of sufficient numbers to allow figures for success or risk to be produced.
 - Side-effect/drawbacks: the laser fibre is inserted via an echo-guided 18 G (1.1 mm) needle. The laser is applied a few times to the tissue of the tumour/acardiac fetus ('interstitial') for a few seconds. The heat produced causes coagulation. The locally generated heat in the acardiac twin should present no risk to the pregnant woman or the other fetus, as the acardiac twin is surrounded by amniotic fluid. A systematic review of 32 articles describing a total of 72 cases⁵³ concluded that interstitial laser treatment was the safest and first-choice option for the treatment of acardiac twins. Radio frequency ablation (RFA) is a new procedure involving the use of a 17 G (1.2 mm) needle to insert three electrodes. The tissue between these electrodes is 'cooked', and the blood ceases to flow.⁵⁴
 - Status: increasingly used in this rare complication of monochorial twins since 2000.⁵⁵ The procedure has been performed a few dozen times in the Netherlands (LUMC), and the results match experience abroad. A publication is in preparation. This treatment must be regarded as still experimental, particularly in view of the small number of cases. Intra-uterine treatment of acardiac twins in general (several techniques are available, see also below) is regarded as an established option, as is also indicated by the fact that it is listed in the NVOG's guideline 13.
 - Risk to the pregnant woman: the risk of puncture to the pregnant woman is practically zero, as described above. The use of a needle to apply the laser under solely ultrasound control presents a potential risk to the pregnant woman. If the laser burns through the tissue where the needle has been inserted, it may reach or penetrate the wall of the uterus. This may not be 'seen' in time on the echoscope. As the procedure is performed under local anaesthetic, the pregnant woman will however immediately sense it. The use of RFA is in theory safer, as the energy remains between the ends of the 'electrodes'.
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As far as is known, no maternal complications of interstitial laser or RFA have been published.

- Level of evidence: level II-2.
- Number of pregnant women treated in the Netherlands each year: 3-8.

3.3 Minimally invasive fetal therapy via endoscopy (fetoscopy)

This term is used in obstetric medicine and other fields to describe endoscopic and similar methods in which tubular instruments with a diameter of up to 1 cm are inserted percutaneously. In Europe, endoscopes and other instruments used in fetal therapy have a diameter of one to three millimetres, while in the United States instruments of up to five millimetres in diameter are sometimes used. Most interventions are nowadays performed purely under local analgesia. Locoregional (epidural analgesia, an injection into the spine) or general analgesia is occasionally used.

The technique was first described in 1974,⁴ since when thousands of fetoscopic interventions have been performed. In the past fifteen years, fetoscopy has been most commonly used in the treatment of twin-to-twin transfusion syndrome (TTS). Several series of studies involving between 100 and 200 patients per study have been published since 2000. These publications report two cases where blood transfusion treatment was needed following haemorrhage of the wall of the uterus. In the Leiden study (February 2008) of over 300 fetoscopic interventions, one pregnant woman developed pulmonary oedema following the procedure, but this rapidly resolved in response to treatment with diuretics. No other cases of physical danger to the pregnant woman have so far been published. It is also unlikely that the insertion of the instrument, which is always carried out under continuous ultrasound monitoring, would present significant risks to the pregnant woman. The same applies to the use of the laser beam. Incorrect or careless application could damage the uterus or even organs outside the uterus, though no cases of such harm have so far been reported.

3.3.1 *Laser coagulation of placental anastomoses*

Indication: twin-to-twin transfusion syndrome (TTS).

- Effect: In all cases of monochorial twins, vascular anastomoses between the two fetuses are present on the placenta. These vascular anastomoses cause imbalance in the bloodstream in 15 per cent of these twin pregnancies, in which one fetus (the donor) chronically loses blood to the other (the recipient). As a consequence, the recipient produces too much amniotic fluid and

its heart comes under excessive strain.

If no treatment is given, 63 to 80 per cent of fetuses will die through premature delivery or heart failure. Using laser beams to seal the vascular anastomoses under fetoscopic imaging is the only treatment that addresses the cause of TTS. A large randomised study found this technique to be superior to the traditional method of repeated amniotic fluid drainage.⁵ A recent series by recognised experts put the chance of at least one fetus surviving following laser treatment at 73 to 90 per cent,⁵⁶⁻⁵⁸ and at 84 per cent in the Netherlands (LUMC).⁵⁹

- Side-effects/drawbacks: the most frequent complication is premature rupture of the membranes, leading to an increased likelihood of premature delivery. In the first Leiden series of 100 cases, membrane rupture within two weeks after the procedure was reported in thirteen cases, with perinatal death of both infants in eight cases.
- Status: this intervention has been the first-choice treatment for TTS since the publication of the Eurofetus trial.⁵ It has also been included in the NVOG's guideline 13.
- Risk to the pregnant woman: abdominal wall or uterine wall haemorrhage, a few cases of temporary fluid in the lungs.
- Level of evidence: level I.
- Long-term follow-up studies reveal the rate of serious neurological abnormalities to be between 6 and 17 per cent.⁶⁰ The outcome is better than that achieved from traditional amniotic fluid drainage, and also superior to treatment given at an earlier stage. Prematurity is clearly associated with the chance of neurological abnormalities, as is also the case with single fetuses and dichorial twins. Scientific assessment in theses by E. Lopriore⁶¹, J. van den Wijngaard⁶², J.M. Middeldorp⁶³ and M. Sueters.⁶⁴
- Number of pregnant women treated in the Netherlands each year: 40-50.

3.3.2 *Umbilical cord coagulation in the case of monochorial multiple pregnancies with one abnormal fetus*

Indication: monochorial pregnancies where one fetus threatens the chance of healthy survival of one or more other fetuses; a fetus has a serious but not lethal disease or abnormality and the parents do not wish that fetus to be born alive. Or: acardiac twin (see 3.2.4).

- Effect: if one fetus in a pair of monochorial twins dies within the uterus, there is a significant chance of the other fetus dying shortly afterwards (12 per cent) or suffering severe neurological damage (18 per cent).⁶⁵ If one fetus in a
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pair of monochorial twins is found to be highly likely to die spontaneously in the uterus as a result of congenital abnormalities or very poor placental function, the other fetus can be protected by coagulating the umbilical cord of the abnormal fetus. This is also an option for cases of acardiac twins described above, as an alternative to interstitial laser

- If one fetus is found to have severe congenital abnormalities but spontaneous death is not very likely, the parents may request 'selective reduction': causing the affected fetus to die, in the same way as choosing termination of pregnancy in the case of single fetuses with serious abnormalities. In the case of dichorial twins, this can be done by injecting potassium chloride into the bloodstream of the affected fetus via a thin needle. This is not an option for monochorial twins because of the vascular anastomoses. Umbilical cord coagulation is then the only option.
- Side-effect/drawbacks: the risks of the procedure are the same as those associated with fetoscopic laser treatment for TTS; the same equipment is used.
- Status: this technique has been used in many centres throughout the world to treat the aforementioned indications for about ten years. Two recent cohort studies (with 80 and 46 patients) show the survival rate of the healthy fetus to be 70-83 per cent. 66 pregnant women have been treated for these indications at LUMC (February 2008), with a comparable survival rate (submitted for publication). This treatment is also listed as an option in the NVOG's (Netherlands Association for Obstetrics and Gynaecology) multiple pregnancies guideline (no. 13) and appears to have passed beyond the experimental stage.
- Risk to the pregnant woman: as the same equipment is used, the risk is in principle identical to that associated with laser treatment for TTS.
- Level of evidence: level II-3.
- Number of pregnant women treated in the Netherlands each year: 10.

3.3.3 *Thoraco-amniotic (from the chest cavity to amniotic fluid) shunt*

Indication: abnormal accumulation of fluid in the fetal chest (hydrothorax and cystic lung tumours) with heart failure.

- Effect: Accumulation of fluid in the chest cavity can lead to dislocation and compression of the heart, the blood vessels leading to the heart, the oesophagus and the lungs. A shunt is inserted with one side in the accumulated fluid. The other end of this silicon tube, two millimetres in diameter, terminates in the amniotic cavity and the fluid drains into this space. This reduces compression on the aforementioned structures. This technique has been in use since the 1980s and has been applied in a few hundred cases. The consensus
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is that the procedure is indicated only if as well as accumulation of fluid in the chest cavity the fetus also has generalised hydrops (accumulation of fluid in other body cavities, such as the stomach and the skin), as a sign of heart failure and imminent death. In this situation the prognosis is very poor if treatment is delayed: 80 to 100 per cent of fetuses will die. Two recent summary articles showed survival rates of 60 to 70 per cent in well selected cases.^{66,67} It is important to note that many fetuses with isolated hydrothorax or isolated lung tumour that survive to delivery are healthy thereafter. It is very important that associated abnormalities are where possible ruled out before the decision to offer therapy is taken. It must also be emphasised that prenatal testing has limitations. Sometimes diseases that could not be detected earlier only become apparent after birth.

- Side-effect/drawbacks: the instrument used to insert the shunt has the same diameter as the fetoscope, and is equally likely to cause premature membrane rupture (10 to 15 per cent).
- Status: if the hydrothorax or lung cyst leads to hydrops, and the fetus has no other abnormalities, inserting a shunt is internationally regarded as an accepted treatment option.
- Risk to the pregnant woman: the instrument has almost exactly the same diameter as the fetoscope used for laser treatment in cases of TTS, with the same chance of haemorrhage in the abdominal or uterine wall, and some cases of transient pulmonary oedema are known. No serious maternal risks have been described in the 200 or so published cases in this group.
- Level of evidence: level II-2.
- Number of pregnant women treated in the Netherlands each year: 3-7.

3.3.4 *Vesico-amniotic (from the bladder to amniotic fluid) shunt*

Indication: Isolated complete bladder outlet obstruction and absence of amniotic fluid as the fetus is unable to urinate.

- Effect: male fetuses can suffer from congenital valvules in the urethra, which produce a typical ultrasound image early in pregnancy. Since the fetus is unable to urinate, urine accumulates in the (mega) bladder and the kidneys are often congested as well. From week fourteen onwards, the amount of amniotic fluid is dependent on fetal urine production. There is a complete absence of amniotic fluid if the fetus cannot urinate. This causes impaired lung development and distorted limb growth. If treatment is delayed, the infant will often die immediately after birth as a result of pulmonary hypoplasia. Chronic kidney congestion often leads to kidney damage at an early
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stage. Infants who survive are very likely to have severe kidney damage. In the 1980s the same technique described above for hydrothorax was performed: shunt treatment, with a small tube placed in the fetal bladder draining into the amniotic fluid.¹¹ Analysis of 73 cases from an international register⁶⁸ showed a 41 per cent survival rate. Selection was tightened in the 1990s. In an attempt to achieve optimum outcomes, practitioners tried to offer shunting only for male fetuses of a normal karyotype, with no other abnormalities, and where repeated urine analyses had shown that there were no indications that serious kidney damage had already occurred (the 'good prognosis group').⁶⁹ Some long-term follow-up studies showed survival rates of 60 per cent in the group selected according to these criteria, with moderate to severe lasting kidney damage and often growth retardation in half of the surviving children.^{70,71} Lung problems were rare in this group. A recent summary article covering 210 published attempts at shunt insertion for this indication found that the procedure failed four times and that complications occurred in 28 cases (three instances of fetal death caused by the procedure).⁷² This analysis also shows that the outcome after shunting was not much better in the 'good prognosis group' than in an untreated control group. The chance of survival of fetuses in the poor prognosis group treated with a shunt was over eight times greater than comparable fetuses that did not receive treatment. However, most of the studies were of mediocre design, and the composition of the control groups was particularly questionable. Incomplete or duplicate publication meant that exact outcome data could not be calculated, but the rough data showed 132 out of 342 fetuses surviving (39 per cent), and kidney function reported as normal for 73 per cent of these. The authors have since arranged a randomised trial (the PLUTO study: www.pluto.bham.ac.uk), but recruitment is proving a rather slow process.

- Side-effects/drawbacks: the technique has the same chance of complications as thoraco-amniotic shunt, with the likelihood of membrane rupture estimated at 10 to 15 per cent. Procedure-related fetal death is estimated at 4 to 5 per cent.⁷³ The shunt is dislocated or does not work properly in 30 to 50 per cent of cases.⁷³ One major criticism of this form of fetal therapy is that it does indeed increase the chance of survival, but that the long-term health of these children is often poor, with growth disorders, poor kidney function, and the need for a kidney transplant during adolescence.
 - Status: some practitioners do mention this treatment option when counselling couples receiving this diagnosis, and some also refer them to a centre. After hearing the information described above, most pregnant women request a termination of the pregnancy either before or after referral. It is recommended
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that this treatment be offered only in the context of scientific research, such as the PLUTO study.

- Risk to the pregnant woman: the instrument has practically the same diameter as the fetoscope used for laser treatment in cases of TTS, with a comparable chance of haemorrhage in the abdominal or uterine wall, and some cases of transient pulmonary oedema are known. No serious maternal risks have been described in the published cases in this group.
- Level of evidence: level II-3.
- Number of pregnant women treated in the Netherlands each year: 0-2.

Fetal therapy abroad

All the treatments described above that are available in the Netherlands are also carried out in most Western countries. Some forms of fetal therapy are not (yet) performed in the Netherlands, but are performed in some centres abroad. Most of these are complex treatments that are still at the trial phase, and may be made available in the Netherlands in the future. Pregnant women are better informed now than in the past, partly thanks to the Internet, and can ask their Dutch doctors for information or even referral. Knowledge about these developments in other countries is important when forming a view as to whether new methods should be introduced and under what conditions. For this reason the studies currently taking place abroad involving human fetuses are briefly described here.

4.1 Fetoscopic tracheal occlusion (temporary blockage of the windpipe)

Indication: severe diaphragmatic (hiatus) hernia.

- This relatively common condition (one in 2,400 births) can often be treated in the neonatal phase, where treatment is always more likely to succeed (see chapter 2). Improved ventilation techniques are the main reason for this. Large centres in other countries report survival percentages of over 80 or even 90 per cent. A recent prospective study of 51 top centres, including some in the Netherlands, showed a survival rate of 69 per cent.⁷⁴ A very poor prognosis group (chance of survival < 25 per cent), selected by measuring lung compression, has a greater chance of survival following fetal treatment
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with temporary insertion of a balloon in the trachea (windpipe) via a fetoscope. Deprest, who pioneered this technique in Leuven, is preparing a randomised trial together with Nicolaides' group in London. Work is also going forward in preparation of a randomised study in the United States.

- Effect: temporary blockage of the fetal windpipe (from 28 to 34 weeks) helps the fetus's lungs grow rapidly. The intestines, which have passed through the hernia in the diaphragm into the chest cavity, are pushed back. Lung function may also be improved.
- Side-effects/drawbacks: the main risks of the technique are premature membrane rupture and the possibility of premature birth. The instrument is the same as that used for fetoscopic laser treatment for TTS. The intervention is performed at a later stage of pregnancy, and as a result prematurely born infants may survive.
- Status: experimental. It will become clear whether this technique has a future after a randomised trial. Until such time, patients can be referred from the Netherlands to Leuven.
- Risk to the pregnant woman: the instrument is the same as the fetoscope used in laser treatment for TTS, with a similar chance of abdominal or uterine wall haemorrhage, and transient pulmonary oedema.
- Level of evidence: level III.

4.2 Fetal heart valve dilatation

Indications: severe aortic valve constriction, pulmonary arterial valve constriction with interventricular septum intact (severe constriction of a heart valve). These heart valve abnormalities cause one of the heart ventricles to be underdeveloped. Children with this condition are usually born alive, but require a series of complex heart operations, resulting in a heart with one ventricle instead of two. The five-year survival rate in this group is 40-65%. Children are at risk of thrombosis, dysrhythmia and there is concern as to their mental development.⁷⁵ The principle of the fetal therapy is the use of a balloon to dilate the narrow valve, allowing the ventricle to grow. The infant will still require surgery after birth, but the heart can then have two functioning ventricles. In almost half of all cases of pulmonary artery constriction, fistulas to the coronary arteries occur, leading to the risk of acute heart failure if treatment is given after birth. The risks may be less if the valve is dilated early in pregnancy.

A second indication is premature closure of the valve between the atria. This sometimes occurs in the case of a severely constricted aortic valve, or reversal (transposition) of the major vessels. If the valve between the atria closes before

birth, this can lead to hydrops and fetal death, or (more often) to death shortly after birth, unless the valve can be opened very soon after birth (within minutes). The closed valve could be opened with a balloon just before birth in order to avoid this emergency surgery.

- Effect: an echoguidance technique is used to insert an 18 G (1.1 mm) needle into the fetal heart. A balloon catheter passes through it to reach the site of the excessively narrow valve. The balloon can then be inflated a few times to widen the valve.
 - Side-effects/drawbacks: the procedure is technically complex and has proved to be unsuccessful in about half of all published cases. If it is a technical success, it is often not possible to then perform additional surgery to create a two-ventricle heart, but if it is a technical failure, repair surgery can sometimes be performed to retain a two-ventricle heart. Acute death is a real danger because the needle penetrates the heart sac and the heart muscle. The diameter of the needle (18G) is small, so the chance of membrane rupture is very small (see above).
 - Status: experimental. A review conducted in 2007 refers to ‘an area full of uncertainties’.⁷⁵ The procedure was conducted a few times in London in the early 1990s, but abandoned because of disappointing results. The Boston group has recently revived the method, and is currently performing most of the experiments. They have carried out 105 (attempted) balloon dilatations so far. Improvements are being sought mainly in patient selection and to find the best time for the procedure. Long-term results of survivors are not yet available. In view of the constantly improving outcomes of paediatric heart surgery, it is uncertain whether this procedure will ever gain a place as an accepted fetal treatment. The procedure has also been successfully carried out a few times in Leuven. The cooperation group made up of the obstetrics and paediatric cardiology groups at LUMC, VUmc and AMC have decided that any candidates for such procedures should for the time being be offered the opportunity to discuss the option in Leuven. At an international level, thorough documentation, registration, long-term follow-up and publication of all cases treated before birth are being strongly urged.⁷⁵
 - Risk to the pregnant woman: as described above, the risk of puncture is practically zero as an 18 G (1.1 mm) needle is used.
 - Level of evidence: level III.
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4.3 Open fetal surgery for fetal tumours

Open fetal surgery means an operation performed under general anaesthetic in which the pregnant woman's abdomen is opened, and then the uterus and membranes are opened along a length of 5 cm or more so that the fetus is directly accessible for surgery which is in content the same as that which would have been performed after birth for the same condition. Once the operation on the fetus is complete, the pregnant woman's uterus and abdomen are re-sutured. She then needs to be kept in hospital until delivery and be given drugs to inhibit labour. This and all subsequent deliveries by the woman will take place by primary section. The technique was developed in San Francisco and is carried out in the US mainly by paediatric surgeons trained there (Philadelphia, Cincinnati and Houston). France is the only European country to have introduced this procedure.

Indication: large fetal tumours with hydrops.

- The procedure is offered in cases of lung tumours where it is almost certain that the fetus would die in the second trimester without this treatment. This treatment is currently the only option for fetuses with large, solid tumours featuring hydrops as a sign of heart failure and imminent death.
 - Effect: the disease affecting the fetus is treated in principle in the same way as if it were to undergo treatment after birth.
 - Side-effects/drawbacks: the pregnant woman has to undergo major abdominal surgery; and, which is more important, a large opening is made in the upper part of the uterus. This means that vaginal delivery, or even contractions, can be dangerous as they make rupture of the uterus more likely. This also applies to subsequent pregnancies. In addition, premature birth is an inevitable complication. The pregnant women are kept under close control by the centre; they are often admitted for a prolonged stay and given medication to inhibit contractions.
 - Status: open fetal surgery is acceptable for a small group of American pregnant women in the case of solid lung tumours with imminent fetal death, which is a rare condition. This procedure is not carried out in Europe. The largest series was published by Adzick's group in Philadelphia.⁷⁶ The survival rate in the 22 cases was 50 per cent, with good lung function in the surviving children.
 - Risk to the pregnant woman: the procedure entails considerable drawbacks for the expectant mother. From her point of view the fetal operation is similar
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to a Caesarean section, and she will also have to give birth by Caesarean section. This will also be the case for all future pregnancies.

- Level of evidence: level II-3.

4.4 Open fetal surgery for neural tube defects

Fetal surgery for neural tube defects (spina bifida) was developed in the hope of minimising damage to the exposed spinal cord caused by chronic exposure to amniotic fluid. It later emerged that it was not possible to prevent spinal cord damage to children who underwent pre-natal surgery, but that they were less likely to suffer from the common complication of hydrocephalus and that where this condition did develop it tended to do so later. A randomised study was launched in the US in 2003 after almost 180 open fetal operations had been performed. This study, the MOMS trial, compared fetal surgery at between 20 and 26 weeks gestation with traditional surgery after birth. The long-term follow-up (covering a period of at least two years after birth) should clarify whether the benefits outweigh the drawbacks.

It has been agreed in the US that apart from the three centres taking part in the trial no other centre will perform fetal surgery for neural tube defects until the MOMS trial has been analysed. This will not be before 2012 or 2013. European practitioners are also waiting for completion of this study. Fetal surgery for neural tube defects is at a decisive but still experimental stage. It is only likely to be introduced in Europe if the MOMS trial is a clear success.

An important difference between this therapy and most of the other treatments described here is that it cannot cure the condition but only reduce the symptoms. The 'price' that has to be paid in the event of fetal surgery is premature birth and even death following the procedure in pregnancies that are not at greater risk of such outcomes if the intervention is not performed. Bruner, one of the pioneers of this procedure, recently wrote:

Aspiring institutions must remember that intrauterine repair of myelomeningocele is elective surgery and does not save life. Even under the best of conditions, it can only threaten life.⁷⁷

- Effect: early closure of the back defect should reduce the secondary damage caused by the spinal cord being exposed to amniotic fluid. Children who undergo this procedure prior to birth may not need a shunt for hydrocephalus as quickly.
 - Side-effects/drawbacks: premature birth and perinatal death following the fetal operation.
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- Status: moratorium while awaiting the results of the MOMS trial.
- Risk to the pregnant woman: every intervention entails considerable drawbacks for the pregnant woman herself. From her point of view the fetal operation is similar to a Caesarean section, and she will also have to give birth by Caesarean section. This will also be the case for all future pregnancies.
- Level of evidence: level II-2.

Fetal therapy in the laboratory phase

5.1 Stem cell therapy

Stem cells are precursors of cells that form specific tissues in the body. In theory, these cells can be introduced into the body and then, as a result of local stimulation, develop into tissue which is defective or deficient in the event of disease. Stem cells can be derived from adults (bone marrow), newborn infants (from umbilical cord blood), from fetuses or from embryos. Embryonic stem cells can in principle divide infinitely, only specialising when they receive a particular 'signal'. Stem cells taken from the bone marrow of adults and umbilical cord stem cells have long been used in transplant medicine to treat deficiencies of blood-forming cells in bone marrow abnormalities and forms of congenital anaemia.

Adults and children also develop a defence reaction when undergoing stem cell therapy if the body recognises the cells as 'alien'. The recipient must first undergo treatment to suppress the immune system, which is associated with many side-effects and complications. It is hoped that by administering stem cells to the fetus (which has less defence against alien cells), the tissues which will grow from the stem cell will not be rejected by the body. This could allow a large number of diseases, particularly those affecting blood-forming tissue but theoretically many others as well, to be treated at an early stage. Some genetic conditions cause serious damage even at the fetal stage. Ever better and earlier diagnosis of these diseases (such as metabolic diseases and blood diseases such

as alpha thalassaemia) means that the expectant parents can more often have the choice of fetal treatment as an alternative to termination.

5.1.1 *Mesenchymal stem cells*

Research into mesenchymal stem cells (MSCs), which can differentiate into tissues such as bone, cartilage, muscle cells and nerve cells, is a recent development. These MSCs can easily be grown in the laboratory, and have immunosuppressant properties that should make them suitable for use in transplants. One concern is however that they might also inhibit the body's defence against cancer cell growth.

However, laboratory research is progressing rather slowly. Even the young fetus appears to have a certain degree of defence against alien cells. Fetal treatment has only been successful in a few cases of a specific, very rare congenital disease (Severe Combined Immunodeficiency, SCID, where the body has no defences at all).

In 2005 a Stockholm group published a case report on a female fetus with osteogenesis imperfecta (which causes weak bone tissue and frequent fractures, even prior to birth) given male donor MSCs at 32 weeks gestation. The child underwent a bone biopsy at the age of nine months and it was found that over 7 per cent of her cells had come from the donor MSCs. Her clinical condition was better than would have been expected if she had not undergone the stem cell therapy.⁷⁸ As far as is known, all other studies carried out on intrauterine MSC administration have been performed on sheep, rabbits, goats, cows, dogs and mice. Researchers describe disappointing results as a consequence of the very low percentages of donor cells that actually function after transplant in the animal receiving treatment.

5.1.2 *Use of modified stem cells*

A new development is the combination of stem cell therapy and gene therapy, where the stem cells are genetically modified to combat rejection. It will probably be many years before clinical trials involving human fetuses are carried out. Even once these trials have been performed it will be essential to wait for long-term outcomes as harmful effects (e.g. the development of cancer) can take many years to become apparent. In a recent article, Harvard scientists have stated that good studies of gravid apes must be carried out before a human trial can be justified.⁷⁹

5.2 Gene therapy

Many diseases are caused by a single gene defect. Current genetic manipulation techniques allow genes to be inserted into cells. This theoretically allows many diseases, including cancer and congenital conditions, to be cured. The *Journal of Gene Medicine* manages a worldwide database of clinical studies involving gene therapy. The database currently contains more than 1,300 trials, ten of which are being carried out in the Netherlands. Most of them are phase I oncology studies.

5.2.1 *Diseases in which the patient's condition progressively declines*

The timely introduction of cells with a non-defective gene should prevent disability caused by diseases in which a genetic defect leads to gradual decline, such as cystic fibrosis (CF), Huntington's chorea and Duchenne muscular dystrophy. Introducing non-defective genes as early as possible, for example at the fetal stage, should also increase the likelihood of the body accepting the alien material (the same principle as described for stem cell therapy). The stem cells themselves can be used as the target of the gene therapy. The chances of success are greater if cells with non-defective genes are able to multiply before large numbers of the 'wrong', cells are present. Another possible use of gene therapy or stem cell therapy is the introduction of 'alien' material at such an early stage that the fetus has not yet developed a defence against it. This will allow the child to be safely treated with a transplant of the same alien material after birth. It may also be possible to genetically modify cells taken from the fetus in the laboratory and then reintroduce them. In principle this is safer, as only the cells in the laboratory will be directly exposed to the (viral) vector.

5.2.2 *Animal research*

Progress in gene therapy is still slow because of the many technical problems and setbacks such as the development of leukaemia and liver tumours following gene therapy. Viruses are normally used to introduce genes, a process that is associated with the risk of infection, miscarriage and gene deletions. In addition, performing injections into organs such as the liver or trachea of young fetuses is a tricky and high-risk procedure. Recent studies on sheep found fetal death rates of three to fifteen per cent.⁸⁰ These risks cause difficult dilemmas when designing human studies.

For the time being, fetal gene therapy is also at the animal experimental stage.^{80,81} The slow rate of progress means that the same phenomenon may occur as has been seen with fetal therapy for diaphragmatic hernia: developments in post-natal treatment are so rapid that fetal therapy with all its associated dangers may no longer be necessary. Better (safer and more expressive) vectors are vital, and as with all the fetal interventions that have been discussed, so are safer ways of introducing them into the uterus and the fetus.

5.3 Fetal surgery using a surgical robot

Remote-controlled surgical robots (such as the Da Vinci, ZEUS or AESOP system) have been in use for over a decade. They have also been tested in fetal surgery on animals.⁸² The benefits compared to open surgery are that they allow the use of endoscopic techniques, meaning that a complete operation can be performed. Avoiding a large incision in the uterus is of course an advantage, but at least three endoscopy instruments still need to be used. These instruments range in diameter from five to ten millimetres, and the risk of ruptured membranes and premature delivery is therefore considerable. For that reason robot surgery is not yet suitable for use in human pregnancies.⁷⁷

5.4 Tissue engineering

A European joint venture, with Dutch participation from Nijmegen (UMC St. Radboud) and Groningen (UMCG) is working on soft tissue engineering with a view to its therapeutic use on neonates and perhaps also in the uterus (www.eurostec.eu). The aim is to use tissue produced in the laboratory to repair closure defects. Examples include abdominal wall defects, diaphragmatic hernia, urogenital abnormalities and spina bifida. The material to be inserted consists of a collagen matrix on which endogenic cells can subsequently settle; the inserted material will eventually be completely replaced by the child's own tissue. It is expected that this method of repair will cause fewer complications than the current surgical approach. The project began in 2007; the first phases involved purely pre-clinical studies, including experiments on animals. The aim is eventually to move on to clinical research. It is hoped that this technique will be suitable not only for application to neonates but also to fetuses.

As described with fetal surgery for neural tube defects (see 4.4), many technical improvements are still needed to make fetal treatment for non-life-threatening conditions acceptable. If the repair method being developed in this research project appears to be a success, and if ways of applying it safely to fetuses as

well as neonates are found, then the balance between advantages and disadvantages may in future tip from the negative to the positive side.

Quality assurance

For over thirty years, intra-uterine blood transfusion for pregnant women with severe red cell alloimmunisation was the only invasive fetal therapy performed in the Netherlands. It was first carried out in 1965 at Leiden University Hospital, now called Leiden University Medical Centre (LUMC). As patients in the Netherlands do not have to travel great distances to receive treatment, and as only 30 to 40 pregnant women a year undergo this treatment, there has never been a need for a second centre.

Some additional indications for fetal therapy have been established over the past decade, and more may arrive in the future. As the field is now expanding, it is important to guarantee the quality of care in this complex and in many respects sensitive field into the future. This final chapter addresses some important aspects of this.

6.1 Concentration

In view of the small number of fetal therapeutic interventions that are carried out in the Netherlands each year, concentration is an important and self-evident instrument for quality assurance. Intra-uterine blood transfusion, the most common form of fetal treatment, is carried out around 90 times a year. Laser treatment for twin-to-twin transfusion syndrome (TTS), the second most common form of therapy, is carried out 40 to 50 times a year. Patients are often referred for these procedures at a late stage of pregnancy, especially in the case of TTS,

and treatment must be given within 24 hours. A centre can only offer continuous care if at least two experienced operators are available. It would therefore seem advisable to limit the number of centres offering invasive fetal therapy in the Netherlands. As with other forms of complex care, quality depends not only on the experience of the operator but also that an entire team is available to provide care before and after the procedure. Intra-uterine transfusions require experienced echoscopists for diagnosis, specialised blood bank doctors, nurses for logistics and to assist during surgery, and specialised neonatologists.

It is difficult to ascertain precise figures on exactly how many operations must be performed under the supervision of an experienced operator but it is probably a few dozen a year.⁵⁹ It can also be assumed that extensive experience in less complex echoguided or endoscopic procedures is beneficial to the practitioner's learning curve.

The argument for concentration is less strong when it comes to non-invasive drug fetal therapy. One important difference is that these interventions do not involve surgical procedures which require practice and training and that are sensitive to learning curves. Nevertheless, in view of the small number of cases, the close relationship between with fetal diagnosis, experience with syndromes and the need for a multidisciplinary approach, it would seem advantageous for this form of treatment to be limited to university centres. Patients may benefit from ease of access to a centre with more experience in a certain field, either in the form of consultation or referral.

These arguments in favour of centralising complex care for rare conditions could also lead to the conclusion that it might be better for some forms of specific treatment to be concentrated in just a few centres in Europe. This could become the reality for some forms of fetal therapy in the years to come, as national frontiers blur and European regulations become increasingly uniform. Joint ventures with a coordinated approach to particular forms of patient care and scientific research throughout Europe should be strongly encouraged.

6.2 Transparency

Transparency is important as well as concentration. Public accountability is vital particularly because this is such a sensitive field in which good care for the pregnant woman is directly related to decisions which also have a major impact on the life and health of her future child. It is important to show that these decisions are taken carefully, on the basis of a multidisciplinary assessment of the treatment options and after careful counselling, and that the further development of indication determination will be based on thorough scientific research.

With a view to giving shape to these ideas, the Netherlands Association for Obstetrics and Gynaecology (NVOG) could work together with the other professional groups concerned to devise a quality standard for fetal therapy. This should express what is currently regarded as best practice. The following issues, among others, could be addressed in detail:

- immediate (emergency) referral of pregnant women who may need fetal therapy to one of the eight university hospitals, or directly to a centre where the therapy in question is offered;
- a careful, and insofar as time permits, as complete as possible, diagnosis process;
- in-depth counselling and informed consent to be provided to and obtained from the pregnant woman, based on objective information regarding the findings, prognosis and treatment options, and on the latest scientific information as to the short- and long-term consequences for the mother and the child;
- the expertise required for each type of treatment and the multidisciplinary nature of decision-making and treatment;
- central records to be kept of all interventions;
- experimental fetal interventions to be carried out wherever possible in the context of well-designed prospective scientific research;
- scientific evaluation of the interventions performed, aimed at improving the methods used;
- long-term follow-up of children undergoing fetal treatment;
- international cooperation in the field of research, evaluation and follow-up;
- conditions for referral to foreign centres for forms of fetal therapy that are not available in the Netherlands;
- regular inspections of treatment centres by independent experts.

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A Committee on Medical Technology Assessment (MTA)

B Levels of evidence

Annexes

A

Committee on Medical Technology Assessment (MTA)

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- Prof. J.A. Knottnerus, *chairman*
President of the Health Council, The Hague,
 - Prof. G.H. Blijham
Professor of Internal Medicine, Chairman of the Board of Directors, University Medical Centre Utrecht
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Dutch Federation of University Medical Centres (formerly known as VAZ), Utrecht
 - Dr. G.H.M. ten Velden†, *scientific secretary*
Health Council, The Hague
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The Health Council and interests

Members of Health Council Committees – which also include the members of the Advisory Council on Health Research (RGO) since 1 February 2008 – are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Levels of evidence

Where a chapter deals with a specific intervention, the level of evidence for the intervention is stated, using the U.S. Preventive Services Task Force classification*

Level I : Properly conducted randomized controlled trial (RCT)

Level II-1 : Well-designed controlled trial without randomization

Level II-2 : Well-designed cohort or case-control analytic study

Level II-3 : Multiple time series with or without the intervention; dramatic results from uncontrolled experiments

Level III : Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

* <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat3.section.30953#30978>
