Etiology, treatment and outcomes of threatened preterm birth

Tobias Adriaan Jules Nijman

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Etiology, treatment and outcomes of threatened preterm birth

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(met een samenvatting in het Nederlands)

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Promotoren:	Prof. dr. A. Franx
	Prof. dr. B.W. Mol
Copromotor:	Dr. M.A. Oudijk

voor papa en mama

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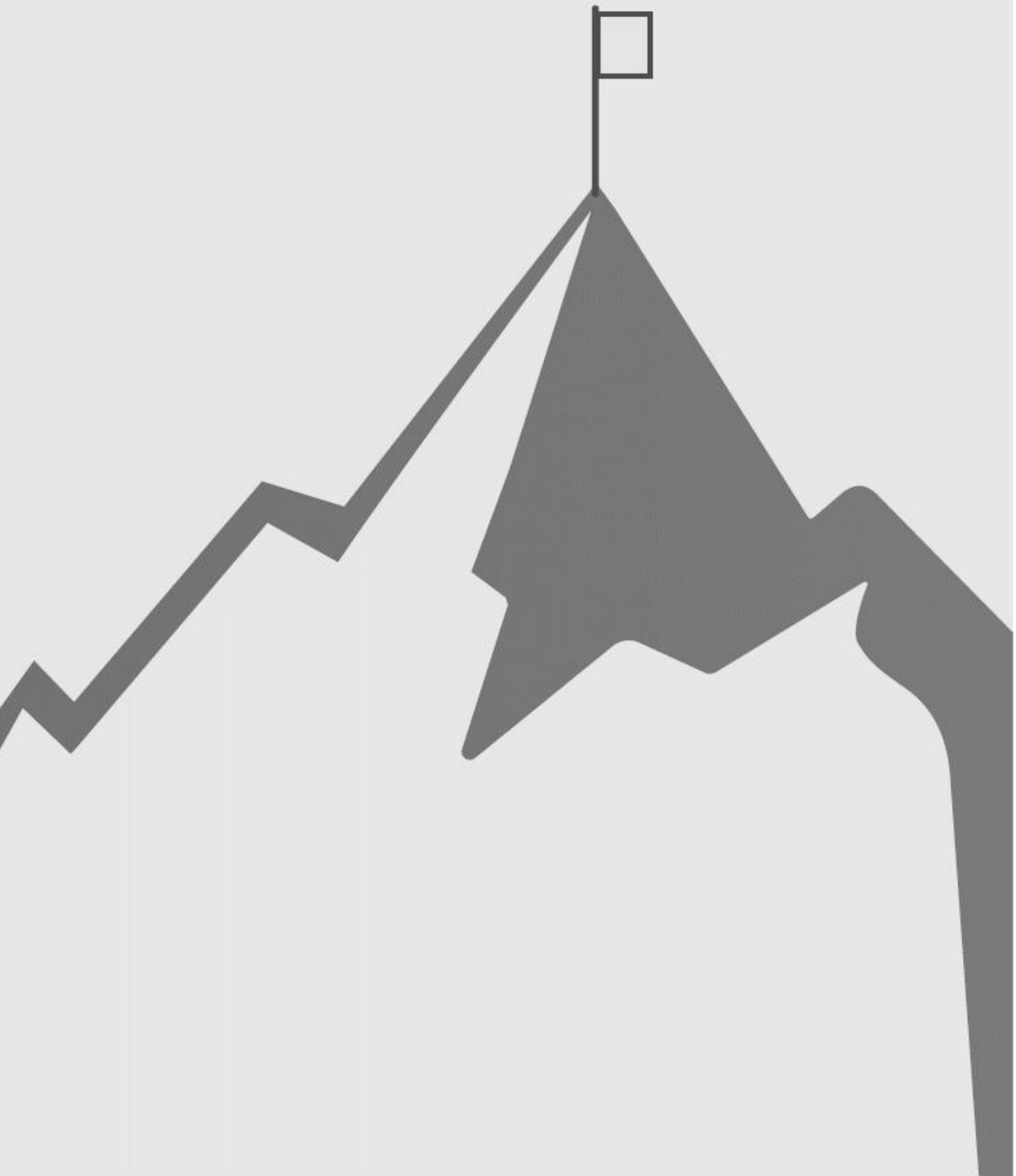

Chapter 1

General introduction and aim of this thesis

General introduction and aim of this thesis

Preterm birth

The normal duration of a pregnancy is 40 weeks, with a range from 37 to 42 weeks. Preterm birth is defined by the World Health Organisation (WHO) as delivery before 37 weeks of gestation.[1] In the Netherlands, it affects approximately 7.7% of all pregnancies.[2] This indicates that every year around 13.000 children are born prematurely in the Netherlands. Approximately 1.4% of these children are born very premature (< 32 weeks of gestation).[2] Worldwide the incidence of preterm birth ranges from 5% in developed countries to 18% in African countries. The estimated 15 million babies that are born preterm every year have a major impact on child health before the age of 5 as well as on the global healthcare system.[3]

Pathophysiology

Two-thirds of preterm births occur after spontaneous onset of labor. The remainder is medically indicated due to maternal or fetal condition, such as preeclampsia, intrauterine growth restriction or fetal congenital malformations.[1] Spontaneous preterm birth includes birth following contractions and intact membranes or labor that starts with premature rupture of the membranes. The etiology of spontaneous preterm birth is complex and not yet completely understood. Both term and preterm labor usually start with the common pathway of labor: increased uterine contractility, cervical dilatation, and rupture of the chorioamniotic membranes.[4] Previously it was assumed that preterm labor was simply labor that starts too soon, however it is now acknowledged that preterm birth is the result of multiple pathological processes.[4,5] This indicates that the common pathway of labor is activated physiologically in the case of labor at term, while in preterm labor several disease processes activate one or more of the components of the common pathway.

Contractions of the uterine muscle are the result of calcium influx in the muscle cell, which is due to opening of calcium-channel canals.[6] A uterine contraction is the result of a coordinated contraction of the muscle cells throughout the whole uterus. Muscle cells in the uterus collaborate and they communicate through gap junctions. The gap junctions allow calcium ions to pass into the uterine muscle cells.[7] During pregnancy formation of gap junctions is inhibited, amongst others, by progesterone. By inhibiting these gap junctions progesterone prevents the uterus from contracting. The formation of gap junctions is also stimulated by uterine overdistension, for instance in twin pregnancies or pregnancies complicated by polyhydramnion.[7] During the pregnancy, the cervix is is closed with firm consistency. Cervical ripening in preparation for dilatation is mediated by changes in extracellular matrix proteins, as well as alteration in epithelial barrier and immune surveillance properties. This leads to decreased strength of the cervix, which is the key for cervical dilatation.[8] The strength and integrity of fetal membranes originate from extracellular membrane proteins including collagens, fibronectin, and laminins.

Increased expression of inflammatory cytokines and chemokines, increased activity of proteases and dissolution of fibronectin lead to decidual or membrane activation. This leads to withdrawal of decidual support, separation of the chorioamniotic membranes from the decidua, and in the end, rupture of the membranes.[9]

Figure 1 shows possible mechanisms responsible for preterm birth.[5] Intra uterine infection or inflammation is strongly associated with spontaneous preterm birth. This is the pathological process with the most firm causal link and for which a defined molecular pathophysiology is known.[10] Infection leads to increased production of cytokines and chemokines which, as mentioned above, subsequently generates decidual or membrane activation.[9,11] Furthermore, the increased cytokines production leads to increased prostaglandin production. Prostaglandins increase uterine contractions and provide cervical ripening.[11] Besides infection and inflammation, decidual hemorrhage and maternal vascular malperfusion lesions in the placenta are associated with preterm labor with intact membranes and preterm prelabor rupture of membranes.[5] Around 30% of women with preterm labor have placental lesions consistent with maternal vascular malperfusion lesions.[12] Furthermore, a similar number of women have failure of physiologic transformation of the myometrial segment of the spiral arteries, which is a phenomenon seen frequently in for instance preeclampsia.[13] Other possible mechanisms for preterm labor are cervical disease (collagen defects, congenital malformations or procedures such as conisation or dilatation and curettage), uterine overdistension (in case of polyhydramnion or multiple pregnancies), maternal stress or breakdown of maternal-fetal tolerance. However in many cases a clear single cause is not found.[5]

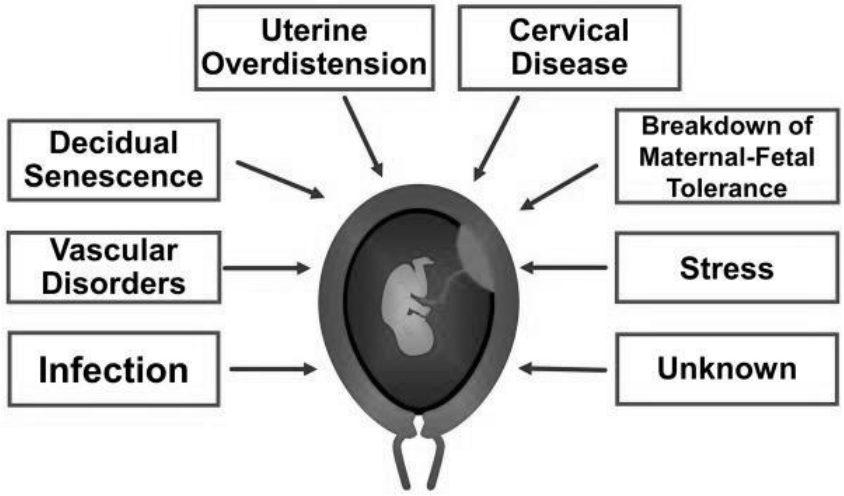

Figure 1: Source: Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. Science. 2014 Aug 15;345(6198):760-5. Published with permission from author.

Consequences

Preterm birth is the leading cause of perinatal and neonatal morbidity and mortality.[1,14] Preterm infants are susceptible to complications in both early and later life. Early complications include pulmonary problems such as infant respiratory distress syndrome and broncho pulmonary dysplasia, cerebral complications such as intraventricular hemorrhage and periventricular leukomalacia and perinatal infections such as sepsis or meningitis.[15] The prevalence of adverse neonatal outcome is strongly related to gestational age at delivery, declining from 77% at 24-27 weeks to less than 2% from 34 weeks onwards.[2] Furthermore preterm birth is associated with long-term neurological and behavioral problems, which are also strongly dependent on gestational age at delivery. Neonates born extreme preterm are prone to have more severe problems; while moderate and late preterm births are associated with milder problems.[16] On the other hand, it has been shown that in children born between 32 and 35 weeks of gestation (mild preterm infants), approximately one third of 7-year-old children experienced difficulties in motor skills, speaking, writing, mathematics, behavior and physical education.[17] Furthermore late preterm infants (born between 34 and 37 weeks of gestation) have shown to be at increased risk for long-term morbidity, such as cerebral palsy and mental retardation, as well as increased risk for problems in school.[18]

Interventions to improve of neonatal outcome

Antenatal corticosteroids

Between 1967 and 1969 Graham Liggins coincidentally found in his research on involvement of corticosteroids on preterm birth that preterm lambs exposed to antenatal corticosteroids had structurally more mature lungs than one would expect. Furthermore these lambs were viable at lower gestational age and had fewer respiratory problems after delivery.[19] In 1972 Liggins and his partner Ross Howie published their revolutionary randomized trial comparing corticosteroids with placebo in women with threatened preterm birth <37 weeks of gestation. The trial showed a reduction in respiratory distress syndrome and decrease of neonatal mortality.[20] Succeeding trials confirmed the findings of Liggins and Howie. The first structured review was published in 1990 and showed that corticosteroids are effective in reducing respiratory distress syndrome and neonatal mortality.[21] It was only in 1994 that the American College of Obstetricians and Gynecologists and the National Institutes of Health (NIH) published their consensus statement, in which the recommendation for the use of a 48 hours course of antenatal corticosteroids in threatened preterm birth was stated.[22] Recent meta-analyses showed beneficial effect of antenatal corticosteroids on neonatal death, infant respiratory distress syndrome, intraventricular hemorrhage and necrotizing enterocolitis.[23] Furthermore long term outcomes such as cerebral palsy, poor psychomotor development and severe disability seemed to be improved by administration of corticosteroids.[24]

Tocolysis

To ensure the administration of corticosteroids and transportation to a center with neonatal intensive care unit facilities, tocolytic therapy can be administered for 48 hours. Throughout the years several types of tocolytic drugs have been used, all with different mechanisms of action. These include β adrenoceptor agonists such as ritodrine and terbutaline, calcium channel blockers such as nifedipine, cyclooxygenase inhibitors such as indomethacin and oxytocin receptor antagonists such as atosiban. A recent meta-analysis in which different tocolytic drugs were compared, showed that most tocolytic drugs are effective in delaying delivery for at least 48 hours.[25] Most trials comparing tocolytic drugs to placebo, no treatment or other tocolytic drugs are powered on the prolongation of pregnancy, while the main goal of tocolysis is to improve neonatal outcomes. Therefore there is still no evidence that tocolytic drugs improve neonatal outcomes. Which tocolytic drug is the most effective and safe has yet to be determined. Currently, based on the effectiveness and safety profile, the Dutch Society of Obstetrics and Gynaecology describes nifedipine and atosiban as the tocolytic drugs as first choise.[26] However, there are no large trials comparing these two drugs, especially in terms of adverse perinatal outcome.

Aim of this thesis

The following questions will be addressed in this thesis:

1. Is there overlap in placental pathology between spontaneous and indicated preterm birth? (chapter 2)
2. What are the current interventions in the treatment of threatened preterm birth and what is the evidence supporting these interventions? (chapter 3)
3. Does atosiban lead to better perinatal outcomes in women with threatened preterm birth when compared to nifedipine? (chapter 4 and 6)
4. What is the cost-effectiveness of tocolysis with atosiban compared to nifedipine? (chapter 5)
5. Does treatment with nifedipine improve perinatal outcomes in women with preterm prelabor rupture of membranes without contractions when compared to placebo? (chapter 7)
6. What is the practice worldwide regarding the treatment of threatened preterm birth and what are the knowledge gaps? (chapter 8)

Outline of this thesis

Chapter 2 describes the results of a case control study, in which we compared the placental histologic results in spontaneous preterm birth and indicated preterm birth.

Chapter 3 reviews the antepartum and intrapartum interventions to prevent preterm birth and its sequelae. The review describes all items in the treatment of threatened preterm birth, including diagnosing threatened preterm birth, antenatal corticosteroids, tocolysis, magnesium sulfate and antibiotic therapy.

Chapter 4 describes the results of the APOSTEL (Assessment of Perinatal Outcome after Specific Tocolysis in Early Labour)-III trial, a randomized controlled trial designed to compare tocolysis with nifedipine and atosiban in terms of perinatal outcome, prolongation of pregnancy and maternal side effects in women with threatened preterm birth.

Chapter 5 presents the results of a cost-effectiveness analysis of tocolysis with nifedipine compared to atosiban (data from the APOSTEL-III trial).

Chapter 6 is a secondary analysis of the APOSTEL-III trial in which we reviewed the effects of nifedipine and atosiban on the neonatal brain in terms of brain injury.

Chapter 7 describes the results of the APOSTEL IV-trial, a randomized placebo controlled trial on prolonged tocolysis with nifedipine compared with placebo in the treatment of preterm prelabor rupture of membranes.

Chapter 8 reports on the results of a survey on the treatment of threatened preterm birth worldwide. Furthermore an inventory on ongoing and planned trials concerning the treatment of threatened preterm birth was performed.

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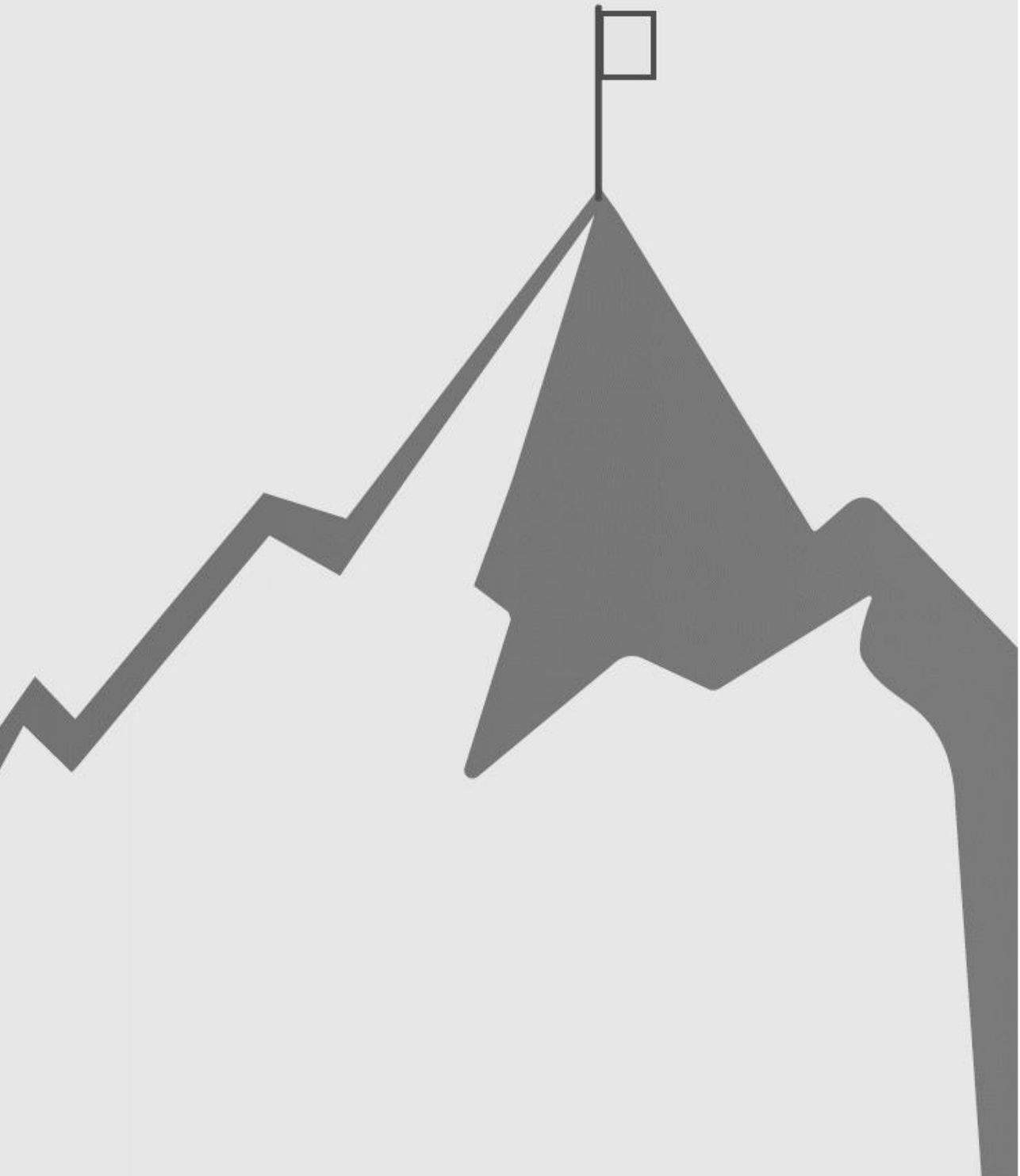

Chapter 2

Placental histology in spontaneous and indicated preterm birth: a case control study.

Tobias A.J. Nijman, Elvira O.G. van Vliet, Manon J.N. Benders,
Ben Willem J. Mol, Arie Franx, Peter G.J. Nikkels, Martijn A. Oudijk

Placenta. 2016 Dec; 48:56-62

Abstract

Introduction

Placental pathology is an important contributor in preterm birth, both spontaneous and indicated. The aim of this study was to describe and compare placental histological features of spontaneous preterm birth versus indicated preterm birth.

Methods

A case control study was performed at the University Medical Center Utrecht. Women with spontaneous or indicated preterm birth (17-37 weeks of gestation) delivered in 2009 were included. Women with a pregnancy complicated by congenital and/or chromosomal abnormalities were excluded. Placentas were systematically examined by an expert pathologist blinded for pregnancy outcome, except for gestational age. Placental histological abnormalities were classified into infectious inflammatory lesions and maternal vascular malperfusion lesions and compared between spontaneous and indicated preterm birth. Analysis was stratified for immature (17-23+6 weeks), extremely (24-27+6 weeks), very (28-31+6 weeks) and moderate/late (32-36+6 weeks) preterm birth.

Results

We included 233 women, 121 women with spontaneous preterm birth and 112 women with indicated preterm birth. Among women with spontaneous extremely preterm birth, higher rates of severe chorioamnionitis were found (56.0% vs. 0%). Furthermore, a shift from infectious-inflammatory lesions to maternal vascular malperfusion lesions was seen after 28 weeks; in women with spontaneous very and moderate/late preterm birth, maternal vascular malperfusion lesions were the main finding (46.8% and 47.7% respectively). In women with indicated preterm birth, maternal vascular malperfusion lesions were most often contributing through all gestational age categories.

Conclusion

Maternal vascular malperfusion lesions are most frequent in both spontaneous and indicated very and moderate/late preterm birth. In spontaneous extreme preterm birth chorioamnionitis is the main finding.

Introduction

Preterm birth is an important risk factor for poor neonatal and neurodevelopmental outcome.[1] Three obstetric clinical pathways can lead to preterm birth: (1) spontaneous preterm birth with intact membranes, (2) preterm prelabor rupture of the membranes (PPROM) and (3) indicated delivery for maternal or fetal indications.[2] Clinical circumstances leading to preterm delivery vary between indicated and spontaneous preterm birth, and neonatal outcomes differ depending on the etiology of preterm birth as well.[3] Placental functioning is of crucial importance in development and protection of the fetus and disorders in placental functioning might put the fetus at risk for poor intrauterine development and preterm birth.[4] There is increasing evidence that disorders in placental functioning are associated with poor neonatal and long term neurodevelopmental outcome in preterm infants.[5-8]

Preterm birth, both spontaneous and indicated, is a multifactorial process. Previous studies have described differences in patterns of placental pathology according to gestational age and cause of preterm delivery. In extreme spontaneous preterm birth (gestational age (GA) < 28 weeks) acute infection or inflammation (chorioamnionitis) is the most common finding.[9] In late spontaneous preterm birth, some studies describe chronic chorioamnionitis to be the most common pathology, whereas others found high rates of vascular lesions as the GA increased.[9-11] Kim et al. found in spontaneous preterm birth, both with intact membranes and ruptured membranes, higher grades of non-physiologic changes of spiral arteries in placental bed biopsies.[12] Furthermore, Arias et al. found vascular lesions in decidual vessels in 34% of the placentas of women with spontaneous preterm birth with intact membranes and 35% vascular lesions in spontaneous preterm birth with PPROM, compared with only 12% in the placentas of healthy term births.[13] Non-physiologic changes of spiral arteries is also a common finding in preeclampsia. In indicated preterm birth, for indications such as preeclampsia, hemolysis elevated liver enzymes and low platelets (HELLP)-syndrome or intra uterine growth restriction the most common placental pathologic findings are low placental weight, ischemia and accelerated villous maturation, which are all maternal vascular malperfusion lesions.[14] These similarities suggest an overlap in pathophysiological mechanism between the clinical conditions preeclampsia and spontaneous preterm birth, however there is little evidence to support this theory. Therefore, the aim of this study was to compare gross and histological characteristics of the placenta in spontaneous and indicated preterm birth between 17 and 36^{+6} weeks of gestation.

Material and methods

Study design

We performed a case control study at the University Medical Center Utrecht, the Netherlands. All women with a singleton pregnancy and a preterm delivery (GA 17-36^{+6}

weeks) in the year 2009 were eligible for inclusion in this study. Spontaneous preterm birth was defined as premature birth after PPROM or premature birth after spontaneous onset of contractions with intact membranes. Indicated preterm birth was defined as termination of pregnancy for maternal or fetal indication, such as preeclampsia, intra uterine growth restriction, or other medical conditions requiring termination of pregnancy. Women with fetuses deceased before labor or infants with major congenital and/or chromosomal abnormalities were excluded, since this is another cause for placental abnormalities.

Placental histology

At the University Medical Center Utrecht it is standard care to send all placentas of premature births to the pathologist for macropathologic and histologic examination. Available placentas were re-examined by an expert perinatal pathologist (PN), blinded for clinical outcome except for gestational age at delivery. Samples were taken from the umbilical cord at the fetal and placental side. Samples were taken from the placental membranes, umbilical cord insertion, and two samples of normal placental parenchyma including decidua and chorionic plate, and additional samples from macroscopical abnormal lesions were taken. Placental histology was conducted and reported according to the Amsterdam Placental Workshop Group Consensus Statement.[15]

Maternal vascular malperfusion lesions

For examination of maternal vascular malperfusion lesions the following microscopical items were scored: distal villous hypoplasia, accelerated villous maturation, increased circulating nucleated red blood cells (NRBC), ischemia and shock villi. Distal villous hypoplasia was defined as the scarcity of villi in relation to the surrounding stem villi. The villi are thin, and relatively long appearing and syncytial knots are increased. Accelerated villous maturation was defined as the presence of small or short hypermature villi for gestational age, often accompanied by an increase in syncytial knots. Increased circulating NRBC's can be a sign of (chronic) fetal hypoxia. Increased NRBC was defined as NRBC present in at least two capillaries in a random 10x field. Furthermore placental weight below the 10^{th} percentile and macroscopic infarction > 5% of the placental parenchyma were classified as maternal vascular malperfusion lesions.[15] Ischemia was defined as hyperchromasia of trophoblast and increased syncytial knotting. Shock villi were scored when stromal villous hemorrhage was present in a small group of at least two villi, usually immature intermediate villi.

Infectious inflammatory lesions

Staging of the maternal and fetal inflammation response was performed according to the Society for Pediatric Pathology. The maternal inflammatory response was qualified as

follows: stage 1: acute subchorionitis or chorionitis; stage 2: acute chorioamnionitis: polymorphonuclear leucocytes extend into fibrous chorion and/or amnion and stage 3: necrotizing chorioamnionitis: polymorph karyorrhexis, amniocyte necrosis and or amnion basement membrane hypereosinophilia. The fetal inflammatory response was staged as: stage 1: chorionic vasculitis or umbilical phlebitis; stage 2: involvement of the umbilical vein and one or more umbilical arteries and stage 3: necrotizing funisitis.[15]
Chronic chorioamnionitis was diagnosed when groups of at least 50 mononuclear cells were present in the chorionic layer of the membranes. Chronic deciduitis was scored when in the placental decidua groups of at least 50 mononuclear cells were present including plasma cells.[15]

Various lesions
(Chronic) villitis of unknown etiology was divided in low and high grade lesions. Low grade was defined as the presence of inflammation affecting fewer than 10 nearby villi in any one focus, with more than one focus required for the diagnosis. High grade was defined as the presence of more foci, on more than one section, at least one of which shows inflammation affecting more than 10 nearby villi. Fetal thrombosis was scored when at least 5 avascular fibrotic villi without inflammation or mineralization were present, or if adherent thrombi in stem vessels were present.

Patterns
To identify patterns of placental histologic characteristics within gestational age categories, four groups of placental histologic abnormalities were formed. First, infectious inflammatory lesions, which included: chorioamnionitis ≥ stage 2, fetal inflammatory response ≥ stage 1, chronic chorioamnionitis and chronic deciduitis. Second, maternal vascular malperfusion lesions included placental weight < 10^{th} percentile, infarction > 5% of the placental parenchyma, distal villous hypoplasia, strongly accelerated villous maturation, increased NRBC, shock villi and ischemic lesions. The third group included women with both infectious and maternal vascular malperfusion lesions. The fourth group included women with no infectious or maternal vascular malperfusion lesions.

Perinatal characteristics
Perinatal characteristics were derived from the medical records. Maternal characteristics included: maternal age (years), smoking, ethnicity, parity and GA at delivery. The following delivery characteristics were recorded: mode of delivery (vaginal delivery, elective and emergency caesarian section). Neonatal characteristics included birth weight (BW), small for gestational age status (BW <p10), Apgar score at 5 minutes <7, and arterial umbilical cord pH <7.10.

Statistical analysis

To study the effect of GA on histological characteristics of placentas, patients were categorized in four categories: immature birth (17-23^{+6} weeks), extremely preterm birth (24-27^{+6} weeks), very preterm birth (28-31^{+6} weeks) and moderate/late preterm birth (32-36^{+6} weeks). Differences between spontaneous and indicated preterm birth groups were analyzed using the X^2-test (Fisher's exact test when the expected count was <5) for categorical variables. For continuous variables T-test or Mann–Whitney U test, when appropriate, was used. For differences in short term neonatal outcomes between types of histological abnormalities logistic regression was used, corrected for GA at delivery. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using Statistical Package for the Social Sciences version 21.0 (IBM Corp.)

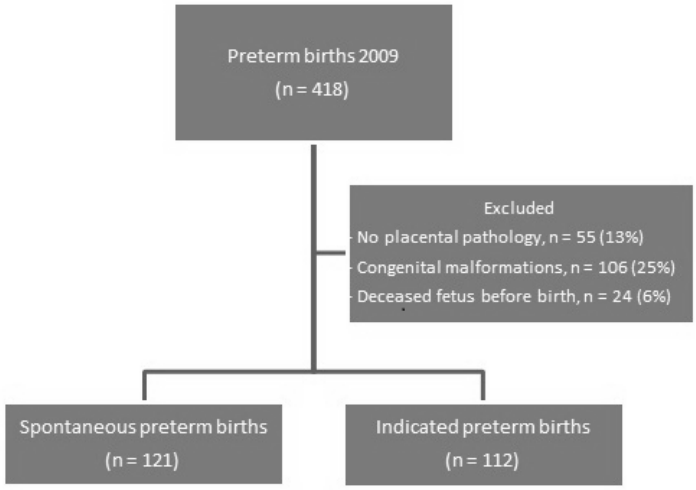

Figure 1. Flow chart

Results

Patient characteristics

In 2009, there were 418 women who delivered preterm (GA 17-36^{+6} weeks) in the UMC, Utrecht. Patients were excluded because of no placental pathology exam available (n = 55), congenital malformations (n = 106) or fetal demise before birth (n = 24). We therefore included 233 patients, of whom 121 had a spontaneous and 112 had an indicated preterm birth (figure 1). Patient characteristics are displayed in table 1. Maternal characteristics such as smoking status, race and parity did not differ between spontaneous and indicated preterm birth. Women with spontaneous preterm birth had a significantly lower age (30.0 years vs. 32.0 years; p = 0.04) and lower GA at delivery (30.7 weeks vs. 31.7 weeks, p =

0.04). As expected more suspected intra uterine infections and women with PPROM were seen in women with a spontaneous preterm birth. Furthermore hypertensive disorders such as preeclampsia and HELLP-syndrome were seen in women with indicated preterm birth. More elective Caesarean sections were performed in women with indicated preterm birth (74.1% vs. 6.6%; p < 0.001). We found no differences in birth weight, Apgar score at 5 minutes <7 and the incidence of umbilical cord pH < 7.10. In women with indicated preterm birth significantly more neonates were born small for GA (29.0% vs. 2.8%; p < 0.001).

Table 1. Patient characteristics

	Spontaneous PTB (n = 121)	**Indicated PTB** (n = 112)	p-value
Maternal characteristics			
Maternal age (years, mean (SD))	30.0 (5.0)	32.0 (6.0)	**0.04**
Non-smoker, n (%)*	67 (90.5)	47 (90.4)	0.60
Caucasian, n (%)	93 (76,9)	90 (80.4)	0.96
Nulliparous women, n (%)	64 (52.9)	68 (60.7)	0.14
GA at delivery (weeks, mean (SD))	30.7 (3.9)	31.7 (3.3)	**0.04**
Suspected intra uterine infection, n (%)	11 (9.1)	1 (0.9)	**0.04**
PPROM	28 (23.1)	1 (0.9)	**< 0.001**
Hypertensive disorders • None • Preeclampsia • HELLP-syndrome • Eclampsia	 119 (98.3) 2 (1.7) 0 (0) 0 (0)	 49 (43.8) 46 (41.1) 1 (0.9) 16 (6.9)	**< 0.001**
Delivery characteristics			
Mode of delivery, n (%) • Vaginal • Elective CS • Emergency CS	 94 (77.7 8 (6.6) 19 (15.7)	 17 (15.2) 83 (74.1) 12 (10.7)	**< 0.001**
Neonatal characteristics			
Birth weight (grams, mean (SD))	1721 (751)	1578 (880)	0.18
Small for GA, n (%)†	3 (2.8)	31 (29.0)	**< 0.001**
Apgar at 5 min < 7, n (%)	21 (17.4)	14 (12.5)	0.20
pH < 7.10, n (%)‡	3 (4.1)	5 (6.2)	0.41

PTB: preterm birth; SD: standard deviation; GA: gestational age; PPROM: premature prelabor rupture of membranes; HELLP: hemolysis elevated liver enzymes low platelets; CS: Cesarean section.

* based on n = 74 for spontaneous PTB and n = 52 for indicated PTB due to missing data
† based on n = 111 for spontaneous PTB and n = 109 for indicated PTB due to missing data
‡ based on n = 74 for spontaneous PTB and n = 81 for indicated PTB due to missing data

Placental histologic results

Results of placental histologic examination are shown in table 2.

Maternal vascular malperfusion lesions

A placental weight below the 10th percentile and accelerated villous maturation was more prevalent in placenta's of women with indicated preterm births compared to spontaneous preterm birth for all gestational age groups except for immature births. Distal villous hypoplasia was less frequently present in spontaneous very preterm birth compared to indicated very preterm birth (4.2% vs. 19.6%; OR 0.55; 95% CI 0.38-0.79). Increased NRBC were more frequently present in indicated extremely preterm birth compared to spontaneous extremely preterm birth (91.7% vs. 28.0%; OR 0.09; 95% CI 0.01-0.60). Infarction > 5% and ischemia were found more often in women with indicated extremely and very preterm birth compared to spontaneous extremely and very preterm birth, this difference was not significant after 32 weeks of GA. The incidence of shock villi was not significantly different between spontaneous and indicated preterm birth.

Infectious inflammatory lesions

In spontaneous extremely and very preterm birth severe chorioamnionitis (≥ stage II) and fetal inflammatory response ≥ stage 1 were more frequently present compared to indicated extremely and very preterm birth. After 32 weeks of GA there was no significant difference between the spontaneous and indicated preterm birth groups in the incidence of severe chorioamnionitis and fetal inflammatory response. The incidence of chronic chorioamnionitis or chronic deciduitis was not different between spontaneous and indicated preterm birth.

Various lesions

Chronic villitis of unknown etiology (all grades) was seen less frequently in spontaneous very preterm birth compared to indicated very preterm birth (4.2% vs. 17.4 %; OR 0.57, 95% CI 0.38-0.83). Fetal thrombosis was less prevalent in spontaneous moderate/late preterm birth (11.4% vs. 28.8%; OR 0.65; 95% CI 0.46-0.91).

Types of placental histologic abnormalities

Figure 2 displays the pattern of placental histologic abnormalities in spontaneous and indicated preterm birth. In spontaneous extremely preterm birth the most common lesions were infectious inflammatory lesions (40.0%). With increasing GA the incidence of infectious lesions decreased (21.3% in very preterm birth and 15.9% in moderate/late preterm birth). A shift from infectious inflammatory lesions to maternal vascular malperfusion lesions was seen after 28 weeks of GA, maternal vascular malperfusion lesions are mainly present (46.8% in very preterm birth and 47.7% in moderate/late preterm birth). In indicated preterm birth maternal vascular malperfusion lesions were predominantly present in all categories of GA.

Table 2. Placental histologic results					
	GA category (weeks)	**Spontaneous PTB (n = 121)**	**Indicated PTB (n =111)**	**OR (95% CI)**	**p-value**
Maternal vascular malperfusion lesions					
Placental weight <p10, n (%)	17-23^{+6}	0 (0)	0 (0)	NA	NA
	24-27^{+6}	2 (8.0)	9 (75.0)	0.14 (0.05-0.42)	**< 0.001**
	28-31^{+6}	5 (10.4)	20 (43.5)	0.47 (0.33-0.68)	**< 0.001**
	32-36^{+6}	5 (11.4)	23 (45.1)	0.51 (0.37-0.71)	**< 0.001**
Infarction > 5%, n (%)	17-23^{+6}	0 (0)	0 (0)	NA	NA
	24-27^{+6}	0 (0)	3 (25.0)	NA	**0.03**
	28-31^{+6}	1 (2.1)	11 (23.9)	0.47 (0.34-0.63)	**< 0.001**
	32-36^{+6}	3 (6.8)	7 (13.5)	0.75 (0.48-1.2)	0.24
Distal villous hypoplasia, n (%)	17-23^{+6}	0 (0)	0 (0)	NA	NA
	24-27^{+6}	0 (0)	1 (8.3)	NA	0.32
	28-31^{+6}	2 (4.2)	9 (19.6)	0.55 (0.38-0.79)	**0.02**
	32-36^{+6}	0 (0)	1 (1.9)	NA	0.54
Accelerated villous maturation, n (%)	17-23^{+6}	0 (0)	0 (0)	NA	NA
	24-27^{+6}	11 (44.0)	11 (91.7)	0.13 (0.02-0.93)	**0.006**
	28-31^{+6}	23 (47.9)	44 (95.7)	0.11 (0.03-0.43)	**< 0.001**
	32-36^{+6}	6 (13.6)	20 (39.2)	0.58 (0.42-0.82)	**0.005**
Increased NRBC, n (%)	17-23^{+6}	2 (66.7)	1 (50.0)	1.00 (0.10-9.6)	0.80
	24-27^{+6}	7 (28.0)	11 (91.7)	0.09 (0.01-0.60)	**< 0.001**
	28-31^{+6}	15 (31.3)	21 (45.7)	0.74 (0.49-1.1)	0.11
	32-36^{+6}	10 (22.7)	16 (30.8)	0.84 (0.57-1.2)	0.26
Ischemia, n (%)	17-23^{+6}	0 (0)	0 (0)	NA	NA
	24-27^{+6}	0 (0)	11 (91.7)	NA	**< 0.001**
	28-31^{+6}	6 (12.5)	32 (69.6)	0.21 (0.12-0.38)	**< 0.001**
	32-36^{+6}	14 (31.1)	18 (34.6)	0.92 (0.62-1.4)	0.42
Shock villi, n (%)	17-23^{+6}	1 (25.0)	0 (0)	NA	0.67
	24-27^{+6}	6 (24.0)	3 (25.0)	0.96 (0.33-2.8)	0.62
	28-31^{+6}	9 (18.8)	7 (15.6)	1.1 (0.62-2.1)	0.45
	32-36^{+6}	4 (9.3)	9 (17.3)	0.76 (0.50-1.1)	0.20
Infectious inflammatory lesions					
Chorioamnionitis ≥ stage II, n (%)	17-23^{+6}	3 (75.0)	0 (0)	NA	0.20
	24-27^{+6}	14 (56.0)	0 (0)	NA	**0.001**
	28-31^{+6}	11 (22.9)	0 (0)	NA	**< 0.001**
	32-36^{+6}	4 (9.1)	2 (3.8)	1.7 (0.53-5.2)	0.26
Fetal inflammatory response ≥ stage 1, n (%)	17-23^{+6}	3 (75.0)	0 (0)	NA	0.50
	24-27^{+6}	11 (44.0)	0 (0)	NA	**0.005**
	28-31^{+6}	10 (21.3)	0 (0)	NA	**0.001**
	32-36^{+6}	5 (11.4)	1 (1.9)	3.4 (0.56-20.5)	0.07
Chronic chorioamnionitis, n (%)	17-23^{+6}	0 (0)	0 (0)	NA	NA
	24-27^{+6}	1 (4.0)	1 (8.3)	0.63 (0.15-2.7)	0.55
	28-31^{+6}	2 (4.2)	6 (13.0)	0.62 (0.39-0.98)	0.12
	32-36^{+6}	4 (9.1)	4 (7.7)	1.09 (0.53-2.2)	0.55
Deciduitis, n (%)	17-23^{+6}	0 (0)	0 (0)	NA	NA
	24-27^{+6}	1 (4.0)	1 (8.3)	0.63 (0.15-2.7)	0.55
	28-31^{+6}	1 (2.1)	1 (2.2)	0.98 (0.24-4.0)	0.74
	32-36^{+6}	3 (6.8)	2 (3.8)	1.4 (0.46-4.1)	0.42
Various lesions					
Villitis of unknown etiology (all grades), n (%)	17-23^{+6}	0 (0)	0 (0)	NA	NA
	24-27^{+6}	1 (4.0)	1 (8.3)	0.63 (0.15-2.7)	0.55
	28-31^{+6}	2 (4.2)	8 (17.4)	0.57 (0.38-0.83)	**0.04**
	32-36^{+6}	8 (18.2)	10 (19.2)	0.97 (0.61-1.5)	0.55
Fetal thrombosis, n (%)	17-23^{+6}	1 (25.0)	0 (0)	NA	0.67
	24-27^{+6}	4 (16.0)	2 (16.7)	0.97 (0.28-3.3)	0.65
	28-31^{+6}	4 (8.3)	10 (21.7)	0.63 (0.42-0.95)	0.06
	32-36^{+6}	5 (11.4)	15 (28.8)	0.65 (0.46-0.91)	**0.03**
GA gestational age; PTB preterm birth; OR Odds ratio; NA not applicable; CI confidence interval; NRBC nucleated red blood cells					

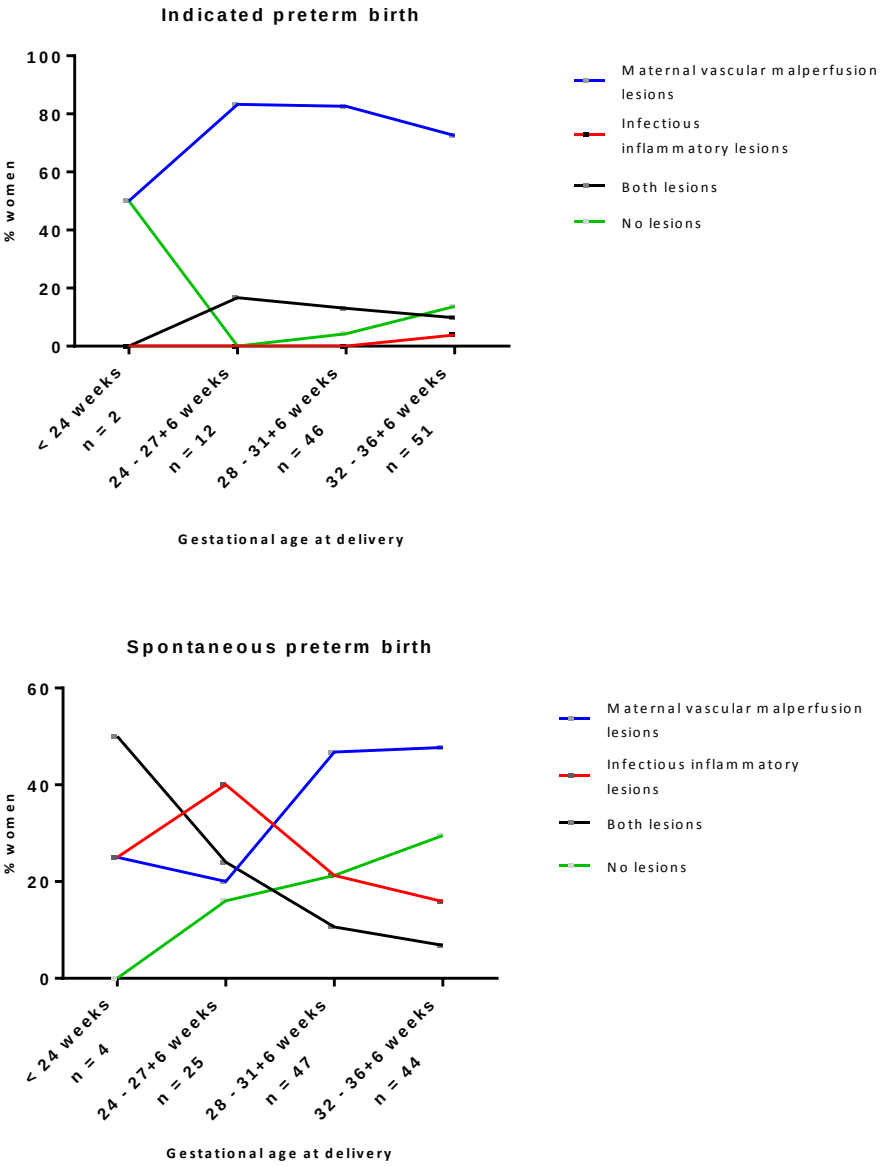

Figure 2. Pattern of placental histologic abnormalities in indicated and spontaneous preterm birth

Discussion

This study found that in spontaneous preterm birth after 28 weeks of gestation the predominant placental pathological abnormalities are maternal vascular malperfusion lesions. In spontaneous extremely preterm birth we found high rates of severe chorioamnionitis and fetal inflammatory response. In indicated preterm birth we found high rates of placental weight below the 10th percentile and accelerated villous maturation throughout all ranges of preterm birth. In indicated very preterm birth, higher rates of ischemia and severe increased NRBC's were observed. After 28 weeks of gestation more overlap was seen between spontaneous and indicated preterm birth, that maternal vascular malperfusion lesions are most frequently present in both groups.

This study has several strengths. Examination of the placentas was done in a structured, pre-specified method and was performed by an expert perinatal pathologist blinded for clinical outcome except for the gestational age at delivery. It was performed according to international accepted terminology.[15] In addition, the study represents a large consecutive cohort in a single center. This study has limitations as well. Due to its retrospective nature this study could not examine all placentas of preterm deliveries, since not all placentas were send for histologic examination. Nonetheless, this number was small (n = 55, 13%). Patient characteristics of women with preterm births without placental examination were significantly different from our study population (GA at delivery and birth weight) and consisted mostly of women with spontaneous preterm birth. This is a potential selection bias of our patients. A possible reason for the missing placentas is that staff considers placental examination less important with higher gestational age. However, the group of women with late preterm births is still the largest. Furthermore we only compared placentas from preterm births and we had no (healthy, term) control group. Due to the fact that four categories were created within the population, some groups contained less then 20 women, therefore statistics need to be interpreted with these small numbers in mind. Furthermore, in our study we looked at inflammatory and infectious lesions as one group of placental pathologic lesions, although mechanisms of action might not be similar. However due to small numbers we were not able to divide into more groups.

Our findings confirm results from previous studies concerning spontaneous preterm birth, that infectious inflammatory lesions, such as acute chorioamnionitis, is the most common finding in spontaneous extremely preterm birth (40.0%).[9] In spontaneous preterm birth between 28-32 weeks the presence of infectious inflammatory lesions is still common (23.5%), however in this gestational age category a shift towards maternal vascular malperfusion lesions was seen. In very and moderate/late preterm birth (> 28 weeks of GA), maternal vascular malperfusion lesions are the main placental lesions. Both findings indicate that in very and moderate/late spontaneous preterm birth infectious

inflammatory lesions are less common and the potential role of maternal vascular malperfusion problems seems larger. This confirms findings of previous studies, indicating a shift from infectious inflammatory lesions to maternal vascular malformation lesions.[12,13,16,17] Arias et al described two different subgroups in spontaneous preterm birth: one of infectious origin and one with vasculopathy. Arias et al found higher gestational age in women with spontaneous preterm birth based on maternal vascular malperfusion placental lesions.[13] This might reflect the same finding as ours. Morgan et al found increased accelerated villous maturation in women with idiopathic preterm birth, however no significant association with gestational age was found.[16] Chronic chorioamnionitis was not frequently observed in spontaneous moderate/late preterm birth (9.1%). The incidence of chronic chorioamnionitis is lower than was found by Lee et al, who found chronic chorioamnionitis to be the most common lesion in late preterm birth. Both our study and Lee et al. used the same definition of chronic chorioamnionitis and were conducted in tertiary hospitals. As patient characteristics, clinical setting and study design seem similar, we do not have a clear explanation for the difference.[10] Signs of maternal vascular malperfusion, such as accelerated villous maturation, increased NRBC's and ischemia were predominantly present in indicated extremely and very preterm birth. This corresponds with findings in previous studies.[14] The finding that maternal vascular malperfusion problems are more frequently present in spontaneous very and moderate/late preterm birth may suggest an overlap in pathophysiological mechanism between clinical obstetric syndromes such as spontaneous preterm birth and preeclampsia. However the mechanism of the pathway leading to either spontaneous preterm birth or preeclampsia is yet to be determined.

This case control study shows that maternal vascular malperfusion lesions are the most frequent placental lesions in very, moderate and late spontaneous preterm birth. Preterm birth is strongly associated with long term neurological and behavioral problems. These problems are inversely associated with GA at delivery.[18] Extremely preterm births are associated with more severe problems and moderate/late preterm births are associated with milder problems.[17] However it has been shown that in children born between 32 and 35 weeks of gestation approximately one third of 7-year-old children was experiencing difficulties in motor skills, speaking, writing, mathematics, behavior and physical education.[19] A systematic review on outcomes of late-preterm infants (born between 34 and 37 weeks of GA) showed that late-preterm infants are at increased risk for long-term morbidity, such as cerebral palsy and mental retardation. Furthermore the risk for problems in school are higher as well.[20] In women with a history of early preeclampsia, low-dose aspirin is used as preventive strategy. It is thought that low-dose aspirin could improve the trophoblastic invasion of the uterine spiral arteries, one of the possible mechanisms behind the development of preeclampsia.[21] If there is an overlap in pathophysiological mechanism between preeclampsia and spontaneous preterm birth, the

beneficial effect of low-dose aspirin also merits evaluation in women at increased risk for spontaneous preterm birth, e.g. women with a spontaneous preterm birth in a previous pregnancy.

Conclusion

In summary, we found that in very and moderate/late preterm birth, both spontaneous and indicated, maternal vascular malperfusion lesions are the most frequent placental pathological abnormalities. In spontaneous extremely preterm birth, however, chorioamnionitis is the most frequently found type of placental lesion.

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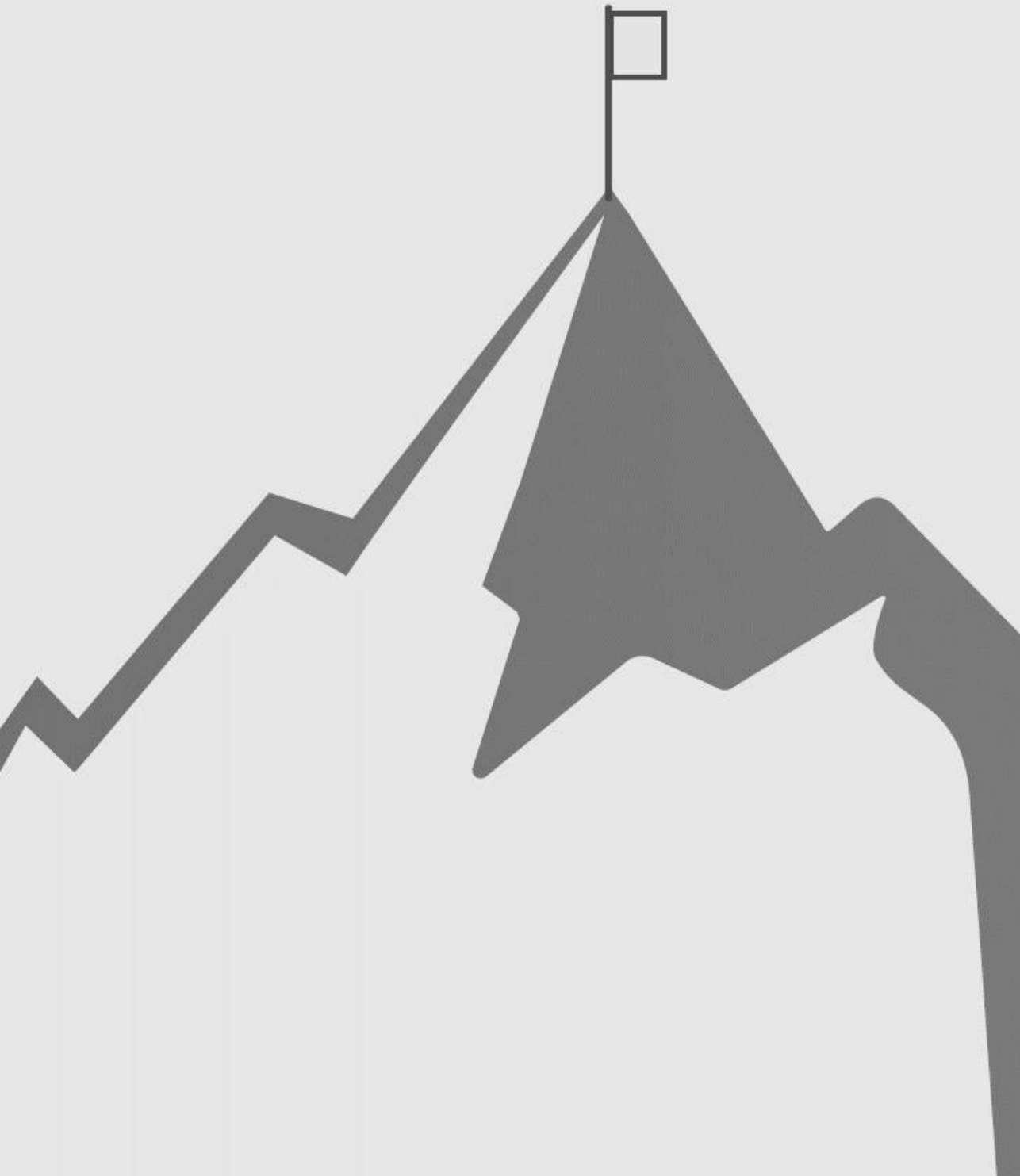

Chapter 3

Antepartum and intrapartum interventions to prevent preterm birth and its sequelae

T.A.J. Nijman, E.O.G. van Vliet, B. Koullali, B.W. Mol, M.A. Oudijk

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Summary

Preterm birth is the main cause of neonatal morbidity and mortality. This review provides an overview of antepartum and intrapartum management of threatened preterm birth. The most effective method to identify women at high risk of delivering within seven days is the combination of cervical length and fetal fibronectin test. Antenatal corticosteroids administered for 48 h improve neonatal outcome. Although tocolysis has been shown to prolong pregnancy, there is no evidence that tocolytic therapy improves neonatal outcomes. Intrapartum administration of magnesium sulfate improves neurologic outcomes, such as cerebral palsy and gross motor function. In women with preterm premature rupture of membranes, prophylactic antibiotic treatment with erythromycin improves short-term neonatal outcomes, but proof of long-term benefit is lacking. In threatened preterm birth with intact membranes, prophylactic antibiotic treatment is thought to be harmful. Critical appraisal of the long-term benefits and harms of all these treatments questions their use.

1. Introduction

Preterm birth complicates 5-13% of all pregnancies worldwide and is the most important cause of neonatal morbidity and mortality [1]. Although disability-free survival rates have increased over the years as a result of improved facilities and treatments, preterm birth is still accountable for 75% of all perinatal deaths and >50% of morbidities [2,3]. Morbidity and mortality are strongly related to gestational age; of those infants born <30 weeks of gestation, only 25% are free of disabilities at the age of five years [3,4]. Many treatments have been investigated to improve neonatal outcomes. The aim of this article is to review current evidence based practice of antepartum and intrapartum interventions in threatened preterm birth to improve neonatal outcome. We discuss the most accurate method of diagnosing threatened preterm birth. Treatments including the use of tocolytic drugs, corticosteroids, magnesium sulfate as neuroprotective agent, and antibiotics are discussed.

2. Diagnosis of threatened preterm birth

Pregnant women with symptoms of threatened preterm birth are a frequent problem in obstetric care. In women with intact membranes and contractions, 12-17% deliver within seven days, whereas around 40-60% of women with preterm premature rupture of membranes (PPROM) deliver within seven days [5,6]. Therefore, to minimize the risk of overtreatment, and to maximize timing of interventions, identification of women at high risk of delivery within seven days is of utmost importance. Historically, risk assessment was based on digital vaginal examination. The addition of transvaginal sonographic measurement of the cervical length is of value in the prediction of preterm birth within one week (sensitivity/specificity: cervical length: 78.1%/82.7% vs vaginal examination: 65.6%/72.4%) [7]. Identification of women at high risk of delivery can be improved by adding fetal fibronectin testing to cervical length measurement. Fetal fibronectin is a protein produced by fetal cells and can found at the border of the chorion and the decidua. Fetal fibronectin is released into the vagina when a preterm delivery is likely to occur and may be measured using a vaginal swab [8]. A recent prospective cohort study showed that women with symptoms of preterm labor and cervical length >30 mm or with cervical length between 15 and 30 mm with negative fetal fibronectin test result have a low risk (<5%) of spontaneous preterm delivery within seven days [9]. A randomized trial, allocating women at low risk of delivering within seven days (intact membranes, cervical length between 10 and 30 mm, and negative fetal fibronectin test) to tocolysis with nifedipine or placebo, showed no differences in prolongation of pregnancy or neonatal outcomes, thereby confirming that these women do not benefit by treatment with tocolysis [10]. Women with symptoms of preterm labor and cervical length <15 or 15-30 mm and positive fetal fibronectin test have a high risk of delivery within seven days (11-52%), therefore treatment is justified [9]. A cost-effectiveness analysis of the use of

cervical length in combination with fetal fibronectin testing showed a possible saving in costs between e1.6 and e8.0 million per 100,000 deliveries [11].

2.1. Conclusion

The use of cervical length measurement in combination with fetal fibronectin test is most accurate and cost-effective to discriminate between women at high and low risk of delivering within seven days.

3. Antenatal corticosteroids

In the late 1960s Graham Liggins, University of Auckland, coincidentally found in his investigation on involvement of corticosteroids on preterm birth that preterm lambs exposed to antenatal corticosteroids had structurally more mature lungs than expected. Furthermore these lambs were viable at lower gestational age and had fewer respiratory problems at birth [12]. In 1972 Liggins and his partner Ross Howie published their landmark randomized trial comparing corticosteroids with placebo in women with threatened preterm birth <37 weeks of gestational age [13]. Liggins and Howie found an improvement in respiratory distress syndrome and neonatal mortality. They recruited 282 women in 22 months starting in 1969. The study was approved by the general staff of the National Women's Hospital, Auckland, New Zealand. Interestingly, they continued to randomize a total of 1142 women until 1974 [14]. Subsequent trials confirmed the findings of Higgins and Howie. The first structured review was published in 1990 and showed that corticosteroids are effective in reducing respiratory distress syndrome and neonatal mortality [15]. In 1994 the American College of Obstetricians and Gynecologists and the National Institutes of Health (NIH) published their consensus statement, recommending the use of antenatal corticosteroids in threatened preterm birth [16]. In retrospect, it took 22 years to translate the results of the trial by Liggins and Howie into international clinical practice.

3.1. Single course of antenatal corticosteroids

A Cochrane review (2006) showed that in women with gestational age between 26+0 and 34+6 weeks treatment with a single course of antenatal corticosteroids for 48 h is associated with a decrease in neonatal death (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.58-0.81; 18 studies, 3956 infants), respiratory distress syndrome (0.66, 0.59-0.73, 21 studies, 4038 infants), intraventricular hemorrhage (0.54, 0.43-0.69; 13 studies, 2872 infants), necrotizing enterocolitis (0.46, 0.29-0.74; eight studies, 1675 infants), respiratory support, intensive care admissions (0.80, 0.65-0.99; two studies, 277 infants), and systemic infections within the first 48 h of life (0.56, 0.38-0.85; five studies, 1319 infants) [14]. A recent cluster-randomized trial, comparing a strategy for improvement of antenatal corticosteroid therapy with standard therapy in six countries with low-resource setting, found no decrease in neonatal mortality despite increasing use of corticosteroids.

In the overall population using the strategy there was even an increase in mortality (RR 1.12, 95% CI 1.02 - 1.22) [17]. The recent World Health Organization (WHO) guideline concerning preterm birth recommends to administer antenatal corticosteroids between 24 and 34 weeks of gestational age; without signs of infection and adequate childbirth care is available [18].

3.2. Repeat course of antenatal corticosteroids

Timing of the administration of antenatal corticosteroids is crucial. While the period of 48 h is arbitrary, the effect of antenatal corticosteroids on neonatal respiratory morbidity decreases after seven days of administration [19]. When women do not deliver within seven days after the initial course of antenatal corticosteroids, and remain at risk for preterm birth, a repeat course of antenatal corticosteroids may be considered. A recent Cochrane review showed that a repeat course reduced the risk of respiratory distress syndrome compared with women not receiving a repeat course (RR 0.83, 95% CI 0.75-0.91; eight trials, 3206 infants) and adverse neonatal outcome (0.84, 0.75-0.94; seven trials, 5094 infants). A reduction in mean birth weight was found in women treated with a repeat course (mean difference (MD) -75.79 g, 95% CI -117.63 to 33.96; nine trials, 5626 infants). However, adjusted birth weight for gestational age did not differ between treatment groups [20]. In long-term follow-up (early childhood) no statistically significant differences were found in infants exposed to repeat antenatal corticosteroids compared with unexposed infants for the primary outcomes (total deaths; survival free of any disability or major disability; disability; or serious adverse outcome) or in the secondary outcome growth assessments [21]. The WHO preterm birth guideline recommends a single repeat course of antenatal corticosteroids when preterm birth does not occur within seven days after the initial dose, and when a subsequent clinical assessment shows that there is a high risk of preterm birth in the next seven days [18].

3.3. Type of corticosteroids

The glucocorticoids used for antenatal administration are dexamethasone and betamethasone. A recent Cochrane review on different types and regimens of corticosteroids showed that dexamethasone was associated with a decreased risk of intraventricular hemorrhage compared with betamethasone (RR 0.44, 95% CI 0.21-0.92; four trials, 549 infants). No statistically significant differences were seen for other primary outcomes such as infant respiratory distress syndrome (1.06, 0.88-1.27; five trials, 753 infants) and perinatal death (1.41, 0.54-3.67; four trials, 596 infants). In secondary outcomes small differences were found, such as rate of admission to the neonatal intensive care unit. However, one trial found that infants in the dexamethasone group had a significantly shorter length of neonatal intensive care unit (NICU) admission (MD -0.91 days, 95% CI -1.77 to 0.05; 70 infants) [22].

3.4. Long-term outcomes

A recent meta-analysis examined long-term neurologic outcomes after a single course of antenatal corticosteroids. Results showed that a single course of antenatal corticosteroids was associated with a decreased risk for cerebral palsy (RR 0.68, 95% CI 0.56 - 0.82; seven studies), poor psychomotor development (0.83, 0.74-0.93), and severe disability (0.79, 0.73-0.85). Steroid treatment increased the rates of intact survival (1.19, 1.06-1.33) [23]. A single course of antenatal corticosteroids appears to have no adverse effects on children's health. However, follow-up of a trial comparing antenatal corticosteroids with usual treatment in term elective cesarean sections found a two-fold increase in children belonging to the lower quarter of academic performance (8.5% vs 17.7%, P = 0.03). Other outcomes, including hyperactivity, behavioral problems, asthma and atopy did not show significant differences [24]. There is increasing evidence that repeat doses of antenatal corticosteroids increase adverse outcomes, including decrease in birth and lung weights, brain growth restriction, and problems such as hyperactivity disorders [24].

3.5. Conclusion

A single course of antenatal corticosteroids significantly improves short- and long-term outcomes from 26 weeks of gestational age onwards. In low-resource settings, these effects are not present. A repeat course of antenatal corticosteroids improves short-term outcome and could be considered after seven days when delivery is imminent; however, repeated doses may be associated with adverse long-term outcome. Dexamethasone and betamethasone are both associated with improved outcome, although dexamethasone seems to perform better on some outcome measures.

4. Tocolysis

To allow corticosteroids to have their maximal effect and, when necessary, transport the patient to a tertiary care center, tocolytic drugs are administered for 48 h. Development of tocolysis started in 1955, the primary goal being to stop imminent premature labor [25]. In subsequent years a diversity of tocolytic drugs has been used. We now review the most frequently administered tocolytics and discuss maintenance tocolysis.

4.1. β-Adrenoreceptor agonists

β-Adrenoreceptor agonists, such as ritodrine and terbutaline, have been used since the 1970s in the treatment of threatened preterm birth. β-adrenoreceptor agonists activate adenyl cyclase to form cyclic adenosine monophosphate. By reducing intracellular calcium through increasing calcium uptake by sarcoplasmic reticulum and phosphorylation of the myosin light-chain kinase, β-adrenoreceptor agonists decrease myosin light-chain kinase activity, resulting in myometrial relaxation [26]. Ritodrine is the only registered β-adrenoreceptor agonist in the USA, but it is no longer available. Furthermore, since the US

Food and Drug Administration (FDA) placed a warning on the label of terbutaline in 2011, popularity has decreased [27].

4.1.1. Effectiveness

B-Adrenoreceptor agonists have been shown to decrease the number of women with threatened preterm birth delivering within 48 h, compared with placebo. A recent Cochrane review determined the RR at 0.68 (95% CI 0.53-0.88; 10 trials, 1209 women). However, there was no reduction in preterm delivery before 37 weeks of gestational age (0.95, 0.88-1.03; 10 trials, 1212 women). β-Adrenoreceptor agonists have no beneficial effect on perinatal death (0.84, 0.46-1.55; 11 trials, 1332 infants), neonatal death (0.90, 0.27-3.00; six trials, 1174 infants) or infant respiratory distress syndrome (0.87, 0.71-1.08; eight trials, 1239 infants) [28].

4.1.2. Side-effects

β-Adrenoreceptor agonists are known to have frequent side-effects. Compared to placebo, there is a higher incidence of palpitations (RR 10.11, 95% CI 6.56-15.58), tachycardia (4.08, 1.55-10.73), chest pain (11.29, 3.81-33.46), dyspnea (3.86, 2.21-6.77), headache (4.07, 2.60-6.35), and tremor (10.74, 6.20-18.59) [28].

4.1.3. Conclusion

Due to the frequency and severity of side-effects, β-adrenoreceptor agonists have been banned from daily practice.

4.2. Cyclo-oxygenase (COX) inhibitors

COX inhibitors, or prostaglandin synthesis inhibitors, decrease the production of prostaglandin. Prostaglandins induce contractions of the uterine muscle by enhancing myometrial gap-junction formation and increasing intracellular calcium concentration. COX enzymes are essential in the production of prostaglandins. The inhibition of COX enzymes results in reduced production of prostaglandins, thereby reducing uterine contractions [29]. Cox inhibitors are used off-label.

4.2.1. Effectiveness

A recent Cochrane review included 20 studies, encompassing 1509 women. Most studies (n = 15) used indomethacin, a nonselective COX inhibitor. When compared with placebo, no difference was found in birth at <48 h after trial entry (RR 0.20, 95% CI 0.03-1.28; two studies, 70 women). Indomethacin resulted in a reduction in preterm birth (<37 weeks of gestational age) in one small study (RR 0.21, 95% CI 0.07-0.62; 36 women) and an increase in gestational age at birth (MD 3.59 weeks, 95% CI 0.65-6.52; two studies, 66 women) and birth weight (MD 716.34 g, 95% CI 425.52-1007.16; two studies, 67 infants). No difference

was found in terms of neonatal morbidity or neonatal mortality. All conclusions should be interpreted with caution, since all were drawn from small numbers (three studies, n = 106) [29]. A recent systematic review and meta-analysis (including 8454 infants) showed an increased risk of severe intraventricular hemorrhage (RR 1.29, 95% CI 1.06-1.56), necrotizing enterocolitis (1.36, 1.08-1.71), and periventricular leukomalacia (1.59, 1.17-2.17) [30]. Compared with β-adrenoreceptor agonists, COX inhibitors resulted in a reduction in birth <48 h (RR 0.27, 95% CI 0.08-0.96; two studies, 100 women) and preterm birth (<37 weeks of gestational age) (0.53, 0.28-0.99, two studies, 80 women). However, no improvement terms of neonatal morbidity or mortality was found.

4.2.2. Side-effects

COX inhibitors were associated with fewer maternal adverse effects compared with β-adrenoreceptors (RR 0.19, 95% CI 0.11-0.31; five studies, 248 women) and maternal adverse effects requiring discontinuation of treatment (0.09, 0.02-0.49; three studies, 166 women). A concerning side-effect of COX inhibitors is closure of the ductus. In the Cochrane review, only one report of closure was seen, out of 287 patients in 10 studies [29].

4.2.3. Conclusion

Indomethacin seems to be effective in prolongation of pregnancy. However, the increased risk of intraventricular hemorrhage, necrotizing enterocolitis, and periventricular leukomalacia is of concern. The use of indomethacin as a tocolytic drug should be avoided.

4.3. Calcium channel blockers

Calcium channel blockers, such as nifedipine, prevent the influx of extracellular calcium ions into the myometrial cell. They are nonspecific for the uterine muscles and mostly used for the treatment of hypertension in adults [31]. Calcium channel blockers are used off-label.

4.3.1. Effectiveness

Two small trials encompassing 173 women compared calcium channel blockers with placebo or no treatment. These trials showed a significant decrease in birth within 48 h after start of treatment compared to no treatment (RR 0.30, 95% CI 0.21-0.43). A higher incidence of maternal adverse effects was found (49.89, 3.13-795.02, one trial, 89 women) compared with placebo. No neonatal outcomes were reported [22]. When comparing calcium channel blockers with oxytocin receptor antagonists, such as atosiban, data from one study showed an increase in gestational age at birth (MD 1.20 completed weeks, 95% CI 0.25-2.15) and reduction in preterm birth <37 weeks of gestation (RR 0.64, 95% CI 0.47-0.89); admissions to the NICU (RR 0.59, 95% CI 0.41-0.85) and duration of admission at the

NICU (MD -5.40 days, 95% CI -10.84 to 0.04). Neonatal mortality and morbidities, such as sepsis, infant respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis showed no significant differences between calcium channel blockers compared with oxytocin receptor antagonists [31]. By comparison with β-adrenoreceptor agonists, calcium channel blockers resulted in an increase in the interval between trial entry and delivery (MD 4.38 days, 95% CI 0.25-8.52) and gestational age (MD 0.71 weeks, 95% CI 0.34-1.09). A decrease in preterm and very preterm birth was found (RR 0.89, 95% CI 0.80-0.98 and RR 0.78, 95% CI 0.66-0.93). Neonatal outcomes were improved with calcium channel blockers: infant respiratory distress syndrome (RR 0.64, 95% CI 0.48-0.86); necrotizing enterocolitis (0.21, 0.05-0.96); intraventricular hemorrhage (0.53, 0.34-0.84); neonatal jaundice (0.72, 0.57-0.92); admissions to NICU (0.74, 0.63-0.87). One trial studied long-term outcome at age 9-12 years and revealed no difference between tocolysis using nifedipine compared with β-adrenoreceptor agonists [31].

4.3.2. Side-effects

Since calcium channel blockers are essentially designed for the treatment of hypertension, most maternal side-effects are related to the effect on the blood pressure. These include hypotension, headache, flushing, nausea, tachycardia and vomiting. When compared with β-adrenoreceptor agonists, fewer maternal adverse effects were found when using calcium channel blockers (RR 0.36, 95% CI 0.24-0.53). Furthermore, fewer maternal adverse effects requiring discontinuation of therapy were seen (0.22, 0.10-0.48). On the other hand, when compared with oxytocin receptor antagonists, side-effects were found more in the calcium channel blocker group (2.61, 1.43-4.74) [31]. One case report described severe hypotension followed by fetal death after tocolysis with nifedipine [32]. A large prospective cohort study showed 0.9% serious adverse drug reaction rate and 1.1% had a mild adverse drug reaction rate. Most adverse reactions were blood pressure-related. Most events occurred within 2-4 h after initiation of tocolytic therapy, therefore monitoring of blood pressure is recommended [33]. Follow-up of children after in utero exposure to nifedipine showed no adverse effects at age 9-12 years [34].

4.3.3. Conclusion

Calcium channel blockers have benefits over the use of placebo or no treatment concerning prolongation of pregnancy. However, no large placebo-controlled trials have been performed and no results on neonatal outcomes are known. Furthermore, when compared with β-adrenoreceptor agonists, calcium channel blockers have benefits regarding prolongation of pregnancy, serious neonatal morbidity, and maternal adverse effects. Compared with oxytocin receptor antagonists more side-effects are found, but calcium channel blockers seem to be more effective in postponing delivery.

4.4. Oxytocin receptor antagonists

Oxytocin is a peptide hormone produced in the hypothalamus, uterus, placenta and amnion. It has a variety of functions, including the stimulation of uterine contractions, thereby playing an important role in the pathway to normal and preterm labor. Oxytocin receptor antagonists, such as atosiban and barusiban, bind to oxytocin receptors in the myometrium. They prevent a rise in intracellular calcium, thereby relaxing the myometrium [35]. The use of oxytocin receptor antagonists is registered for the indication tocolysis. However, in the USA and Australia, for example, it is not available (or FDA-approved) [27].

4.4.1. Effectiveness

When comparing oxytocin receptor antagonists with placebo, no difference was shown in birth within 48 h after trial entry (RR 1.05, 95% CI 0.15-7.43; two studies, 152 women), perinatal mortality (RR 2.25, 95% CI 0.79-6.38; two studies, 729 infants), or major neonatal morbidity. No differences were found in preterm birth <37 weeks of gestation or other adverse neonatal outcomes, except for a small reduction in birth weight (MD -138.86 g, 95% CI -250.53 to -27.18; two studies, 676 infants). Compared to placebo, one study found an increase in extremely preterm birth (<28 weeks of gestation) when using atosiban (RR 3.11, 95% CI 1.02-9.51) and an increase in infant deaths (up to 12 months) (RR 6.13, 95% CI 1.38-27.13). However, this might be caused by the higher number of women with gestational age <26 weeks in the atosiban group. Furthermore, oxytocin receptor antagonists resulted in an increase in maternal adverse drug reactions requiring end of treatment compared with placebo (RR 4.02, 95% CI 2.05-7.85) [35]. A recent Cochrane review showed that oxytocin receptor antagonists compared with β-adrenoreceptor agonists had no statistically significant difference in birth within 48 h after trial entry (0.89, 0.66-1.22; eight studies, 1389 women), very preterm birth (1.70, 0.89-3.23; one study, 145 women), extremely preterm birth (0.84, 0.37-1.92; one study, 244 women), or perinatal mortality (0.55, 0.21-1.48; three studies, 816 infants). Concerning major neonatal morbidity, no differences were found, although numbers were small. Oxytocin receptor antagonists had fewer maternal adverse effects requiring termination of treatment (0.05, 0.02-0.11; five studies, 1161 women) [35]. When compared with nifedipine no difference in delivery within 48 h was found. Fewer maternal side-effects were seen in oxytocin receptor antagonists. Elaborated comparison can be found in the heading 'calcium channel blockers' [35].

4.4.2. Side-effects

Oxytocin receptor antagonists have a superior safety profile compared with other tocolytics. A large prospective cohort study showed no serious and only 0.2% mild adverse reactions when using atosiban as tocolytic drug (RR 0.07, 95% CI 0.01-0.4) [33].

4.4.3. Conclusion

The Cochrane review did not show superiority of oxytocin receptor antagonists (mostly atosiban) as a tocolytic agent compared with placebo, β-adrenoreceptor agonists or calcium channel blockers (mostly nifedipine) in terms of pregnancy prolongation or neonatal outcomes. However, use of oxytocin receptor antagonists was associated with fewer maternal adverse effects than was treatment with β-adrenoreceptor agonists or calcium channel blockers.

4.5. Network meta-analysis

A large network meta-analysis was performed to determine which tocolytic drug had the greatest probability of being the best, in terms of delaying delivery, neonatal mortality, neonatal respiratory distress syndrome, and maternal side-effects. For successfully delaying delivery, prostaglandin inhibitors had the highest probability of being the most efficacious (83%). For both reducing neonatal mortality and neonatal respiratory distress syndrome, calcium channel blockers had highest rank in the probability of being the best tocolytic drugs. Prostaglandin inhibitors had the best maternal safety profile followed by oxytocin receptor antagonists. The conclusion of the analysis was that prostaglandin inhibitors and calcium channel blockers had the highest probability of delaying delivery and improving neonatal outcomes [36].

4.6. Maintenance tocolysis

Neonatal morbidity and mortality are inversely related to gestational age, therefore it has been suggested that prolongation of pregnancy ensures better pregnancy outcomes. We now discuss maintenance tocolysis using nifedipine, oxytocin receptor antagonists, progesterone, and magnesium sulfate.

4.6.1.1 Nifedipine

A recent Cochrane meta-analysis investigating maintenance tocolysis using nifedipine found no differences between treatment with nifedipine and placebo in the incidence of preterm birth (RR 0.97, 95% CI 0.87-1.09; five trials, 681 women), or neonatal death (0.75, 0.05-11.76; two trials, 133 infants). In women treated with nifedipine, prolongation of pregnancy was significantly longer, but no differences between groups were shown for birth at <34 weeks of gestation, birth at <28 weeks of gestation, birth within seven days of treatment, or gestational age at birth [37].

4.6.1.2 Conclusion

Maintenance tocolysis using nifedipine is not recommended.

4.6.2.1 Oxytocin receptor antagonists

A Cochrane review including one trial of 513 women found that when compared with placebo, atosiban did not reduce preterm birth before 37 weeks (RR 0.89, 95% CI 0.71-1.12), 32 weeks (0.85, 0.47-1.55), or 28 weeks (0.75, 0.28-2.01). No differences were found in neonatal morbidity or in perinatal mortality [38].

4.6.2.2 Conclusion

There is not sufficient evidence to support maintenance tocolysis with oxytocin receptor antagonists.

4.7. Progesterone

A recent systematic review and meta-analysis showed that women who were treated with vaginal progesterone maintenance tocolysis, after 48 h of tocolytic therapy, had a significantly lower rate of preterm birth <37 weeks of gestational age (42% vs 58%; RR, 0.71, 95% CI, 0.57-0.90; three trials, 298 women). Women who received vaginal progesterone had significantly longer latency (MD 13.80 days, 95% CI, 3.97-23.63; four trials, 368 women), higher gestational age at delivery (MD 1.29 weeks, 95% CI, 0.43-2.15; four trials, 368 women), and lower rate of neonatal sepsis (2% vs 7%; RR, 0.34, 95% CI, 0.12-0.98; four trials, 368 women). However, it was indicated that more (well-designed, placebo-controlled) trials were required to draw definite conclusions [39].

4.8 Magnesium sulfate

The mechanism of action of magnesium sulfate as a maintenance tocolytic drug is only partially understood. Magnesium reduces the frequency of depolarization of smooth muscle by modulating calcium uptake, binding, and distribution in smooth muscle cells. This results in inhibition of uterine contractions [40].

4.8.1. Effectiveness

A recent Cochrane review showed no differences in the incidence of preterm birth <37 weeks of gestational age when magnesium sulfate maintenance therapy was compared with placebo or no treatment (RR 1.05, 95% CI 0.80-1.40; two trials, 99 women). When magnesium sulfate was compared with other tocolytic therapy no differences were found (0.99, 0.57-1.72; two trials, 100 women). Perinatal mortality was not different between magnesium sulfate and placebo or no treatment (5.00, 0.25-99.16; one trial, 50 infants). This was the same when compared with alternative treatments [40].

4.8.2. Side-effects

Fewer side-effects were reported using magnesium sulfate (RR 0.67, 95% CI 0.47-0.96; three trials, 237 women), including palpitations or tachycardia (0.26, 0.13-0.52; three trials, 237 women) than women receiving alternative therapies such as β-adrenoreceptor

agonists. However, there was more diarrhea in women receiving magnesium sulfate (6.79, 1.26-36.72; three trials, 237 women) [40].

4.8.3. Conclusion

There is not sufficient evidence to support the role of magnesium sulfate as tocolytic drug in threatened preterm birth.

4.9 Tocolytic therapy: conclusion

Tocolytic therapy prolongs pregnancy in case of threatened pretermbirth. Calciumchannel blockers seemto be preferred with the highest effectiveness; oxytocin receptor antagonists have a more favorable safety profile, but seem to be less effective if compared to placebo. No clear evidence is available that tocolytic drugs themselves reduce neonatal morbidity and mortality. Their use should therefore be restricted to delay delivery in order to transport a patient to a facility with NICU facilities if gestational age is less than 32e34 weeks and to allow corticosteroids to have their effect on neonatal outcome. WHO does not recommend tocolytic treatments (acute or maintenance treatments) for women with threatened preterm birth for the purpose of improving newborn outcomes [18]. Large placebo-controlled trials are required to investigate the effect of tocolysis on neonatal outcome.

5. Magnesium sulfate as neuroprotective agent

Cerebral palsy is described as "a group of disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain" [41]. Preterm babies are at high risk for poor neurological outcomes, including periventricular leukomalacia and intraventricular hemorrhage. Cerebral palsy is mostly seen in infant periventricular leukomalacia, but can also be found in infants with intraventricular hemorrhage [42]. Although the mechanisms behind the neuroprotective effects of magnesium sulfate are still not well understood, several studies have examined whether it is beneficial as a neuroprotective agent.

5.1. Effectiveness

Three large randomized clinical trials were conducted comparing magnesium sulfate as neuroprotective agent compared with placebo. Only one trial was able to show a significant reduction in moderate-severe cerebral palsy (RR 0.55, 95% CI 0.32-0.95) [43]. A Cochrane review (2010) included five large trials (6145 infants) and found a significant reduction in the risk of cerebral palsy (0.68, 0.54-0.87; five trials, 6145 infants). There was also a significant reduction in the rate of substantial gross motor dysfunction (0.61, 0.44-0.85, four trials, 5980 infants). One smaller trial (n = 156) found higher rates of perinatal

mortality when using magnesium (risk difference 10.7%, 95% CI 2.9-18.5%, P = 0.02), but magnesium was unlikely to be the cause of deaths in seven out of 10 cases [44]. Furthermore, no statistically significant effect of magnesium sulfate therapy was seen on perinatal mortality in a Cochrane review (RR 1.04, 95% CI 0.92-1.17; five trials, 6145 infants); neither was there a significant difference in other neurological impairments or disabilities in the first few years of life. Concerning minor maternal side-effects, there were higher rates in the magnesium groups, but no significant effects on major maternal complications [45].

5.2. Long-term outcomes

One of the trials (ACTOMgSO4) performed a follow-up study to investigate outcomes at age 6-11 years. Mortality, cerebral palsy, motor function, IQ, basic academic skills, attention and executive function, behavior, growth, and functional outcomes were measured. Information was obtained on 669 infants (77% of the survivors). There were no significant differences between long-term outcomes in children exposed to magnesium and children exposed to placebo, including mortality (RR 0.80, 95% CI 0.62-1.03), cerebral palsy (OR 1.26, 95% CI 0.84-1.91), and abnormal motor function (OR 1.16, 0.88-1.52). However, the study group concluded that more research should be performed to confirm these results [46].

5.3. Conclusion

Antenatal administration of magnesium sulfate before preterm delivery reduces the rate of cerebral palsy, but more research is required to draw conclusions on the effect on long-term (neurological) outcomes. The WHO guideline recommends magnesium sulfate in cases of threatened preterm birth with gestational age <32 weeks [18].

6. Antibiotics

6.1. Premature preterm rupture of membranes (PPROM)

Infection plays an important role in PPROM. However, there is debate whether PPROM is a cause or a consequence of infection. Some bacteria may produce collagenases, mucinases and proteases, which weaken the amnion and chorion and may lead to rupture of the membranes. Moreover, when the membranes have ruptured the barrier between the intrauterine and extra uterine environments has been impaired. Therefore the risk of an intrauterine infection is increased [47].

6.1.1. Efficacy

A large randomized clinical trial (ORACLE I trial, n = 4826) showed that treatment with erythromycin improved short-term adverse neonatal outcome, including reduction in delivery within seven days after randomization, reduction in neonatal treatment with

surfactant, reduction in the rate of positive neonatal blood cultures, reduction in chronic lung disease (neonatal ventilation or oxygen at >28 days of age), fewer major cerebral abnormalities and reduction in the composite outcome (death, chronic lung disease, and major cerebral abnormality). Coamoxiclav significantly increased necrotizing enterocolitis [48]. A recent Cochrane review confirmed the results of the ORACLE I trial. The Cochrane review found a significant reduction in chorioamnionitis (RR 0.66, 95% CI 0.46-0.96) and a reduction in delivery within 48 h (0.71, 0.58-0.87) and seven days (0.79, 0.71-0.89). The incidence of neonatal infection was decreased (0.67, 0.52-0.85), as was the use of surfactant (0.83, 0.72-0.96), oxygen therapy (0.88, 0.81-0.96), and abnormal cerebral ultrasound scan (0.81, 0.68-0.98). However, co-amoxiclav was associated with an increased risk of neonatal necrotizing enterocolitis (4.72, 1.57-14.23) [47].

6.1.2. Long-term outcomes

Based on questionnaires from 3298 (75%) eligible children, follow-up of this trial at age 7 years revealed few differences between children treated with antibiotics or placebo [49].

6.1.3. Conclusion

Antibiotic treatment with erythromycin improves short-term neonatal outcomes and is therefore recommended in PPROM. This recommendation is confirmed in the WHO guideline [18].

6.2. Preterm labor with intact membranes

6.2.1. Efficacy

A recent Cochrane review, mostly based on data from the ORACLE II trial, showed no significant difference in perinatal or infant mortality for infants of women allocated to any prophylactic antibiotics compared with no antibiotics. More neonatal deaths were seen in infants of women receiving any prophylactic antibiotics when compared with placebo (RR 1.57, 95% CI 1.03-2.40). Other short-term outcomes showed no reduction in the group allocated to antibiotics [50,51].

6.2.2. Long-term outcome

Follow-up of the ORACLE II trial (3196, 71%) showed an increase in functional impairment among children at 7 years of age who were exposed to erythromycin. In both antibiotics (co-amoxiclav and erythromycin) the risk of cerebral palsy was increased, although the overall risk of this disorder was low [52].

6.2.3. Conclusion

Routine prophylactic antibiotic therapy is not recommended in preterm labor with intact membranes. This recommendation is confirmed in the WHO guideline [18].

Practice points

- The most effective method to identify women with symptoms of threatened preterm birth at high risk of delivering within seven days is the combination of cervical length and fetal fibronectin test.
- Antenatal corticosteroids have been demonstrated to improve neonatal outcome and should be administered in women with threatened preterm birth. Repeat courses have additional value after seven days of the first course; however, possible adverse long-term outcome effects are of concern.
- Tocolytic therapy has been proven to prolong pregnancy, but there is no evidence of an impact on neonatal outcome. Its use should be restricted to 48 h in order to transport the patient with threatened preterm birth to a center with NICU facilities and to allow for corticosteroids to be administered.
- Maintenance tocolysis does not improve neonatal outcome and is not recommended.
- Magnesium sulfate improves short-term neurologic outcomes, such as cerebral palsy and gross motor function and should be administered in women with imminent preterm delivery at <32 weeks of gestation.
- In women with PPROM, erythromycin improves short-term neonatal outcome, and should therefore be administered.
- In women with threatened preterm birth with intact membranes, the routine use of antibiotics is not recommended.

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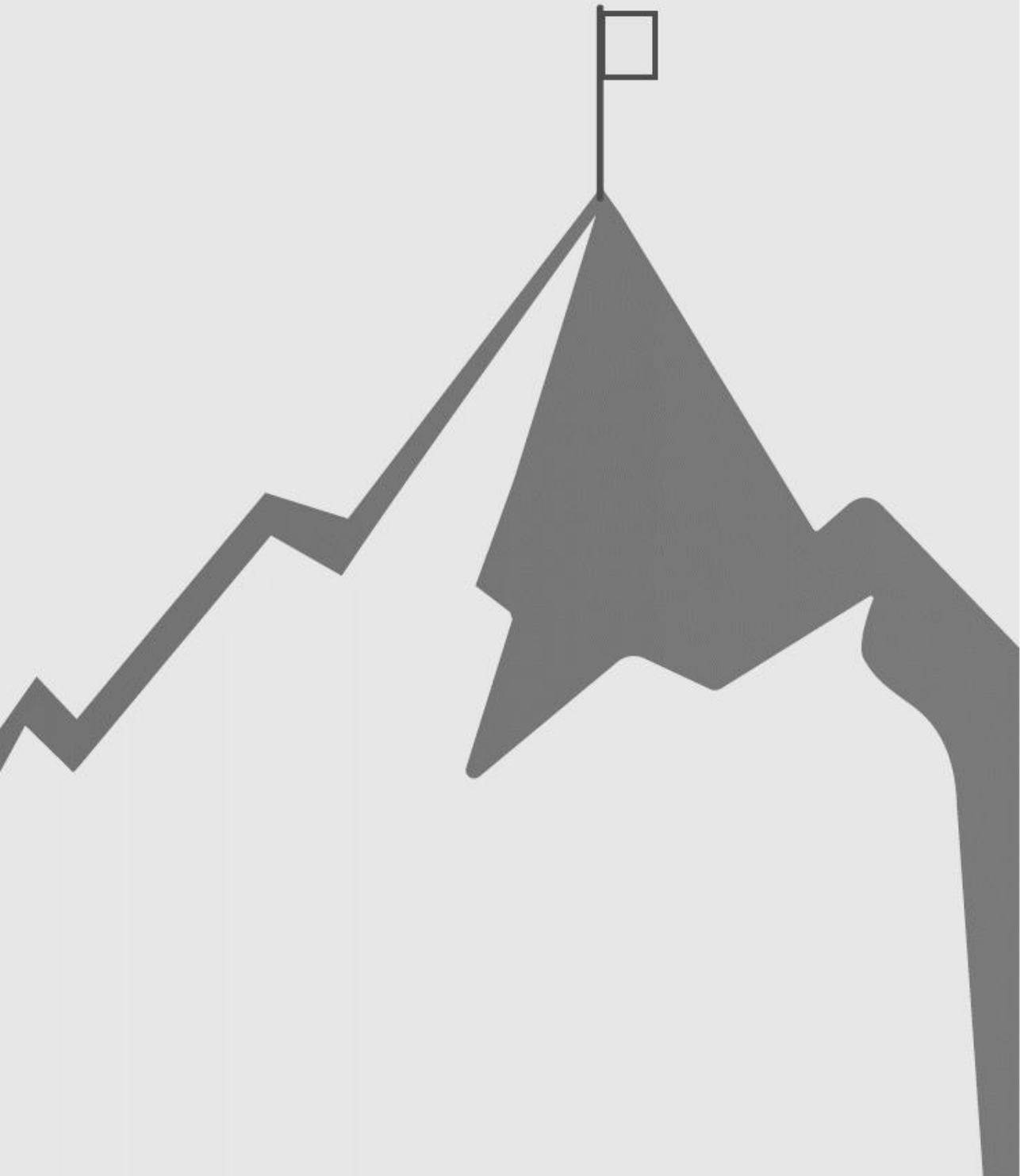

Chapter 4

Nifedipine versus atosiban for threatened preterm birth (APOSTEL III): a multicentre, randomised controlled trial

van Vliet EO, Nijman TA, Schuit E, Heida KY, Opmeer BC, Kok M, Gyselaers W, Porath MM, Woiski M, Bax CJ, Bloemenkamp KW, Scheepers HC, Jacquemyn Y, van Beek E, Duvekot JJ, Franssen MT, Papatsonis DN, Kok JH, van der Post JA, Franx A, Mol BW, Oudijk MA.

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Abstract

Background

In women with threatened preterm birth, delay of delivery by 48 h allows antenatal corticosteroids to improve neonatal outcomes. For this reason, tocolytics are often administered for 48 h; however, there is no consensus about which drug results in the best maternal and neonatal outcomes. In the APOSTEL III trial we aimed to compare the effectiveness and safety of the calcium-channel blocker nifedipine and the oxytocin inhibitor atosiban in women with threatened preterm birth.

Methods

We did this multicentre, randomised controlled trial in ten tertiary and nine teaching hospitals in the Netherlands and Belgium. Women with threatened preterm birth (gestational age 25–34 weeks) were randomly assigned (1:1) to either oral nifedipine or intravenous atosiban for 48 h. An independent data manager used a web-based computerised programme to randomly assign women in permuted block sizes of four, with groups stratified by centre. Clinicians, outcome assessors, and women were not masked to treatment group. The primary outcome was a composite of adverse perinatal outcomes, which included perinatal mortality, bronchopulmonary dysplasia, sepsis, intraventricular haemorrhage, periventricular leukomalacia, and necrotising enterocolitis. Analysis was done in all women and babies with follow-up data. The study is registered at the Dutch Clinical Trial Registry, number NTR2947.

Findings

Between July 6, 2011, and July 7, 2014, we randomly assigned 254 women to nifedipine and 256 to atosiban. Primary outcome data were available for 248 women and 297 babies in the nifedipine group and 255 women and 294 babies in the atosiban group. The primary outcome occurred in 42 babies (14%) in the nifedipine group and in 45 (15%) in the atosiban group (relative risk [RR] 0·91, 95% CI 0·61–1·37). 16 (5%) babies died in the nifedipine group and seven (2%) died in the atosiban group (RR 2·20, 95% CI 0·91–5·33); all deaths were deemed unlikely to be related to the study drug. Maternal adverse events did not differ between groups.

Interpretation

In women with threatened preterm birth, 48 h of tocolysis with nifedipine or atosiban results in similar perinatal outcomes. Future clinical research should focus on large placebo-controlled trials, powered for perinatal outcomes.

Funding

ZonMw (the Netherlands Organisation for Health Research and Development).

Introduction

Preterm birth is associated with 50% of neonatal morbidity and 50–75% of neonatal mortality worldwide and affects 5–13% of all pregnancies in high-income countries.[1-5] Additionally, preterm birth can cause long-term physical and developmental impairment and thereby has a substantial impact on infant, parents, families, and health-care costs.[1,2] To improve outcomes in preterm babies, women in labour before 34 weeks of gestation receive antenatal corticosteroids to enhance fetal lung maturation.[6] To allow optimal effect of maternal steroid administration, most perinatal centres attempt to delay birth by administrating tocolytic drugs for 48 h.[7] Previous meta-analyses have shown that tocolytic drugs are effective in delaying delivery by 48 h and 7 days.[8,9] Several types of tocolytic drugs are used as treatment in preterm labour, including β adrenoceptor agonists, cyclooxygenase inhibitors (COX), magnesium sulphate, calcium-channel blockers and oxytocin receptor antagonists. Uncertainty remains over which tocolytic should be drug of choice.

Studies of β adrenoceptor agonists have shown contradictory results for its ability to postpone delivery and decrease neonatal mortality compared with placebo and their use has been largely abandoned in clinical practice due to a substantial side-effect profile.[9,10] For COX inhibitors, no effect on perinatal mortality and morbidity has been reported and some concerns exist about potential adverse effects on neonatal outcomes; a recent meta-analysis found an increase in intraventricular haemorrhage, necrotising enterocolitis, and periventricular leukomalacia with administration of COX inhibitors compared with placebo.[11,12] For initial tocolysis, calcium-channel blockers or oxytocin antagonists for 48 h are recommended because they have the best efficacy to side-effect ratio; however it has not yet been established which drug leads to the best outcomes.[13-15] Three small randomised trials comparing the calcium-channel blocker nifedipine with the oxytocin antagonist atosiban have shown contradictory results.[16-18] One study (n=145) found a lower prevalence of delivery within 7 days, but a higher prevalence of delivery within 48 h after nifedipine tocolysis compared with atosiban.[18] The two other trials (n=80 and n=63) did not find a significant difference in the ability of either drug to delay delivery for 48 h.[16,17] Salim and colleagues showed a shorter length of stay at the neonatal intensive care unit for babies from women in the nifedipine group as compared with those from women in the atosiban group.[18] The two trials that reported on neonatal outcome did not show a significant difference, but were underpowered.[17,18]

Research in context

Evidence before this study

We searched Medline, Embase, and the Cochrane Library from inception until Nov 24, 2015, without language limitation. We used the following search strategy “atosiban AND nifedipi* AND tocoly*” and included randomised clinical trials comparing nifedipine and

atosiban as tocolytic therapy in women with threatened preterm birth. We excluded quasi-randomised trials. We found 223 records—48 articles in Medline, 162 articles in Embase, and 13 in the Cochrane Library. After reviewing manuscripts we found two trials meeting our inclusion criteria (Salim and colleagues, 2012; and Kashanian and colleagues, 2005). Both studies had a low risk of bias according to the Cochrane Collaboration's risk of bias tool. Outcome measures in the meta-analysis were neonatal mortality, prolongation of pregnancy in days, and prolongation of pregnancy by more than 48 h. No pooled estimate could be calculated for neonatal mortality because no babies died in the study by Salim and colleagues, and Kashanian and colleagues did not report this outcome. In the two studies, prolongation of pregnancy (days) was similar between nifedipine and atosiban groups (pooled mean difference −0·25 days, 95% CI −11·89 to 11·39; 225 women). Prolongation of pregnancy by more than 48 h also did not differ between nifedipine and atosiban groups (pooled relative risk [RR] 1·02, 95% CI 0·87–1·19; 225 women).

Added value of this study

Our study is the largest randomised trial to compare nifedipine and atosiban. Our primary outcome was a composite of adverse perinatal outcomes, which we believe is the most important outcome measure because improving neonatal outcome is the ultimate goal of tocolysis. Randomised trials published so far were not powered to detect differences in neonatal outcomes. We report similar adverse perinatal outcome rates in nifedipine and atosiban, as well as comparable delays in delivery for 48 h. Inclusion of our study data in meta-analysis with findings from Salim and colleagues showed a non-significant increase in neonatal death between nifedipine and atosiban treatment groups (pooled RR 2·12, 95% CI 0·88–5·13; 780 babies). In a meta-analysis including data from all three studies, prolongation of pregnancy in days remained similar between nifedipine and atosiban groups (pooled mean difference 0·54 days, 95% CI −5·67 to 6·76; 727 women), as did prolongation of pregnancy of more than 48 h (risk ratio 1·03, 95% CI 0·94–1·12; 727 women).

Implications of all the available evidence

Our study findings showed that tocolysis for 48 h with nifedipine or atosiban results in similar adverse perinatal outcome rates and prolongation of pregnancy. The choice between nifedipine and atosiban must be based on the effectiveness, safety, adverse effects, and costs of these tocolytic drugs. Further large placebo-controlled trials are needed to assess the effect of tocolytic drugs on perinatal outcomes.

In view of this uncertainty, we started the Assessment of Perinatal Outcome after Specific Tocolysis in Early Labour (APOSTEL-III) study, a multicentre randomised clinical trial in which we aimed to compare the calcium-channel blocker nifedipine with the oxytocin antagonist atosiban in women with threatened preterm birth.

Methods

Study design and participants

We did this multicentre, randomised controlled trial in 19 centres (ten tertiary care centres with a neonatal intensive care unit facility and nine secondary centres) in 18 cities in the Netherlands and Belgium that collaborate in the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology. The protocol has been published previously.[19] Women were eligible if they were aged 18 years or older and had threatened preterm birth at between 250/7 weeks and 340/7 weeks of gestation. Threatened preterm birth was defined as at least three uterine contractions per 30 min and presence of one of the following: cervical length of 10 mm or less, both a cervical length of 11–30 mm and a positive fetal fibronectin test, or presence of ruptured amniotic membranes. Women with singleton or multiple pregnancies were eligible. Exclusion criteria were a contraindication for tocolysis (severe vaginal bleeding or signs of intrauterine infection), hypertension or current use of antihypertensive drugs, history of myocardial infarction or angina pectoris, cerclage, cervical dilatation greater than 5 cm, tocolytic treatment for more than 6 h before arrival in a participating centre, or a previous episode of tocolytic treatment. Women with a fetus showing signs of fetal distress or a fetus suspected of chromosomal or structural anomalies were not included. Eligible women were identified and counselled by the local staff or research coordinators in the participating hospitals. This study was approved by the ethics committee of the Academic Medical Centre Amsterdam (reference number MEC AMC 09/258) and the boards of management of all participating hospitals. All women provided written informed consent.

Randomisation and masking

An independent data manager used a web-based computerised program to randomly assign women to nifedipine or atosiban in a 1:1 ratio, with assignment done in permuted blocks of four and stratified by centre. Because of the nature of the interventions, oral medication, and intravenous medication, clinical staff or women were not masked.

Procedures

In the nifedipine group, the initial dose was 20 mg nifedipine (two 10 mg capsules) orally in the first hour, followed by 20 mg slow-release nifedipine per 6 h for the next 47 h. In the first hour after the start of nifedipine administration, blood pressure and heart rate were measured every 15 min. If blood pressure remained within the normal limits,

treatment continued with blood pressure and heart rate measured four times every 24 h. In the atosiban group, women received a bolus injection of 6·75 mg intravenous in 1 min, followed by 18 mg/h for 3 h, followed by a maintenance dosage of 6 mg/h for 45 h. Antenatal corticosteroids were administered according to guidelines from the Dutch Society of Obstetrics and Gynecology (NVOG) for management of preterm birth, which advise antenatal corticosteroids to women with threatened preterm birth at less than 34 weeks gestation. We gave magnesium sulphate for neuroprotection to women with threatened preterm birth at less than 32 weeks gestation, according to guidelines from NVOG. The provision of prophylactic antibiotics was at the discretion of the attending physician.

Trained research staff documented demographic characteristics, obstetric and medical history, and data for pregnancy and delivery until the day of discharge from hospital of both mother and baby. Data were entered in an online electronic case report form by research nurses and midwives (Oracle Clinical version 4.5.3; Redwood City, CA, USA).
Bronchopulmonary dysplasia was diagnosed according to the international consensus guideline as described by Jobe and Bancalari at time of discharge home or at 36 weeks of corrected gestational age.[20] Culture-proven sepsis was diagnosed based on clinical signs and a positive culture of the blood sample. Intraventricular haemorrhage and periventricular leukomalacia were diagnosed by repeated neonatal cranial ultrasound by the neonatologist according to the guidelines on neuroimaging described by de Vries and colleagues and Ment and colleagues.[21,22] Necrotising enterocolitis was staged by methods reported by Bell.[23]

All perinatal deaths were assessed by a panel of two neonatologists and two consultant obstetricians who were not involved in the trial. The members individually reviewed all cases of perinatal death while remaining blinded to the administered study drug. They assessed whether the perinatal deaths could be causally related to the study drug using WHO categories of: certain, probable, possible, unlikely, conditional, and non-assessable.[24] When at least a 75% consensus was reached the conclusion was considered valid.

Outcomes
The primary outcome measure was a composite of adverse perinatal outcome composed of perinatal in-hospital mortality and the following severe perinatal morbidities: bronchopulmonary dysplasia, culture-proven sepsis, intraventricular haemorrhage higher than grade 2, periventricular leukomalacia higher than grade 1, and necrotising enterocolitis higher than Bell's stage 1. All babies with one or more of these outcomes before hospital discharge were deemed to have met the primary outcome criteria.

Prespecified secondary outcome measures on the maternal level were gestational age at delivery; time from randomisation to delivery (prolongation of pregnancy); and rates of maternal death and side-effects leading to discontinuation of study drug. Prespecified secondary outcomes on the neonatal level were the individual components of the composite perinatal outcome (bronchopulmonary dysplasia, culture-proven sepsis, intraventricular haemorrhage higher than grade 2, periventricular leukomalacia higher than grade 1, and necrotising enterocolitis higher than stage 1); days of stay in a neonatal intensive-care unit (NICU) after birth; days of ventilation support after birth; total days in hospital until corrected age 3 months; number of babies with apnoea; number of babies with asphyxia; number of babies with proven meningitis; number of babies with pneumothorax; and number of babies with convulsions. Secondary outcomes were assessed up to discharge of the baby from hospital unless otherwise specified.

Statistical analysis

We designed the trial to detect a reduction in the prevalence of the primary outcome from 25% to 15%. We calculated that we would need to enrol 500 women (250 in each group) to provide a power of 80% at a two-sided significance level of 0·05.

Primary and secondary outcomes were analysed in the modified intention-to-treat population; all women and babies with follow-up data were included. We assessed the primary outcome on a neonatal level with a generalised estimating equations model (GEEs) for binomial data with a log-link function and using an unstructured correlation matrix, resulting in a calculated relative risk (RR) and 95% CI. We accounted for interdependence between outcomes in multiple pregnancies by considering the mother as a cluster variable.[25] Secondary outcomes on the neonatal level were calculated in a similar way to the primary outcome. Continuous outcomes on the neonatal level were assessed with linear quantile mixed models with mother as the grouping variable, resulting in a median difference with 95% CI. Prolongation of pregnancy and gestational age at delivery were evaluated by Cox proportional hazards regression and Kaplan-Meier estimates, accounting for differing gestational age at entry, and tested with the log-rank test. Gestational age at delivery was censored at 37 weeks of gestation because the interest of the effectiveness of tocolytic therapy is mainly focused on preterm birth and not necessarily on overall gestational age at delivery. The proportional hazards assumption was verified by plotting Schoenfeld residuals over time.[26] Outcomes on the maternal level were assessed by a binomial regression model with log-link function.

We analysed the following subgroups: PPROM status (PPROM vs intact membranes), gestational age at randomisation (<30 weeks vs ≥30 weeks), number of fetuses (multiple vs singleton pregnancies), and history of preterm birth (yes vs no). Subgroup effects were investigated for adverse perinatal outcome and prolongation of pregnancy. Subgroup effects were assessed by including an interaction term between the subgrouping variable

and treatment allocation as covariate to the regression model. When the interaction term was statistically significant (pinteraction<0·05) a stratified subgroup analysis was done to study the effect of treatment in different strata of the subgroups. Furthermore, the effect of the treatment was assessed in women with a positive fibronectin test, and those with a cervical length <10 mm.

We did a planned interim analysis based on the outcomes of 145 women, at which the data safety monitoring committee noted no conditions to stop the trial. All analyses were adjusted for the interim analyses with the O'Brien-Fleming α spending function. As a result, we deemed a nominal p value of less than 0·049 as indicative of statistical significance. We corrected 95% CIs to account for this by using an α of 0·049 instead of 0·05 for their calculation.

Serious adverse events (perinatal death, maternal mortality or severe maternal morbidity, including intensive-care unit admission) were reported to the central committee on research involving human subjects and to the ethics committee of the Academic Medical Centre, Amsterdam. We analysed data with R, version 3.1.1; specifically, we did GEE using the gee library and did linear quantile mixed models using the lqmm library. We used a data safety and monitoring committee composed of four independent academics from the Acadamic Medical Centre, Amsterdam and the University Medical Centre, Leiden. The study is registered at the Dutch Clinical Trial Registry, number NTR2947.

Role of the funding source

The funder of the study, ZonMw, had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 6, 2011, and July 7, 2014, we enrolled 510 women. We randomly assigned 254 women to the nifedipine group and 256 to the atosiban group (figure 1, table 1). The last measure of outcomes was on Sept 11, 2014. Outcome data were available for 248 women in the nifedipine group and 255 in the atosiban group, corresponding to 297 and 294 babies, respectively (figure 1).

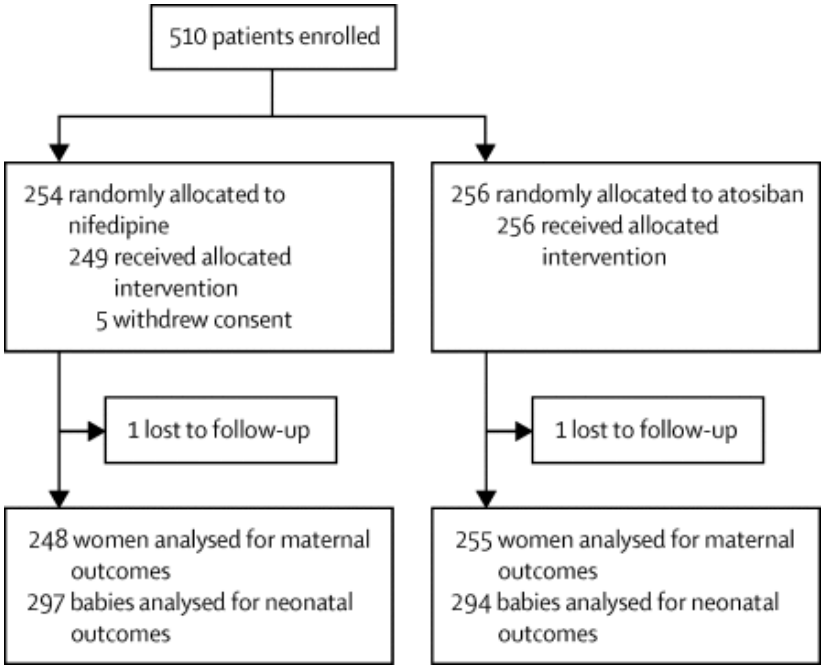

Figure 1. Study Profile

In the primary analysis, 42 (14%) of 297 babies in the nifedipine group and 45 (15%) of 294 in the atosiban group had the adverse perinatal outcome (RR 0·91, 95% CI 0·61–1·37; table 2). Gestational age at delivery was similar between the groups (table 2). Median prolongation of pregnancy was 7 days (IQR 1·0–40·0) for women in the nifedipine group and 4 days (1·0–38·0) for those in the atosiban group, with the Kaplan-Meier curve of time to pregnancy showing no significant difference (figure 2). The Schoenfeld residuals for gestational age at delivery and prolongation of pregnancy showed a random pattern with time, indicating the proportional hazards assumption is realistic (data not shown).

Table 1. Baseline characteristics

	Nifedipine group (n=249)	Atosiban group (n=256)
Age (years)	30·7 (26·2–34·0)	30·2 (27·2–33·0)
Body-mass index (kg/m^2)*	23·1 (20·8–25·8)	22·8 (20·6–25·6)
White race	180/220 (82%)	184/227 (81%)
Nulliparous	160/248 (65%)	170/255 (67%)
Previous preterm birth	33 (13%)	30 (12%)
Gestational age at study entry (weeks)	30·3 (28·4–32·1)	30·3 (28·1–31·7)
Multiple pregnancy		
Twin	49 (20%)	37 (14)
Triplet	0	1 (<1%)
PPROM at study entry	85/248 (34%)	88/255 (35%)
Previous tocolytic treatment	47/244 (19%)	61/255 (24%)
Vaginal examination at study entry	114/245 (47%)	122/256 (48%)
Dilatation (cm)†	1 (1–2)	1 (1–2)
Cervical length (mm)‡	15 (9–22)	14 (8–23)

Data are median (IQR), n (%), or n/N (%). PPROM = preterm prelabor rupture of membranes.
* n=198 for nifedipine group and n=207 for atosiban group; † n=112 for nifedipine group and n=121 for atosiban group; ‡ n=159 for nifedipine group and n=153 for atosiban group.

The individual rates of bronchopulmonary dysplasia, sepsis, intraventricular haemorrhage, periventricular leukomalacia, and necrotising enterocolitis were similar between groups (table 2). 16 (5%) babies died in the nifedipine group and seven (2%) babies died in the atosiban group (RR 2·20, 95% CI 0·91–5·33). A panel of experts independently assessed these deaths and classified all as unlikely to be caused directly by the study drug (appendix).

In the nifedipine group, 155 (52%) babies were admitted to the NICU, compared with 182 (62%) in the atosiban group (RR 0·85, 95% CI 0·73–0·99, table 2). 42 (14%) of the babies in the nifedipine group needed ventilation support, compared to 53 (19%) babies in the atosiban group (RR 0·76, 95% CI 0·51–1·12). Days on ventilation, time in hospital, and rates of apnoea, asphyxia, meningitis, and pneumothorax in babies also did not differ (table 2). We did not collect data for convulsions because the study group decided it was not clinically relevant.

Table 2. Perinatal outcomes

	Nifedipine group	Atosiban group	RR, HR, or difference (95% CI)
Perinatal outcomes			
Number of babies analysed	297	294	..
Adverse perinatal composite outcome (primary analysis)	42 (14%)	(15%)	RR 0·91 (0·61–1·37)
Perinatal death	16 (5%)	7 (2%)	RR 2·20 (0·91–5·33)
Bronchopulmonary dysplasia	11 (4%)	21 (7%)	RR 0·55 (0·27–1·15)
Culture-proven sepsis	25 (8%)	25 (9%)	RR 0·97 (0·55–1·70)
Intraventricular haemorrhage (grade >2)	5 (2%)	2 (1%)	RR 2·47 (0·48–12·75)
Periventricular leukomalacia (grade >1)	1 (<1%)	2 (1%)	RR 0·49 (0·05–5·46)
Necrotising enterocolitis (stage >1)	7 (2%)	4 (1%)	RR 1·72 (0·51–5·83)
NICU admittance	155 (52·2)	182 (61·9)	RR 0·85 (0·73–0·99)
Length of admission at NICU (days)	17 (7·0–43·0)	17 (7·0–39·8)	Difference −1 (−5·52 to 3·52)
Ventilation support*	42 (14%)	53 (19%)	RR 0·76 (0·51–1·12)
Time on ventilation support (days)*	3 (1·3–9·5)	3 (1·0–8·0)	Difference −0·33 (−2·82 to 2·16)
Total days in hospital until 3 months corrected age	24 (5·0–46·0)	28 (9·0–52·0)	Difference −2·88 (−8·37 to 2·61)
Apnoea	20 (7%)	25 (9%)	RR 0·73 (0·41–1·32)
Asphyxia	2 (1%)	2 (1%)	RR 0·99 (0·14–7·06)
Proven meningitis	5 (2%)	2 (1%)	RR 2·44 (0·48–12·49)
Pneumothorax	2 (1%)	5 (2%)	RR 0·40 (0·08–2·04)
Maternal outcomes			
Number of women analysed	248	255	..
Gestational age at delivery (weeks)	33·1 (30·5–37·0)	32·4 (30·1–35·8)	HR 0·86 (0·70–1·05)
Prolongation of pregnancy (time to delivery)			
Continuous (days)	7 (1·0–40·0)	4 (1·0–38·0)	HR 0·88 (0·72–1·07)
≥48 h	169 (68%)	168 (66%)	RR 1·04 (0·92–1·17)
≥7 days	127 (51%)	116 (45%)	RR 1·13 (0·94–1·36)
Maternal deaths	0	0	..
Discontinuation of study drug	74/248 (30%)	75/253 (30%)‡	RR 1·01 (0·77–1·32)
Due to progression to labour†	66/248 (27%)	70/253 (28%)‡	RR 0·97 (0·73–1·30)
Due to side-effects†	15/248 (6%)	7/253 (3%)‡	RR 2·20 (0·91–5·33)
Unknown†	2/248 (1%)	2/253 (1%)‡	..

Outcome data are n (%), n/N (%), or median (IQR). RR=relative risk. HR=hazard ratio. NICU=neonatal intensive care unit.

* n=292 for nifedipine and n=286 for atosiban; † Study drug could be discontinued for more than one reason;

‡ Two women in the atosiban group had missing data.

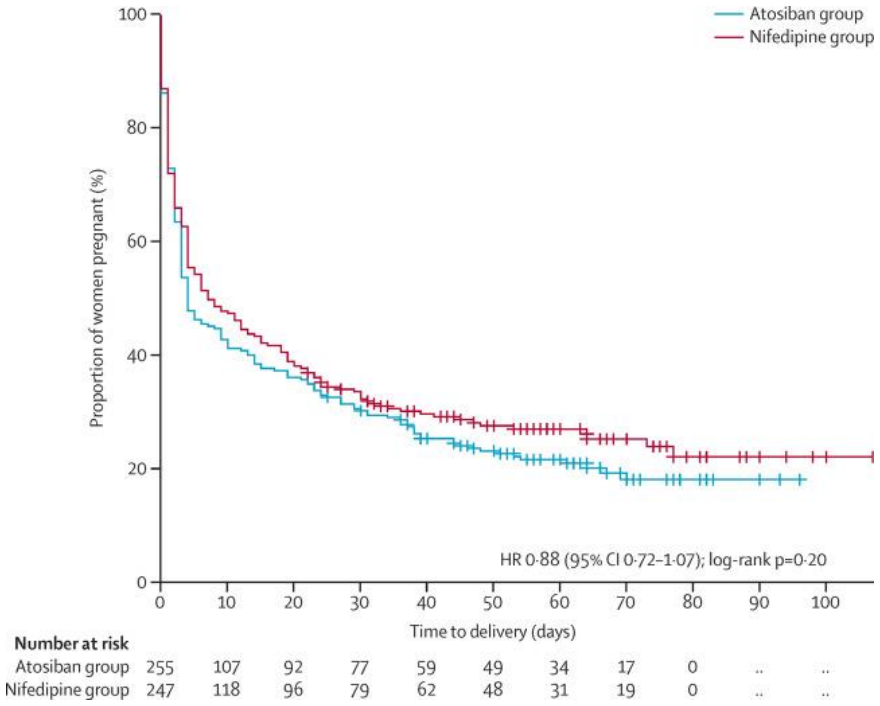

Figure 2. Time to delivery

No women died. 74 women (30%) in the nifedipine group and 75 (29%) in the atosiban group discontinued the study drug (RR 1·01, 95% CI 0·77–1·32), mainly due to progression into labour (table 2). Side-effects leading to discontinuation of study drug were reported in 15 (6%) women in the nifedipine group and seven (3%) in the atosiban group (table 2). Side-effects and adverse events in women were similar between group assignments and are listed in table 3.

In women without PPROM at study entry, time to delivery was longer in women assigned to treatment with nifedipine (median 24 days, IQR 4·0–54·8) than for those assigned to atosiban (14 days, 2·0–51·5; figure 3; appendix). Adverse perinatal outcome rates did not differ between group assignments in women with and without PPROM (RR 0·90, 95% CI 0·56–1·43). No significant interactions were found between drug allocation and the adverse perinatal outcomes or prolongation of pregnancy for the other subgroups (appendix); hence no effect sizes were calculated in different strata of the subgroups. No significant effects of treatment assignment were found in women with a positive fibronectin test or a cervical length smaller than 10 mm (appendix).

Table 3. Adverse events in women

	Nifedipine group (n=248)	Atosiban group (n=255)
Side-effects leading to discontinuation of study drug		
Signs of fetal asphyxia	1 (<1%)	2 (1%)
Suspected intrauterine infection	6 (2%)	1 (<1%)
Maternal liver disease	1 (<1%)	0
Other	11 (4%)	4 (2%)
Progression into labour	66 (27%)	70/253 (28%)*
Complications after randomisation		
Hypotension	0	1 (<1%)
Hypertension	8 (3%)	8 (3%)
PE/HELLP	3 (1%)	2 (1%)
Eclampsia	0	1 (<1%)
Pregnancy diabetes	1 (<1%)	3 (1%)
IUGR	2 (2%)	5 (2%)

Data are n (%) or n/N (%). PE=preeclampsia. HELLP=haemolysis elevated liver enzymes and low platelets. IUGR=intrauterine growth restriction.

* Two women in the atosiban group had missing data.

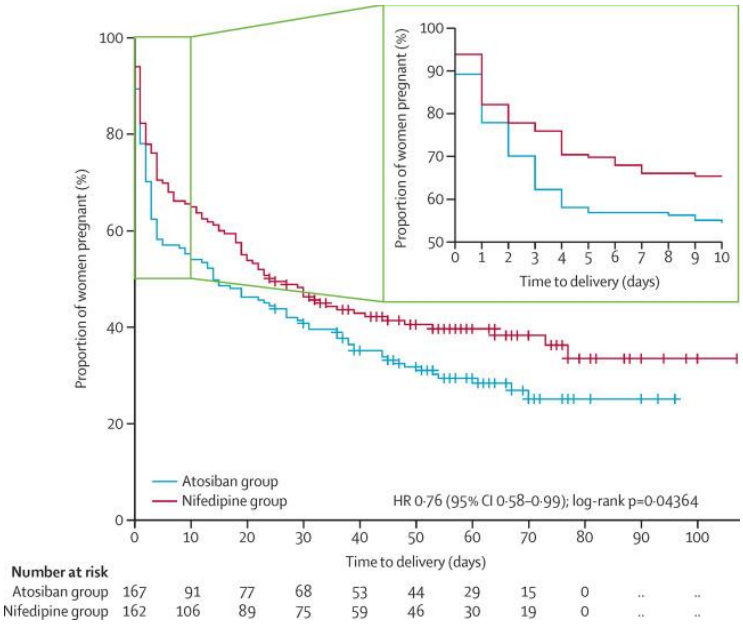

Figure 3. Time to delivery in women without PPROM

Discussion

In this multicentre, randomised controlled trial, we show that 48 h of tocolysis with nifedipine and atosiban resulted in similar rates of adverse perinatal outcomes in babies born to women with threatened preterm birth. Unexpectedly, a non-significant higher perinatal mortality rate was found in the nifedipine group (table 2). This finding is of concern and warrants more investigation into the use of this tocolytic drug. Almost all neonatal and maternal secondary outcomes were similar; however, NICU admittance rates were lower in the nifedipine group (52%) than in the atosiban group (62%; RR 0·85, 95% CI 0·73–0·99).

Our study has several strengths. First, our primary outcome measure reflects the main goal of tocolysis, which is to improve neonatal outcome and not prolongation of pregnancy in itself. Previous trials on this topic were not sufficiently powered to examine neonatal outcomes.[16-18] Second, to our knowledge this is the largest randomised controlled trial to directly compare the effectiveness and safety of the widely used tocolytic drugs nifedipine and atosiban in a multicentre setting. Third, we aimed to include women at high risk of preterm delivery. Indeed, more than half of the women in our study delivered within 7 days after inclusion, and more than 75% delivered preterm, a contrast with previous trials in which most women did not deliver shortly after randomisation.[17,18]

Our study also has some limitations. Because of the different administration routes of the interventions (oral vs intravenous), our study was not masked. This factor might have caused bias, although it is unlikely to have an impact on the main outcomes of the study since all women received an active drug and since our outcome measures could be objectively assessed. Second, perinatal death was part of our composite outcome measure. Although the use of a composite outcome is common practice and can help to make statistically reliable comparisons with a smaller population, it also has a limitation since it ignores clinical differences in the components of the composite outcome, and considers more severe (eg, death) and less severe outcomes (eg, bronchopulmonary dysplasia) as equal. Also, certain mechanisms can have different effects on parts of the composite outcome; for example, prolongation of pregnancy could improve respiratory perinatal outcome but lead to more fetal deaths due to circulatory instability. Our study was not powered to reliably assess the treatment effect on the level of the individual components of the composite outcome.

Subgroup analyses showed a longer duration of pregnancy in women without ruptured membranes who were treated with nifedipine (appendix). However, this prolongation of pregnancy did not improve perinatal outcomes. A statistically non-significant, but possibly clinically relevant, increase in neonatal death was noted in the nifedipine group, although the expert panel could not find a direct causal association between the drugs and mortality (table 2; appendix). It could be postulated that the administration of nifedipine in pregnant women has an adverse effect on the fetus, for example by lowering maternal

blood pressure and reducing placental perfusion. Animal studies have described changes in uterine blood flow and occurrence of fetal acidaemia, but studies in humans showed no adverse effects on umbilical artery blood flow or fetal movements.[28-35] Investigators have reported fetal death after tocolysis with nifedipine, most likely due to maternal hypotension.[36] A prospective cohort study from the Netherlands and Belgium concluded that maternal adverse events, mainly hypotension and tachycardia, were more frequent with the use of nifedipine.[37] In our study, no severe maternal side-effects were observed and review of the charts of the perinatal deaths did not reveal any deaths in which mothers had severe hypotension (appendix). However, the safety of nifedipine in pregnancy has not been studied extensively, and worldwide nifedipine is not registered for use in pregnancy.[38] This fact is of concern, especially since nifedipine is recommended as a first-line tocolytical drug in international guidelines.[39,40] Since our expert panel could not find a direct causal association between the drug and deaths, we could not find evidence in our study for a clinical effect of the proposed pathophysiological mechanism.

Atosiban has a favourable reported adverse event profile and is registered for the use in pregnancy in many countries; however, it is not readily available throughout the world. The costs of atosiban also exceed the costs of other tocolytic drugs such as nifedipine. Most importantly, the debate about the effectiveness and safety of tocolysis in general is inconclusive. There is little proof that tocolysis, and thereby prolongation of pregnancy in threatened preterm birth in general, improves perinatal outcome and it might even be harmful.[13,41] This dearth was recognised by an international panel of experts who advised in the new WHO guidelines against the use of any tocolytics other than to facilitate intrauterine transfer.[42] We therefore recommend the initiation of large placebo-controlled trials to assess treatment of preterm labour, with adverse perinatal outcome being the primary outcome.

Appendix

Analysis of perinatal mortality/ Serious adverse events

A panel of experts independently assessed the cases of perinatal mortality, and classified all of the cases as unlikely to be caused directly by the study medication. Among the deceased infants, GA at birth was comparable between the groups (median (IQR) of 27·0 (26·3–28·2) weeks in the nifedipine group and 28·3 weeks (25·7–29·9) in the atosiban group). Prolongation of pregnancy was comparable between the 2 groups (median (IQR) 36·0 hours (11·3–87·0) for nifedipine versus 42·0 hours (15·0–320·0) for atosiban). Two infants died in utero or during delivery. For the deceased children, the median time between birth and death was 6 days for the nifedipine group (range 0–40 days) and 5 days for the atosiban group (range 0–45 days). Six (38%) of the deceased infants in the nifedipine group were multiples, versus 2 (29%) in the atosiban group. Five infants died because of lethal congenital malformations not known at the time of inclusion (three in the nifedipine group and two in the atosiban group). None of the mothers or neonates had clinically relevant hypotension (difference in systolic or diastolic blood pressure > 20mmHg).

Table 1. Analysis of perinatal mortality

	Nifedipine (n=16)	**Atosiban (n=7)**
GA at birth, weeks, median (IQR)	27·0 (26·3–28·2)	28·3 (25·7–29·9)
Prolongation of pregnancy, hours	36·0 (11·3–87·0)	42·0 (15·0–320·0)
Interval from birth to death, days, median (IQR)	6 (2–16)	5 (3–15)
Crossover, n (%)	1 (6%)	1 (14%)
Multiples, n (%)	6 (38%)	2 (29%)
Congenital malformations, n (%)	3 (19%)	2 (29%)
Completed course corticosteroids, n (%)	8 (50%)	3 (43%)

Subgroup analysis

	Nifedipine group n = 248	Atosiban group n = 255	Relative risk (95% CI) or $p_{interaction}$
Adverse perinatal outcome (neonatal level)			
Ruptured membranes at study entry			$p_{interaction}$=0·98
Yes	12/100 (12%)	14/106 (13%)	
No	29/196 (15%)	31/188 (16%)	
Gestational age at randomisation			$p_{interaction}$=0·62
<30 weeks	33/132 (25%)	36/136 (26%)	
≥30 weeks	7/158 (4%)	9/158 (6%)	
Positive fibronectin test	7/69 (10%)	8/78 (10%)	RR 0·99 (0·37–2·62)
Cervical length <10mm	14/62 (23%)	9/57 (16%)	RR 1·43 (0·67–3·08)
Multiple pregnancy			$p_{interaction}$=0·83
Yes	14/98 (14%)	11/77 (14%)	
No	28/199 (14%)	34/218 (16%)	
Previous preterm birth			$p_{interaction}$=0·10
Yes	2/34 (6%)	7/33 (21%)	
No	40/263 (15%)	38/260 (15%)	
Prolongation of pregnancy (maternal level)			
Ruptured membranes at study entry			$p_{interaction}$=0·0412
Yes (n=173)	2·0 (0·0–5·3)	3·0 (1·0–6·0)	HR 1·22 (0·90–1·6)
No (n=329)	24 (4·0–54·8)	14 (2·0–51·5)	HR 0·76 (0·58–0·99)
Gestational age at randomisation			$p_{interaction}$=0·21
<30 weeks (n=228)	12·5 (2·0–58·8)	10·0 (2·0–54·0)	
≥30 weeks (n= 274)	5·0 (1·0–32·0)	3·0 (1·0–24·5)	
Positive fibronectin test (n=130)	41·0 (12·0–66·0)	38·0 (4·0–59·5)	HR 0·73 (0·46–1·16)
Cervical length <10mm (n=97)	6·0 (1·0 – 42·0)	2·0 (1·0–12·8)	HR 0·70 (0·45–1·08)
Multiple pregnancy			$p_{interaction}$=0·23
Yes (n =87)	4 (1·0–24·5)	3·5 (1·0–20·3)	
No (n=415)	8·5 (1·0–45·0)	4·0 (1·0–44·0)	
Previous preterm birth			$p_{interaction}$=0·61
Yes (n=62)	30·0 (9·5–64·5)	4·5 (2·0–33·3)	
No (n=438)	6·0 (1·0–36·5)	4·0 (1·0–38·0)	

Outcome data are n/N (%) or median (IQR). RR=relative risk. HR=hazard ratio. Indicates the effect of treatment assignment on the neonatal or maternal level outcome.

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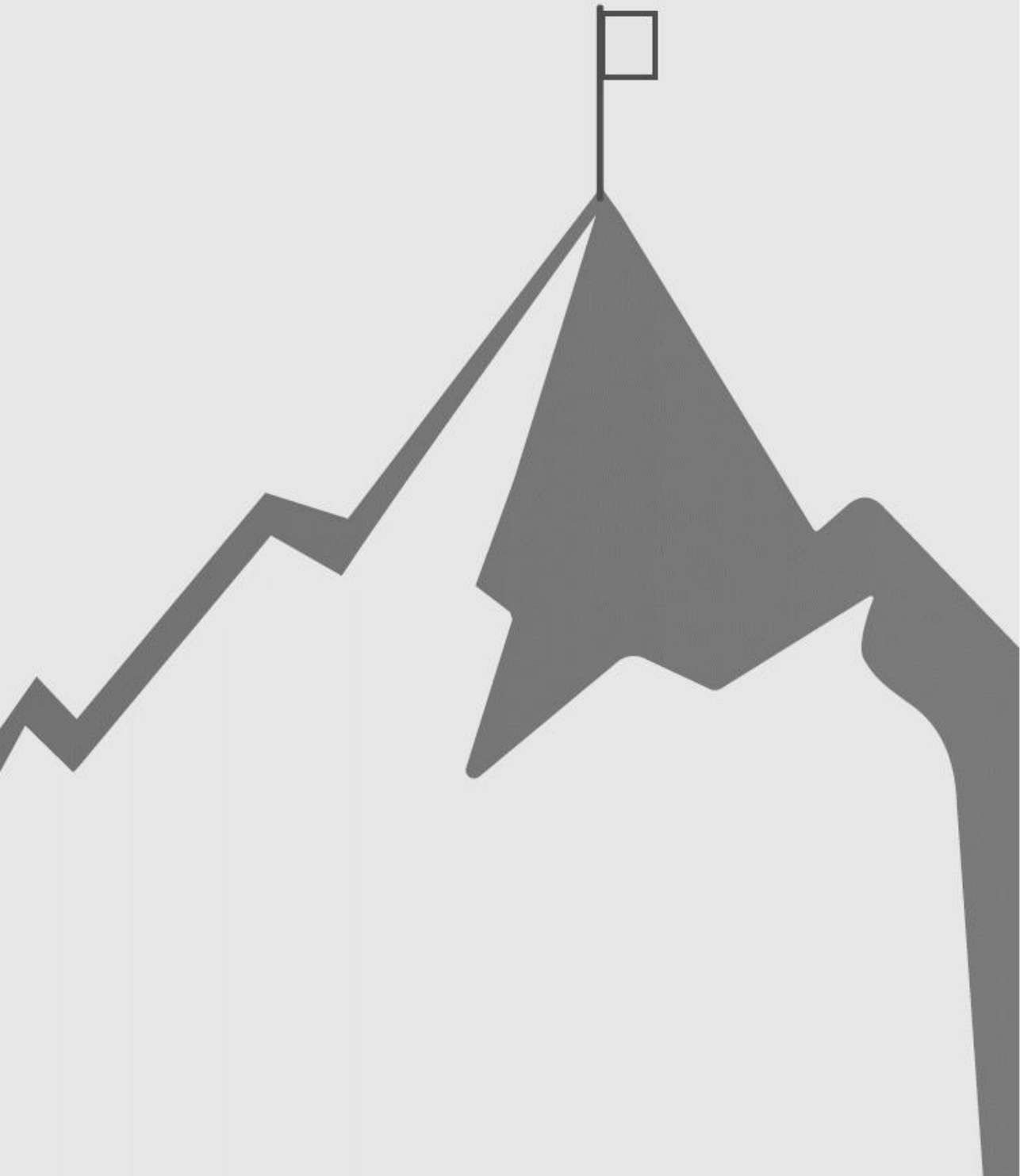

Chapter 5

Cost effectiveness of nifedipine compared to atosiban in the treatment of threatened preterm birth (APOSTEL III trial)

T.A.J. Nijman, G.J. van Baaren, E.O.G. van Vliet, M. Kok, W. Gyselaers, M.M. Porath,M. Woiski, C.J. Bax, K.W.M. Bloemenkamp, A. Franx, B.W. Mol, M.A. Oudijk

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Abstract

Objective
To assess the cost-effectiveness of treatment with nifedipine compared to atosiban in women with threatened preterm birth.

Design
An economic analysis alongside a randomized clinical trial (the APOSTEL III study).

Setting
Obstetric departments of ten academic hospitals and nine non-academic hospitals in the Netherlands and Belgium

Population
Women with threatened preterm birth between 25 and 34 weeks of gestation, randomized for tocolysis with nifedipine or atosiban

Methods
The economic analysis assessed the costs in the time between of randomization and 6 weeks postpartum

Main Outcome Measures
Primary outcome was a composite of adverse perinatal outcomes. Incremental cost-effectiveness ratios were calculated, which represent the costs to prevent one adverse neonatal outcome. The analysis was performed from a societal perspective.

Results
Mean costs per patient in the nifedipine group (n = 248) and atosiban (n = 255) were €45 476 versus €51 064, respectively (mean difference €5 588 in favor of nifedipine (95% confidence interval –13 448 to 1 618)). The difference in costs was mainly driven by a lower neonatal intensive care unit admission (NICU) rate in the nifedipine group of 52.2% compared to 61.9% (RR 0.85; 95% CI 0.73-0.99) in the atosiban group. Incremental cost-effectiveness ratios showed no differences in the primary outcome, although costs were higher for atosiban.

Conclusions
Treatment with nifedipine in women with threatened preterm birth results in lower costs when compared to treatment with atosiban, therefore atosiban does not seem to be a cost effective strategy. However, the safety of nifedipine warrants further investigation.

Introduction

Preterm birth is a major contributor to perinatal morbidity and mortality. Preterm born infants are at high risk for complications in both early and later life. These complications, including short term complications such as infection, intraventricular hemorrhage and necrotizing enterocolitis and long term complications such as neurodevelopmental problems and disability, put a major burden on the national healthcare. Worldwide, around 11% of the children are born preterm every year, which comes down to approximately 15 million children.[1]

For threatening preterm birth diagnosed or suspected prior to 34 weeks gestation most current guidelines recommend a 48-hour course of antenatal corticosteroids to improve neonatal outcome.[2-4] To allow administration of corticosteroids, tocolytic therapy is administered for 48 hours in most countries. Which tocolytic drug is most effective and safe is still questionable. Therefore the APOSTEL III trial (Assessment of Perinatal Outcome by use of Specific Tocolysis in Early Labour) was performed. Results were recently published in the Lancet.[5] In this trial we compared the effectiveness and safety of nifedipine and atosiban, two widely used tocolytic drugs, in women with threatened preterm birth. Primary outcome was a composite of adverse neonatal outcome. Results showed a comparable composite adverse neonatal outcome. A statistically non-significant higher perinatal mortality (one of the components of the composite outcome) was observed in children exposed to nifedipine. Children exposed to nifedipine had significant less neonatal intensive care unit (NICU) admissions compared to children exposed to atosiban. In the United States alone, preterm birth was estimated to cost over $26 billion annually.[6] Prevention of preterm birth or improvement of neonatal outcomes could decrease these costs. Furthermore expensive but ineffective healthcare management leads to higher costs.[7] Therefore not only clinical but also the economic aspects of our trial are important to assess. We performed an economic analysis comparing costs and effects of the treatment with nifedipine and atosiban in women with a threatened preterm birth.

Methods

Study design

We performed an economic analysis alongside the APOSTEL III trial. The study protocol and results of this trial have been published previously.[5,8] The study was approved by the ethics committee of the Academic Medical Centre Amsterdam (Reference number MEC AMC 09/258) and the boards of management of all participating hospitals. It was conducted in 19 centers (9 secondary and 10 tertiary care centers) in the Netherlands and Belgium that collaborate in the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology (www.studies-obsgyn.nl). The study was registered at the Dutch Clinical Trial Registry as NTR2947. This study was funded by ZonMw, the Dutch

Organization for Health Research and Development Healthcare Rational Medicine program, grant number 836011005.
The APOSTEL III trial included women with a gestational age between 25 and 33+6 weeks and a threatened preterm birth. Threatened preterm birth was defined as at least three uterine contractions per 30 minutes, and one of the following items: 1) cervical length of ≤ 10 mm, or 2) a cervical length of 11-30 mm and a positive fetal fibronectin test, or 3) ruptured amniotic membranes. Both women with a singleton and a multiple pregnancy were included. Women were randomized to treatment with either nifedipine or atosiban for 48 hours. Treatment schedule is enclosed as Appendix I. The primary outcome was a composite of adverse perinatal outcome, including perinatal mortality and severe perinatal morbidity (bronchopulmonary dysplasia (BPD), culture proven sepsis, intraventricular hemorrhage > grade 2, periventricular leukomalacia (PVL) > grade 1, and necrotizing enterocolitis (NEC) > stage 1).

Outcome data were available for 248 women in the nifedipine group and 255 women in the atosiban group, resulting in 297 and 294 neonates, respectively. The occurrence of the primary outcome was similar between nifedipine and atosiban (42 children (14.1%) in the nifedipine group and 45 (15.3%) in the atosiban group (relative risk (RR) 0.91; 95% confidence interval (CI) 0.61-1.37). Perinatal mortality occurred in 16 children (5.4%) in the nifedipine group compared to seven children (2.4%) in the atosiban group (RR 2.20; 95% CI 0.91-5.33). Fewer neonates were admitted to the NICU in the nifedipine group (155 neonates (52.2%) compared to 182 neonates (61.9%) in the atosiban group (RR 0.85; 95% CI 0.73-0.99)). The length of NICU stay was comparable (median (IQR) 17 days (7.0-43.0) in the nifedipine group versus 17 days (7.0-39.8) in the atosiban group (median difference (95% CI) -1 (-5.52-3.52)).

Economic evaluation
This economic analysis was set up as a cost effectiveness analysis with the composite adverse perinatal outcome as effectiveness measure. We used a societal perspective including effects and direct medical costs between the time of randomization and discharge of the neonate(s), and costs concerning travel and productivity loss. Discounting of costs was not necessary since all costs occurred within one year (2013).[9,10] This economic analysis, including estimation of unit costs is based on the Dutch guidelines for economic evaluations.[11]

Resource use
We collected required data for the resource use in the web-based Case Report Form used for the primary analysis as well. The antepartum/delivery phase we included the use of tocolysis (either atosiban or nifedipine), antibiotic therapy, analgetics during labor, mode

of delivery, manual placental removal and blood transfusions. Antepartum maternal admissions (home care, ward, medium care or intensive care) were combined with postpartum admissions. Obstetric procedures, e.g. vaginal delivery, instrumental delivery, Cesarean section were counted separately to compare the resource between the groups. For twin pregnancies, deliveries were counted as shown in table 1. Furthermore we included neonatal admission (ward, medium care of intensive care), days of neonatal intubation, days of continuous positive airway pressure (CPAP), surfactant use, travel costs and maternal productivity loss. Each day of neonatal or maternal admission was calculated according the level of care: home-care, ward, medium care or intensive care. For twins pregnancies total costs of both children were summed up. Extra costs for admission of the neonates to the maternal ward were not added, since we assumed that these extra costs were included in maternal admission costs.

Unit costs

Unit costs were estimated using different methods and sources, all in line with recent guidelines on costs in healthcare services (table 2).[11,12] Unit costs were expressed in € (2013 value) using the consumer pricing index.[13] We retrieved unit cost estimates for maternal and neonatal admissions from the financial departments of one participating academic hospital and one participating non-academic hospital, subtracting costs not applicable to our population (top-down calculation). Mean costs from academic and non-academic hospital were used. Medication prices were obtained from the Dutch drug registry.[14] The value of productivity loss was calculated using the friction method. This method assumes that workers who are withdrawn from work because of ill health, or an admitted child, will be replaced after an adaption period, this is called the friction period. In this case the fiction period is set at 10 weeks, so the productivity loss is limited to a period of 10 weeks. Maternity leave was taken into account.[11] There were no data concerning the father. Travel costs were calculated using standard distances and costs retrieved from Dutch guidelines on costs in healthcare services.[11]

Statistical analyses

Analyses were performed according the intention-to-treat principle. To assess differences in resource use we used non-parametric Mann-Whitney U-test. Costs were calculated by multiplying the quantity of resource use and unit costs. Mean and median costs were calculated for the total trial period and split in antepartum/delivery phase and postpartum phase. To combine the costs with primary outcome (adverse perinatal outcome rate), incremental cost-effectiveness ratios (ICERs) were calculated. An ICER was defined as the ratio of the difference in costs and the difference in effectiveness between nifedipine and atosiban.[9,15] An ICER reflects the costs needed to prevent one composite adverse perinatal outcome by use of atosiban. To determine the 95% CI around the difference in mean costs

and ICERs we used non-parametric bootstrapping. For this we used 1000 non-parametric bootstrap replications with the replacement from the original data and calculating the statistic of interest (mean costs and effects, and ICERs).[15] Uncertainty in the main results was visualized by plotting the cost-effectiveness plane and cost-effectiveness acceptability curves.[16]

Table 1. Mode of delivery

Mode	**Counted**
V/V	1 V
V/I	1 V / 1 I
V/C	1 V / 1 C
I / V	1 I / 1 V
I / I	1 I
C / C	1 C
V: vaginal; I: instrumental; C: Cesarean section	

Sensitivity and scenario analysis

To test the robustness of our findings we performed multiple sensitivity analyses. In six univariate analyses we examined the influence of assumptions and unit cost estimates, mostly in hospital admissions, for both mother and the neonates. In model 1 and 2 we estimated cost differences in academic and non-academic setting. Since multiple pregnancies were included we tested cost differences for singleton and multiple pregnancies separated in model 3 and 4. In model 5 and 6 we tested for differences in gestational age at delivery. In model 5 we analyzed neonates born > 30 weeks of gestation and in model 6 neonates born ≤ 30 weeks of gestation. All analyses were performed in SPSS version 20.0 (Chicago, IL, USA) and Microsoft Excel 2003.

Results

A total of 510 women were enrolled in the trial, of whom 254 to nifedipine and 256 to atosiban. Due to withdrawal of informed consent (n = 5, in the nifedipine group) and two patients losses-to-follow-up (one in both groups) 503 women were available for the economic evaluation, 248 in the nifedipine group and 255 in the atosiban group, resulting in 297 and 294 children, respectively. Average volumes of resources used and total costs in both groups are presented in Table S1 (Appendix 1).

Resource use

Regarding antepartum/delivery resource use, women allocated to nifedipine received tocolysis for a significant shorter time compared to women in the atosiban group (mean 36.2 hours versus 38.4 hours, $p < 0.01$). Other differences in antepartum/delivery resource

Table 2. Costs analysis: units of resource, unit costs, valuation method and volume source.

Variable	Unit	Unit cost (€)*	Valuation method (source)
Admission (mother)			
Ward	Day	391†	Top-down calculation
Medium care	Day	594†	Top-down calculation
ICU	Day	1 895†	Top-down calculation
Admission (child)			
Maternal ward	Day	391†	Top-down calculation
Medium care	Day	594†	Top-down calculation
Neonatal ICU	Day	1 647†	Top-down calculation
Medication			
Tocolysis Nifedipine Atosiban	Per 48 hours	 0.64 668	Dutch Pharmacotherapeutic Compass[13]
Antibiotic therapy	Treatment	34	Dutch Pharmacotherapeutic Compass[13]
Delivery			
Vaginal delivery	Procedure	1 199†	Top-down calculation
Instrumental delivery	Procedure	1 417†	Top-down calculation
Cesarean section	Procedure	2 115†	Top-down calculation
Manual removal placenta	Procedure	179†	Top-down calculation
Transfusion	Gift	219	Dutch costing guideline[11]
Analgetics during labour			
Pethidine	Treatment	3	Dutch Pharmacotherapeutic Compass[13]
Spinal/epidural	Treatment	182	Top-down calculation
Remifentanyl	Treatment	137	Dutch Pharmacotherapeutic Compass[13]
Extra care			
Intubation	Day	113	Dutch Health Authority Tariff[12]
CPAP	Day	36	Dutch Health Authority Tariff[12]
Surfactant	Treatment	1 031	Dutch Pharmacotherapeutic Compass[13]
Travel/productivity loss			
Travel cost	km	0.21	Dutch costing guideline[11]
Productivity loss	Hour	42	Dutch costing guideline[11]

*€ values are those of 2011. †Mean of the unit cost for an academic hospital and a general hospital.

CPAP, continuous positive airway pressure; ICU, intensive care unit

use were not significantly different between the groups. Fewer neonates were admitted to the NICU in the nifedipine group (155 neonates (52.2%) compared to 182 neonates (61.9%) in the atosiban group (RR 0.85; 95% CI 0.73-0.99)). The length of NICU stay was comparable (median (IQR) 17 days (7.0-43.0) in the nifedipine group versus 17 days (7.0-39.8) in the atosiban group (median difference (95% CI) -1 (-5.52-3.52)). As displayed in Table S1, when analyzing singleton and multiple pregnancies separately, significantly less firstborn of twins were admitted to the NICU in the nifedipine group compared to the

atosiban group (60% versus 79%, p = 0.04). No other significant differences were found between the groups.

Costs

A summary of mean and median costs per woman is presented in table 3. Mean costs in the antepartum/delivery phase were lower in the nifedipine group, the mean difference was - €526 (€1 531 vs. €2 057). This difference was mainly driven by the difference in costs of the tocolytic therapy (mean costs for nifedipine were €0.5 vs. €550 for atosiban). The costs of other components in the antepartum/delivery phase were similar. Costs of maternal admission were lower in the nifedipine group, the mean difference was - €51. Costs of neonatal admission were lower in the nifedipine group (€39 559 vs. €44 361, mean difference - €4 802). Travel costs were lower in the nifedipine group, the mean difference was - €67. Total costs postpartum were lower in the nifedipine group, the mean difference between the groups was - €5 062. Mean total costs were significantly lower in the nifedipine group (€45 476 vs. €51 064, mean difference - €5 588 (95% CI –13 448 to 1 618)).

Table 3. Costs per woman

	Nifedipine (n = 248)		**Atosiban (n = 255)**		**Mean difference (N-A)***
Variable	*Mean cost*	*Median cost (IQR)*	*Mean cost*	*Median cost (IQR)*	
Antepartum costs					
Tocolysis	0.5	0.6 (0.3-0.6)	550	663 (329-677)	-549
Antibiotic therapy	14	0 (0-34)	15	0 (0-34)	-1
Analgetics during labor	41	0 (0-3)	46	0 (0-137)	-5
Delivery	1 461	1 199 (1 199-1 462)	1 436	1 199 (1 199-1 462)	25
Packed cells	14	0 (0-0)	10	0 (0-0)	4
Total antepartum	1 531	1 370 (1 200-1 870)	2 057	1 912 (1 748-2 268)	-526
Postpartum costs					
Maternal admission	3 546	2 737 (1 955-4 301)	3 597	2 737 (1 564-3 910)	-51
Neonatal admission	39 559	20 174 (3 128-49 845)	44 361	28 002 (5 935-64 239)	-4 802
Neonatal extra care	402	0 (0-161)	570	0 (0-446)	-168
Travel costs	334	270 (47-517)	401	318 (94-588)	-67
Productivity loss	104	0 (0-0)	77	0 (0-0)	27
Total postpartum	43 945	24 561 (7 446-53 959)	49 007	32 908 (11 035-67 825)	-5 062
Total costs (95% CI)†	45 476	25 868 (8 874-55 463)	51 064	35 591 (12 929-69 961)	-5 588 (-13 448 to 1 618)

All cost data are given as €, with values being those of 2013.
* Cost of nifedipine group (N) minus costs of atosiban group (A).
† Non-parametric confidence interval bases on 1000 bootstrap replications
IQR: interquartile range; CI: confidence interval

Table 4. Sensitivity analyses				
	Cost (€)*			
	Nifedipine	**Atosiban**	**Mean difference (N-A)†**	**95% CI**
	Mean cost	*Mean cost*		
Base case	45 476	51 064	- 5 588	(-13 425 to 1 262)
Model 1: Value admissions by using academic unit prices only	50 547	56 877	- 6 330	-14 241 to 1 891
Model 2: Value admissions by using general unit prices only	41 008	45 863	- 4 855	-12 561 to 2 461
Model 3: Including only singleton pregnancies (n = 414)	34 722	42 273	- 7 551	-12 986 to -1 216
Model 4: Including only multiple pregnancies (n = 89)	88 060	99 749	- 11 689	- 21 847 to -2 219
Model 5: Including only women < 30 weeks of gestation at study entry (n = 229)	65 612	69 183	- 3 571	-12 134 to 5 381
Model 6: Including only women ≥ 30 weeks of gestation at study entry (n = 274)	28 893	35 702	- 6 809	-10 861 to 2 820
* € Values are those of 2013; †costs of nifedipine group minus atosiban group				

Cost-effectiveness

Results in the main APOSTEL III manuscript showed similar adverse perinatal outcome rates between the nifedipine and atosiban group (14.1% in the nifedipine group and 15.3% in the atosiban group (RR 0.91; 95% CI 0.61-1.37). Perinatal mortality was non-significantly higher in the nifedipine group. The cost-effectiveness plane combines costs and effectiveness. Each point in the cost-effectiveness plane indicates the additional costs and health gain of treatment with nifedipine compared to atosiban in each bootstrap sample (figure 1). The ICER scatter shows that 65% is spread in the upper left and 29% in the upper right quadrant, indicating that our trial did not find significant differences in the reduction of composite adverse perinatal outcome rate (x-axis) but the costs (y-axis) of atosiban are higher. The ICER scatter for perinatal death spreads mostly in the right upper quadrant, indicating less perinatal deaths at higher costs for atosiban. For results located in the upper right quadrant, it depends the willingness to pay (WTP) for these health gains whether these are concerned cost-effective (figure 2).

Sensitivity analyses

Table 4 shows results of the sensitivity analyses, performed to test the robustness of the findings using the base case. Using the base case, the difference in mean total costs were -€5 588 (95% CI -13 425 to 1 262) in favor of nifedipine. For the total study population, when using unit prices for academic hospital setting (model 1) the difference increased to -€6 330 (95% CI -14 241 to 1 891). When using unit prices for general hospital setting (model 2) the difference decreased to -€4 855 (95% CI -12 561 to 2 461). In both models the costs were lower in the nifedipine group. In model 3 we included only singleton pregnancies (n = 414), the mean total costs were lower in the nifedipine group with a

difference of -€7 551 (95% CI -12 986 to -1 216). Including only multiple pregnancies (n = 89) we found a difference of -€11 689 (95% CI -21 847 to -2 219) in favor of the nifedipine group. In model 5 we included women with a gestational age < 30 weeks (n = 229). Costs between nifedipine and atosiban were also lower in the nifedipine group with a difference of -€3 571 (-12 134 to 5 381). In model 6 we included women with a gestational age ≥ 30 weeks (n = 274). In this model costs were lower in the nifedipine group with a difference in mean total costs of -€6 809 (95% CI -10 861 to 2 820).

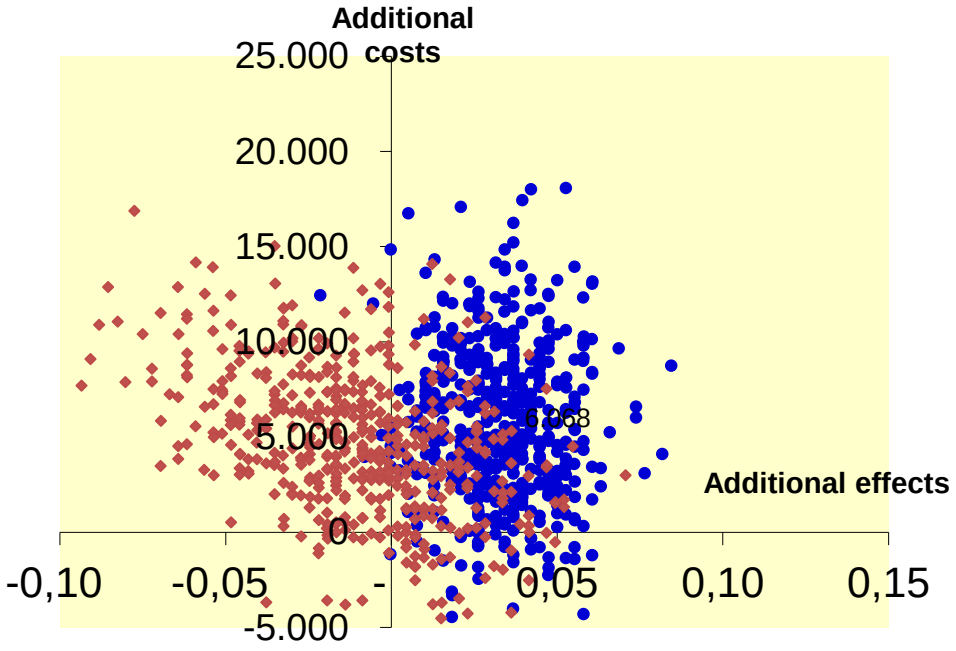

Figure 1. Cost-effectiveness plane. Each point in the cost-effectiveness plane represents the additional costs and health gain of treatment with nifedipine compared with atosiban (multiple samples from original data set). Colour represents clinical outcome measures: ✦ , for the composite adverse perinatal outcome. ● , for perinatal death only.

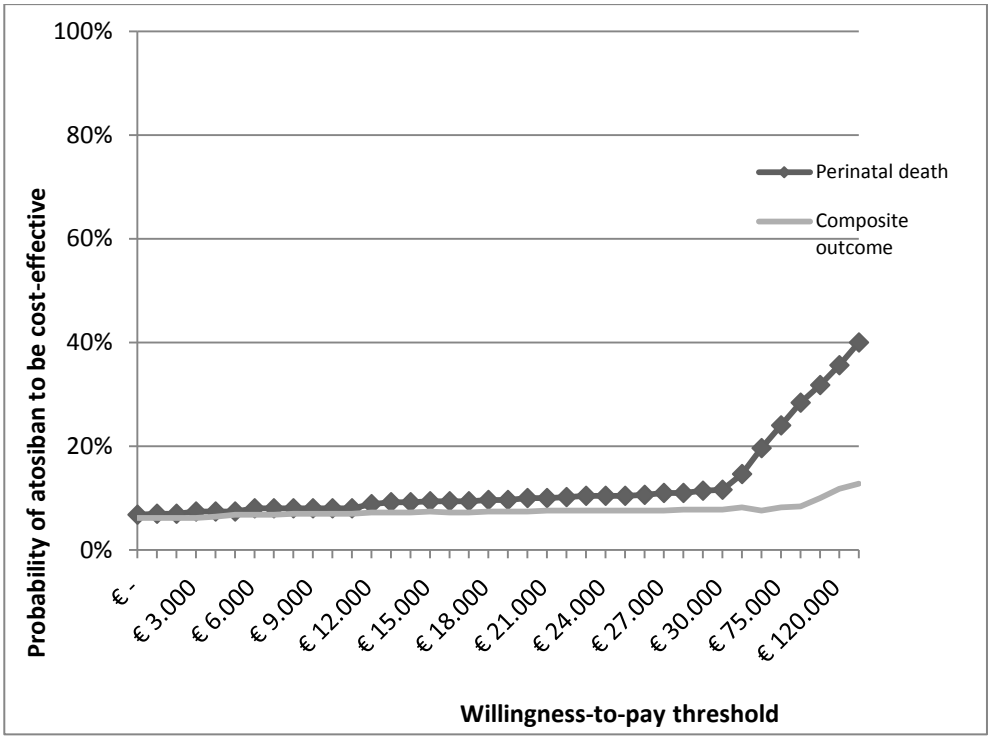

Figure 2. Cost acceptability curves, showing the probability of atosiban to be cost-effective of nifedipine for different outcomes: the composite adverse perinatal outcome ( ) and perinatal death ( ). The probability increases as result of an increase in willingness-to-pay.

Discussion

Main findings

In the current study, we assessed the costs associated with the use of nifedipine compared to atosiban as tocolytic therapy in women with threatened preterm birth between 25 en 33+6 weeks of gestation. The analysis was performed from a societal perspective alongside the APOSTEL III trial. The results showed that mean costs in women treated with nifedipine were lower compared to women treated with atosiban. In the primary analysis, the composite adverse perinatal outcome was comparable between the groups. The cost difference was mainly driven by higher costs for atosiban in the postpartum phase, because more neonates were admitted to the NICU in the atosiban group. The cost effectiveness plane and the ICER scatter showed that atosiban is not a cost effective strategy. Sensitivity analyses showed lower mean costs for nifedipine in all

different models (using academic vs. general hospital prices, singleton vs. multiple pregnancies and women with gestational age < 30 weeks and ≥ 30 weeks).

Strengths and limitations

One of the strengths of this study is it's large sample size and multicentric and randomized design. Besides this, the large number and diversity of participating hospitals, the large sample size and the well-organized structure of the trials within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology are likely to extend both the internal and external validity of our results.

This study has several limitations. The primary outcome of the trial was a composite of adverse perinatal outcome, therefore the economic analysis used this outcome as well. However, interpretation of a composite outcome can be difficult. A possible solution for this problem is the use of the quality-adjusted life year (QALY) which is an aggregated health metric. However, with the use of QALYs several problems arise. First, in our primary study both maternal and neonatal outcomes were taken into account, and therefore both should be combined in the QALYs. However, there is little date on how this could be achieved.[17] Second, a QALY-based analysis should preferably take long-term outcomes in to account as well. Since the primary outcome of the APOSTEL III trial only included the first six weeks postpartum this was not possible.

A second limitation is the short time horizon of this economic analysis. As mentioned before, the composite outcome included only six weeks postpartum. Nonetheless, we can speculate on the long-term impact on the costs. The differences in costs are mainly driven by lower NICU admission rates in the nifedipine group. The use of nifedipine and atosiban resulted in comparable short term perinatal outcomes. Therefore it may be expected that long-term costs will also be comparable. Recently we initiated the APOSTEL-III follow-up study, which will provide more insight on the effect on long-term outcomes and costs.

Interpretation

To our knowledge this is the first economic evaluation comparing the costs of the use if nifedipine and atosiban in the treatment of threatened preterm birth in a prospective manner. Therefore we cannot compare our results with other economic evaluations. Our study showed similar perinatal outcomes using nifedipine and atosiban, this was in line with previous trials, however these trials did not take costs into account.[18-20]

Preterm birth is the most common cause of neonatal mortality and morbidity. Our study showed a similar composite adverse perinatal outcome rate for the use of nifedipine and atosiban. The costs were lower in women treated with nifedipine. This difference was mainly driven by lower NICU admission rates in the nifedipine group. However, the perinatal death rate was more than two times higher in the nifedipine group (16 versus 7, RR 2.20; 95% CI 0.91-5.33). When looked at the ICER scatter for perinatal death as

outcome, it spreads mostly in the right upper quadrant. This means that atosiban has a tendency to reduce the perinatal death rate at higher costs. In this case the WTP becomes important.

Future research

Our primary study is the largest randomized clinical trial comparing nifedipine and atosiban so far. We found similar adverse perinatal outcomes and cost-effectiveness. Though, evidence showing tocolytic drugs by itself improve neonatal outcome is still lacking. We recommend new placebo controlled randomized clinical trials of tocolytics, assessing both clinical and cost effectiveness.

Conclusion

Treatment with nifedipine in women with threatened preterm birth results in lower costs when compared to treatment with atosiban, therefore atosiban does not seem to be a cost effective strategy. However, the safety of nifedipine warrants further investigation.

Appendix S1. Resource use											
		Nifedipine (n = 248)					**Atosiban (n = 255)**				
	Unit	*% patients using care*	*Mean volume **	*Mean Volume***	*Total Costs (€)*	*Mean Costs pp (€)*	*% patients using care*	*Mean volume **	*Mean Volume***	*Total Costs (€)*	*Mean Costs pp (€)*
Antibiotic treatment	Treatment	41.1	x	0.41	3 468	14	43.9	x	0.44	3 808	15
Tocolysis duration	Hours	100	36.2	36.2	127	0.5	100	38.4	38.4	140 355	550
Pethidin	Unit	3.6	X	0.04	27	0.1	2.7	X	0.03	21	0.1
Epidural	Unit	15.7	X	0.16	7 098	29	18.4	X	0.18	8 554	34
Epidural after pethidin	Unit	0.8	X	0.08	370	1.5	0.8	X	0.08	370	1.5
Spinal	Unit	0.4	X	0.04	182	0.7	1.6	X	0.02	728	2.9
Remifentanyl	Unit	7.3	X	0.07	2 466	9.9	5.9	X	0.06	2 055	8.1
Total analgetics					10 143	41				11 728	46
Packed cells	Unit	3.2	2.0	0.06	3 501	14	2.0	2.4	0.05	2 626	10
Manual placental removal	Unit	9.3	X	0.09	4 128	17	7.1	X	0.07	3 231	13
Delivery singletons (maternal level)		**Nifedipine (n = 198)**					**Atosiban (n = 216)**				
Total costs (incl instrumental attempt, Cesarean)	Unit	100.0	X	1.00	275 774	1 393	100.0	X	1.00	295 042	1 366
Delivery multiples (maternal level)		**Nifedipine (n = 50)**					**Atosiban (n = 39)**				
Total costs (incl instrumental attempt, Cesarean)	Unit	100.0	X	1.00	82 451	1 649	100.0	X	1.00	67 781	1 738
Total antepartum + delivery					379 592	1 531				524 571	2 057
		Nifedipine (n = 248)					**Atosiban (n = 255)**				
Maternal admission	Days	100.0	9.07	9.1	879 295	3 546	100.0	9.2	9.2	917 219	3 597
Admission singletons		**Nifedipine (n = 198)**					**Atosiban (n = 216)**				
Admission NICU	Days	47.0	25.9	12.2	3 969 629	20 049	55.1	27.6	15.2	5 402 649	25 012
Admission MC	Days	43.9	27.3	12.0	1 408 530	7 114	50.0	29.3	14.7	1 878 634	8 697
Admission ward	Days	26.8	9.6	2.6	198 613	1 003	25.0	11.5	2.9	243 575	1 128
Admission multiples		**Nifedipine (n = 50)**					**Atosiban (n = 39)**				
1st child											
Admission NICU	Days	60.0	34.5	20.7	1 706 446	34 129	79.5	26.3	20.9	1 340 779	34 379
Admission MC	Days	56.0	26.5	14.8	441 019	8 820	69.2	27.9	19.3	446 955	11 460
Admission ward	Days	12.0	9.7	1.2	22 676	454	17.9	23.3	4.2	63 728	1 634
2nd child											
Admission NICU	Days	60.0	28.1	16.9	1 390 194	27 804	71.8	26.3	18.9	1 212 302	31 085
Admission MC	Days	54.0	28.2	15.2	452 297	9 046	61.5	29.2	18.0	416 089	10 669
Admission ward	Days	20.0	9.8	2.0	22 676	454	23.1	32.3	7.5	63 728	1 634
Neonatal admission total					9 810 695	39 559				11 312 015	44 361

		Nifedipine (n = 198)					**Atosiban (n = 216)**				
Extra neonatal care (singletons)											
Intubation	Days	13.6	7.2	0.98	21 901	111	19.0	6.4	1.2	29 691	137
CPAP	Days	36.9	9.1	3.4	23 111	117	42.6	13.4	5.7	44 004	204
Surfactant	Treatment	9.1	X	0.09	18 558	94	13.4	X	0.13	29899	138
Extra neonatal care (multiples)		**Nifedipine (n = 50)**					**Atosiban (n = 39)**				
1st child											
Intubation	Days	18.0	5.4	0.97	5 532	111	15.4	4.5	0.69	3 048	78
CPAP	Days	32.0	8.3	2.7	4 758	95	48.7	14.0	6.8	9 516	244
Surfactant	Treatment	16.0	X	0.16	8 248	165	15.4	X	0.15	6186	159
2nd child											
Intubation	Days	14.0	5.7	0.80	4516	90	15.4	2.8	0.43	1 919	49
CPAP	Days	52.0	6.4	3.3	5903	118	56.4	11.8	6.7	9 302	239
Surfactant	Treatment	14.0	X	0.14	7217	144	23.1	X	0.23	9 279	238
Neonatal extra care total					99 744	402				145 456	570
		Nifedipine (n = 248)					**Atosiban (n = 255)**				
Productivity loss	Hours	1.6	19.3	0.31	25 872	78	2.4	9.8	0.24	19 824	104
Travel	Km	87.1	1 825	1 590	82 790	334	90.2	2 115	1 908	102 183	401
Total postpartum costs					10 898 396	43 945				12 496 696	49 007
Total costs					11 277 988	45 476				13 021 267	51 064

IQR: inter quartile range; C-section: Cesarean section; NICU: neonatal intensive care unit; MC: medium care; CPAP: continuous positive airway pressure; km: kilometer.
*Of patients using care
** Of all patients

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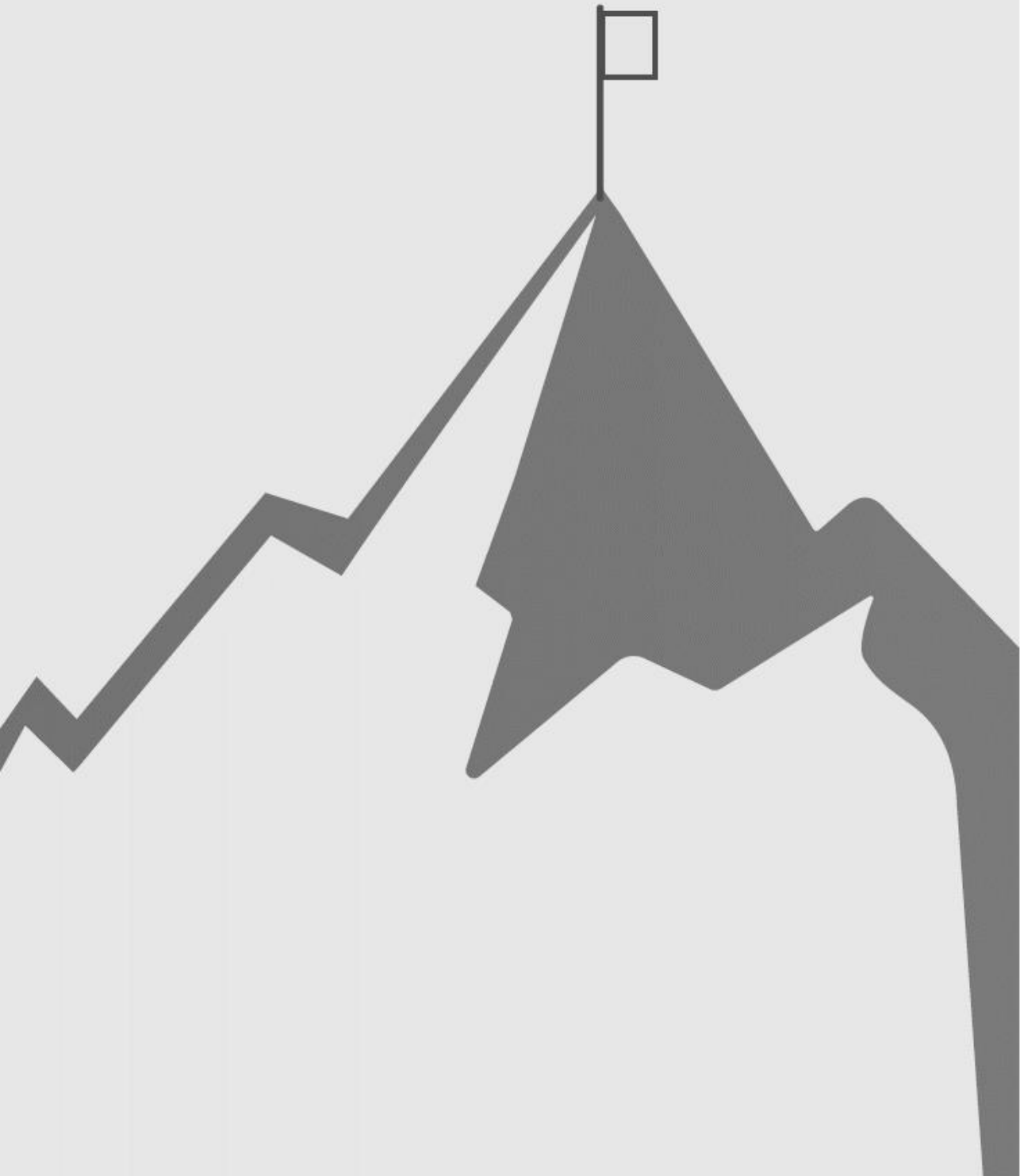

Chapter 6

The effects of nifedipine and atosiban on the neonatal brain: a secondary analysis of the APOSTEL III trial.

T.A.J. Nijman, M.M. Goedhart, C.N. Naaktgeboren, T.R. de Haan,
D.C. Vijlbrief, B.W. Mol, M.J.N. Benders, A. Franx, M.A. Oudijk

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Abstract

Objective

Brain injury in prematurely born neonates is strongly associated with poor neurodevelopmental outcome. The aim of our study is to evaluate if nifedipine reduces overall brain injury compared to atosiban in women with threatened preterm birth.

Methods

We performed a secondary analysis of the APOSTEL III-trial. This was a randomized clinical trial which allocated women with threatened preterm labor between 25-34 weeks of gestation to nifedipine or atosiban. For this secondary analysis, we included women delivering at ≤ 32 weeks of gestational age in the two main contributing centers, the University Medical Center Utrecht and Academic Medical Center in Amsterdam. To evaluate type and severity of our primary outcome brain injury, all neonatal ultrasounds made during neonatal intensive care admission and medium care admission were analyzed. A sensitivity analysis assessing differences in baseline or known risk factors for brain injury, was performed to test the robustness of our results.

Results

We studied 117 neonates, born from 102 women, of which 51 neonates had been exposed to nifedipine and 66 to atosiban. Brain injury was observed in 22 neonates (43.1%) in the nifedipine group and in 37 (56.1%) neonates in the atosiban (RR 0.60; 95% CI: 0.29-1.24). The sensitivity analysis, with adjustment for maternal age and gestational age at randomization, showed no statistical difference of brain injury (OR 0.58; 95% CI 0.27-1.27).

Conclusion

In children born before 32 weeks after the use of tocolytics, the prevalence of brain injury was high. No large differences were found between nifedipine and atosiban in terms of overall brain injury.

Introduction

Preterm birth is strongly associated with brain injury and causes 50% of all neurologic disabilities in childhood.(1–3) Neonates born before 32 weeks of gestation have the highest risk of poor neurologic outcome.(4–7) Severe brain injury on ultrasound increases the risk of developing cerebral palsy and motor disability.(8) Milder types of brain injury, such as intraventricular hemorrhage (IVH) grade 1 and 2, also show an independent association with neurosensory impairment, developmental delay and cerebral palsy.(9) Therefore identifying type and severity of brain injury is predictive for the prognosis of preterm born infants.

Serial ultrasound scanning is widely used to diagnose brain injury with a variable sensitivity and specificity. The accuracy depends on the severity and type of cerebral injury, the experience of the performer and the existence of a standardized ultrasound protocol.(10)

Since brain injury is strongly associated with poor neonatal prognosis, the evaluation of pharmacologic strategies for threatened preterm birth should include the effect on brain injury. A recently published Cochrane review shows the neuroprotective effects of magnesium sulphate administered during preterm delivery.(11) As a result of these neuroprotective abilities a reduction in cerebral palsy at 2 years of age and mortality has been described.(12)

Interventions aimed to improve neonatal outcome in preterm birth, also include administration of tocolytic drugs to women in threatened preterm birth. The most commonly used tocolytic drugs are atosiban, an oxytocin receptor antagonist, and nifedipine, a calcium channel blocking agent.(13) Nifedipine, through its calcium blocking properties, might have a similar protective effect on brain injury as magnesium sulphate. Several in vitro en in vivo studies on nifedipine indicate a neuroprotective effect based on reduction in ischemic neuronal cell damage and reduction of fluctuations in intra cerebral blood pressure (14),(15),(16). Atosiban is not assumed to have direct neuroprotective effects. In addition, both drugs may have an indirect effect on brain injury by delaying preterm birth. In view of the high percentage of brain injury in premature neonates and the widespread use of nifedipine and atosiban in the treatment of threatened preterm birth, an evaluation of the neuroprotective effects of these drugs is needed. We hypothesized that tocolysis by nifedipine, compared to atosiban, reduces overall brain injury in prematurely born neonates.

Methods

Study design

We performed a secondary analysis on the APOSTEL III-study (Assessment of Perinatal Outcome after Specific Tocolysis in Early Labor), recently published in the Lancet(17). This was a randomized clinical trial conducted in 19 hospitals in the Netherlands and Belgium.

The APOSTEL III-study compared two commonly used tocolytic drugs, atosiban and nifedipine, in women with threatened preterm birth. In this study women with threatened preterm birth between 25-34 weeks of gestation were included. Threatened preterm birth was defined as at least 3 contractions per 30 minutes and (1) a cervical length of < 10 mm, (2) a cervical length of 11-30 mm and a positive fibronectin test or (3) ruptured membranes.(13) Women were randomized and received nifedipine or atosiban for 48 hours. Corticosteroids and antibiotics were administered according to local protocol.

Study population

For the secondary analysis we selected a cohort of all women who delivered ≤ 32 weeks of gestation in the University Medical Center Utrecht (UMCU) and Academic Medical Center Amsterdam (AMC). These neonates were selected since neonates born before 32 weeks of gestation have the highest risk of poor neurological outcome. Neonates born with lethal congenital anomalies (not known at the time of inclusion) or no determination of outcome in the two included centers were excluded, as were their mothers.

Patient characteristics

Maternal characteristics were maternal age at randomization, body-mass-index, gestational age at randomization, parity, multiple pregnancies, preterm premature rupture of membranes (PPROM) and tocolysis before randomization.

Perinatal characteristics consisted of total tocolysis time and the time from start of tocolysis until delivery and were evaluated to show comparable exposure to study medication in both groups. Administration of a full course of antenatal corticosteroids was defined as two doses with the first dose at least 48 hours before birth. As the initial first dose of steroids is given at the same time as the start of tocolysis, a full course steroid also indicates the percentage of pregnancies with a prolongation of pregnancy more than 48 hours. Suspicion of intrauterine infection was defined as maternal temperature > 37.8, fetal tachycardia (heart rate > 150 beats/min) or maternal tachycardia (heart rate > 120 beats/min). Caesarean section included elective and emergency Caesarean sections with different indications. Caesarean section for fetal distress is separately shown.

Postnatal characteristics consisted of gestational age at birth, birth weight and birth weight z-score. A low Apgar score is defined as an Apgar < 7 after 5 minutes and asphyxia if arterial pH was less than 7.05 combined with a base deficit greater than 12 mmol/l. Arterial umbilical cord pH is also individually determined as a continuous variable. Primary intubation includes all infants with an immediate intubation in the delivery room. Intensive perinatal resuscitation is defined as requirement of insufflations breaths or a more intensive treatment for resuscitation. We also determined severe neonatal morbidity which acquired treatment during NICU admission, including hypotension (requiring inotropics), infant respiratory distress syndrome (requiring treatment with one

or more courses surfactant), need for mechanical ventilation, culture proven sepsis, persistent ductus arteriosus (requiring treatment with one or more courses indomethacin or ibuprofen and/or surgical treatment), necrotizing enterocolitis (including conservative and surgical treatment) and mortality.

Outcome measures

All neonates received sequential ultrasound scanning, during NICU and MC admission, from day 0 till discharge home or transfer to another hospital. To minimize observer variability, the ultrasound scans were all reviewed by one experienced neonatologist (DCV), who was blinded to study medication and perinatal events.

The primary outcome was defined as the presence and severity of brain injury: no brain injury, mild brain injury or severe brain injury. The most severe degree of brain injury during NICU or MC admission is evaluated and graded as shown in table 1. Patients without ultrasounds performed after day 6 are graded as missing in scoring for PVL grade 1.

Table 1**. Scoring table for the degree of brain injury**

Grade	Severity of Injury	Type of Injury
Grade 0	No brain injury	None
Grade 1	Mild brain injury	• Grades 1 and 2 intraventricular hemorrhage (Papile et al 1978[16]) • Persistent pathologic non-decreasing inhomogeneous flaring between day 7-14 (PVL grade 1, de Vries et al. 1993[38]) • Thinning of the corpus callosum • Pronounced ventricles (increased anterior horn width or ventricular index <2SD or thalamo-occipital distance <24 mm) • Dilated ventricles (Anterior horn width or ventricular index >2SD or the thalamo-occipital distance >24 mm, Brouwer et al. 2012[39])
Grade 2	Severe brain injury	• Intraventricular hemorrhage grade III or parenchymal/periventricular hemorrhagic infarction (grade III and IV IVH, papile et al 1978[16]) • Post hemorrhagic ventricular dilatation (IVH followed by progressive ventricle enlargement (> 2SD) requiring intervention,Whitelaw et al. 2004[40]) • Intracerebral local cystic lesions • Cystic periventricular leukomalacia (PVL grade 2-4, De Vries et al.) • Cerebellar hemorrhage • Parenchymal infarction • Intraparenchymal hemorrhage.

IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; SD: standard deviation.

Data analysis

Because only a subset the entire APOSTEL III population was included in this secondary analysis , patients in the treatment arms may not be comparable. Therefore baseline characteristics were compared, as well as the peri- and postnatal factors to assess comparability of the treatment arms and identify differences which could confound the results. For continuous variables independent samples T-tests or Mann-Whitney U-test were used (when appropriate). For categorical variables the Chi-square test or Fisher exact test were used.

Twins are strongly correlated due to similar intrauterine and perinatal exposure to factors influencing brain injury and mixed-effect models and general estimating equations are often recommended to account for this correlation. However, in this particular situation with a low percentage of twins and a binary outcome, ordinary logistic regression is recommended.(18) Therefore logistic regression analysis in a combined group with multiples and singletons was used to determine association with outcome. To adjust for potential confounding introduced by the selection of a subgroup of patients in this study, we also performed analyses to adjust for differences in baseline characteristics and known risk factors (gestational age at inclusion). Furthermore, a subgroup analysis was performed in women delivering within 24 hours after termination of tocolysis to analyze the immediate effect of study medication on the neonatal brain during delivery.

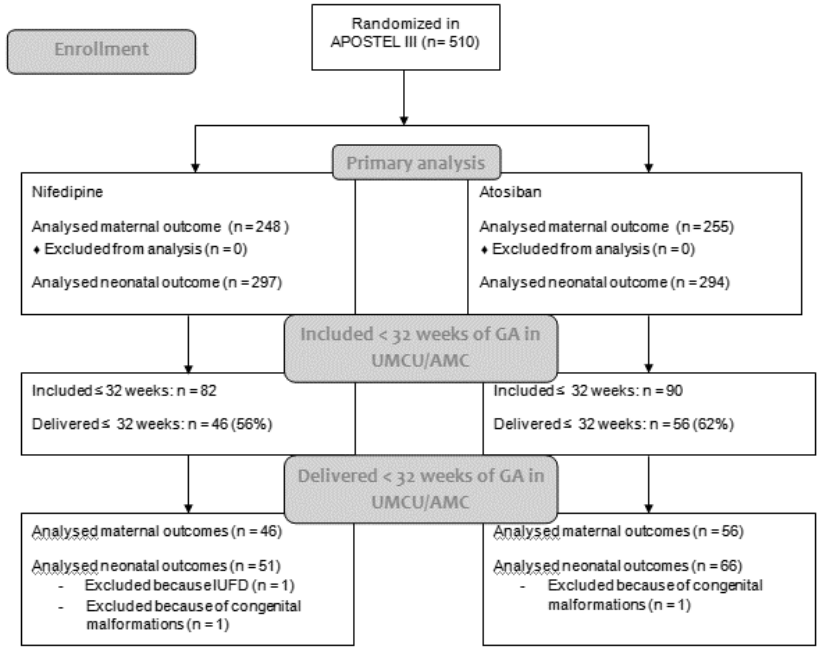

Figure 1. Flowchart

Results

Study population and patient characteristics

The APOSTEL III study randomized 248 women for nifedipine and 255 for atosiban, resulting in 297 and 294 children respectively. In the centers participating in this secondary analysis, 82 women randomized for nifedipine and 90 women randomized for atosiban were included ≤ 32 weeks of gestation. Of women randomized for nifedipine, 56% delivered ≤ 32 weeks of gestation compared to 62% for atosiban (p = 0.41). Therefore, we included 102 women in this analysis, resulting in 119 children born alive between 25-32 weeks of gestational age. Two patients were excluded because of lethal congenital anomalies, resulting in 117 neonates eligible for data analysis with 51 in the nifedipine group and 66 in the atosiban (Figure 1).

Table 2. **Maternal baseline characteristics**

	Nifedipine (n = 46)	**Atosiban (n = 56)**	**p-value**
Age mother (mean ± SD)	32.4 ± 5.8	30.2 ± 4.5	0.03
BMI (kg/m2)	23.0 (21.3-24.9)	22.8 (20.8-26.1)	0.87
Gestational age at randomization	29.1 (27.1-30.3)	28.21 (26.6-30.6)	0.46
Nulliparous	31(67.4)	42 (75)	0.40
Multiple pregnancy	6 (13)	9 (16,1)	0.67
PPROM	19 (41.4)	19 (33.9)	0.44
Tocolysis before randomization	10 (21.7)	18 (32.1)	0.24

SD: standard deviation; BMI: body mass index; PPROM: preterm premature rupture of membranes
Data are medians (interquartile range) or n (%) unless otherwise specified.

Maternal baseline characteristics are presented in table 2. Maternal characteristics are comparable for both groups, except for maternal age. Multiple pregnancies were present in 6 (13%) of women allocated to nifedipine and 9 (16%) in the atosiban group. Table 3 shows the perinatal characteristics. Total tocolysis time, a full course of steroids and administration of magnesium sulphate were comparable between the groups. The rate of Caesarean section was similar in both groups (33% in the nifedipine group and 20% in the atosiban group, p = 0.09) For women delivered by Caesarean section, there was a significant difference in Caesarean sections for fetal distress between the nifedipine group (47%) and the atosiban group, (15%; p = 0.02). The postnatal characteristics were comparable between the groups, except for the umbilical arterial cord pH at birth, which

was significantly higher in the nifedipine group (7.32 vs. 7.26, p = 0.01, see table 3). Due to failure of obtaining blood gasses, there was a high percentage of missing values in both groups.

Outcomes

In total, 540 ultrasounds were reviewed during NICU and medium care (MC) admission, including 203 in the nifedipine and 337 in the atosiban group. The median (IQR) number of ultrasounds analyzed per patient in the nifedipine group was 3 (3-5) and 5 (3-7) in the atosiban group. In table 4, the primary outcome based on ultrasound findings is shown and divided in types of brain injury. After grading all neonates in absent, mild or severe brain injury, there was no significant difference between the groups during NICU and MC admission (p = 0.26, see table 4). In total, mild and severe brain injury was observed in 22 (43.1%) neonates in the nifedipine group and 37 (56.1%) neonates in the atosiban group (RR 0.60; 95% CI: 0.29-1.24). Components of the primary outcome were not significantly different between the study groups (see table 4).

Adjustment for maternal age and gestational age at randomization, showed similar rates of brain injury (OR 0.58 95%CI: 0.27-1.26). Furthermore, no difference in brain injury was detected in a selected group of patients born within 24 hours after administration of tocolysis (OR 0.7; 95% CI: 0.27-1.85).

Caesarean section with suspected fetal distress as indication was the only clinically relevant perinatal factor that was more often seen in the nifedipine group. Therefore logistic regression was performed to test if there was an association between Caesarean section and brain injury. Brain injury was significantly reduced by Caesarean section (OR 0.32; 95% CI: 0.13-0.77). Multivariate analysis with Caesarean section for fetal distress and type of tocolysis decreased the effect of nifedipine on a reduction of brain injury (OR 0.68; 95% CI: 0.31-1.44)

Table 3. **Perinatal characteristics**

	Nifedipine (n = 51)	**Atosiban (n = 66)**	**p-value**
Prenatal characteristics			
Tocolysis time (hours)	40.45 (7.00-47.25)	31.38 (13.94-48.00)	0.44
Time start tocolysis until delivery (hours)	53.55 (12,67-120.35)	42.78 (17.32-79.04)	0.35
Steroids (full course)	27 (52.9)	32 (48.5)	0.63
Suspicion of Intra uterine infection	7 (13.7)	3 (4.5)	0.10
Administration of magnesium sulphate	13 (25.5)	17 (25.8)	0.66
Cesarean section	17 (33)	13 (19.7)	0.09
Cesarean section for fetal distress	8 (47%)	2 (15%)	0.02
Postnatal characteristics			
Gestational age at birth (weeks)	29.86 (28.29-30.71)	28.79 (27.04-30.86)	0.34
Gender (male)	35 (68.6)	38 (57.6)	0.22
Birth weight (grams)	1358 (1165-1600)	1310 (995-1566.25)	0.42
Birth weight z-score	0.62 (0.13-0.97)	0.64 (0.09-1.11)	0.56
Cord blood arterial pH*	7.32 (7.25-7.37)	7.26 (7.20-7.31)	0.01
Low apgar score	6 (11.8)	10 (15.2)	0.60
Asphyxia*	0 (0)	1 (2.4)	0.25
Primary intubation	2 (3.9)	5 (7.6)	0.41
Intensive resuscitation (>PEEP/CPAP)	19 (37.3)	30 (45.5)	0.37
Mechanical ventilation	16 (31.4)	23 (34.8)	0.69
Hypotension (requiring inotropes)	7 (13.7)	6 (9.1)	0.43
Sepsis (culture proven)	10 (19.6)	15 (22.7)	0.68
IRDS (requiring treatment)	13 (25.5)	23 (34.8)	0.28
PDA (requiring treatment)	10 (19.6)	16 (24.6)	0.55
NEC	3 (6.1)	2 (3.0)	0.42
Mortality	7 (13.7)	4 (6.1)	0.16

PEEP: positive end expiration pressure; CPAP: continuous positive airway pressure; IRDS: infant respiratory distress syndrome; PDA: persistent ductus arteriosus; NEC: necrotizing enterocolitis
Data are medians (interquartile range) or n (%)
**** pH arterial cord missing n= 24 (nifedipine) /14 (atosiban); asphyxia missing = 24 (nifedipine) /13 (atosiban)***

Table 4. **Brain injury per treatment arm**

	Nifedipine (n = 51)	**Atosiban (n = 66)**	**p-value**
Ultrasound findings			
IVH 1	5 (9.8)	11(16.7)	0.28
IVH 2	11 (21.6)	11 (16.7)	0.50
IVH 3	0 (0.0)	2 (3.0)	0.21
IVH 4	2 (3.9)	1 (1.5)	0.41
Total IVH	18 (35.3)	25 (37.9)	0.77
PVL grade 1*	2 (6.7)	7 (14.9)	0.18
Parenchymal infarct	1 (2.0)	1 (1.5)	0.85
Intraparenchymal bleeding	1 (2.0)	0 (0)	0.25
Thinning of corpus callosum	0 (0.0)	1 (1.5)	0.38
Cerebellar hemorrhage	1 (2)	3 (5)	0.45
Pronounced ventricles	7 (13.7)	12 (18.2)	0.72
Ventricle dilatation (posterior horn >24mm)	2 (3.9)	8 (12.1)	0.18
Type of brain injury during NICU/MC admission			
No brain injury	29 (56.9)	29 (43.9)	**0.26**
Mild brain injury	17(33.3)	32 (48.5)	
Severe brain injury	5 (9.8)	5 (7.6)	

IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; NICU: neonatal intensive care unit; MC: medium care
Data are n(%), there are patients with more than one type of brain injury
**** Only patients with an ultrasound after day 7 are included Atosiban/nifedipine 47/29***

one expert specialist (DCV), thereby minimizing the risk of intra-observer variability. There are also limitations of our study. In this secondary analysis, we used a non-randomly selected subgroup of the randomized population. Baseline characteristics however appeared to be similar between the groups, with the exception of maternal age. As this variable was not seen as a clinically relevant factor influencing neonatal outcome, the study groups in the secondary analysis were assumed to be comparable. Nevertheless, brain injury is a multifactorial problem with peri- and postnatal factors influencing outcome. As most of the peri- and postnatal factors are equally distributed between the study medication groups, we assumed type of tocolysis as the most influencing factor on brain injury. These assumptions should be taken with caution as the inclusion criteria for this secondary analysis reduced the sample size leading to an increased risk of under

powering and enabling clinically relevant risk factors to influence outcome without showing significance.

The only significant perinatal outcome in our study was Caesarean section performed for fetal distress. More Caesarean sections for fetal distress were performed in the nifedipine group. Several Doppler studies show significant changes in fetal and placental circulation after nifedipine exposure, suggesting that nifedipine may cause fetal distress.(22,23) In contrast, these studies reported no influence of nifedipine on fetal heart rate, as did de Heus et al. in a direct comparison between nifedipine and atosiban exposure.(24) These results are supported by Salim and Valdes et al. reporting less Caesarean sections in the nifedipine group as compared to atosiban and betamimetics respectively.(20,25) Additional analysis within our study showed that Caesarean section is associated with a significant reduction in brain injury. These findings are in line with previously published data in extremely low birth weight neonates.(26,27) However, two recently published reviews of literature found inconclusive evidence on the benefits of Caesarean section on brain injury and neurodevelopmental outcome.(28,29) Statistical analysis of the fetal presentation between the medication groups was not possible due to small groups. Reviewing the cases in our study showed no influence of breech presentation on fetal distress as outcome (50% (n=4) breech in the nifedipine group, 100% (n=2) breech in the atosiban group). Adding Caesarean section (for fetal distress) in the multivariate analysis increased the OR, closer to one. An explanation for this is that nifedipine leads to more Caesarean sections for fetal distress. As mentioned before Caesarean sections might be protective for the fetal brain. Therefore the effect of nifedipine on brain injury is smaller when corrected for Caesarean sections on fetal indication. Since evidence is inconclusive and the population in our study is small, it is not possible to conclude that less brain injury in the nifedipine group can be explained by higher rates of Caesarean sections, protecting the infants against prolonged perinatal asphyxia.

MRI imaging has shown higher sensitivity and specificity in determining type and severity of brain injury compared to ultrasound. However, MRI imaging is only indicated in the first days of life if signs of neurologic disability (e.g. hypotonia and convulsions) and at term age to predict neurodevelopmental outcome. (30,31) As a result only the minority of the included patients received a MRI and made a more specific analysis of ischemic brain injury not possible in our population.

The added value of this study is that all types of brain injury were assessed and, also mild types of brain injury were comparable between the two groups. This is important since increasing evidence shows that mild brain injury, such as grades 1-2 intraventricular hemorrhage, is also associated with poor neurodevelopmental outcome.(32,33) Therefore, a significant difference in outcome of mild brain injury could also be clinically relevant. In our study 67.3% of all brain injury is due to or a combination of mild intraventricular hemorrhage grades 1-2. As nifedipine could lead to a reduction of

fluctuations in blood pressure, especially during delivery, we assumed a protective effect of nifedipine on development of IVH. A Cochrane meta-analysis showed a non-significant lower incidence of IVH when using nifedipine compared to any other type of tocolysis.(34) Our results show no difference between atosiban and nifedipine for total IVH as well in analyses for each grade separately.

The subgroup analysis of patients that delivered during or within 24 hours after administration of tocolytic drugs, provided us with data on the possible direct effect of the drugs during delivery. Nifedipine is most likely to have an effect on the fetus while it is present in the blood during delivery, as it crosses the placenta with a ratio of 0.77-0.99 compared to atosiban with a minimal placental transfer of 0.124.(35–37) However, it is unsure that clinically relevant serum levels are reached in the fetus during tocolysis. Our study implies that there is no direct effect of nifedipine, as neonates born within 24 hours after tocolysis showed no difference in brain injury.

In conclusion, nifedipine administered as tocolytic treatment, is not associated with a reduction in brain injury in prematurely born neonates, when compared to atosiban.

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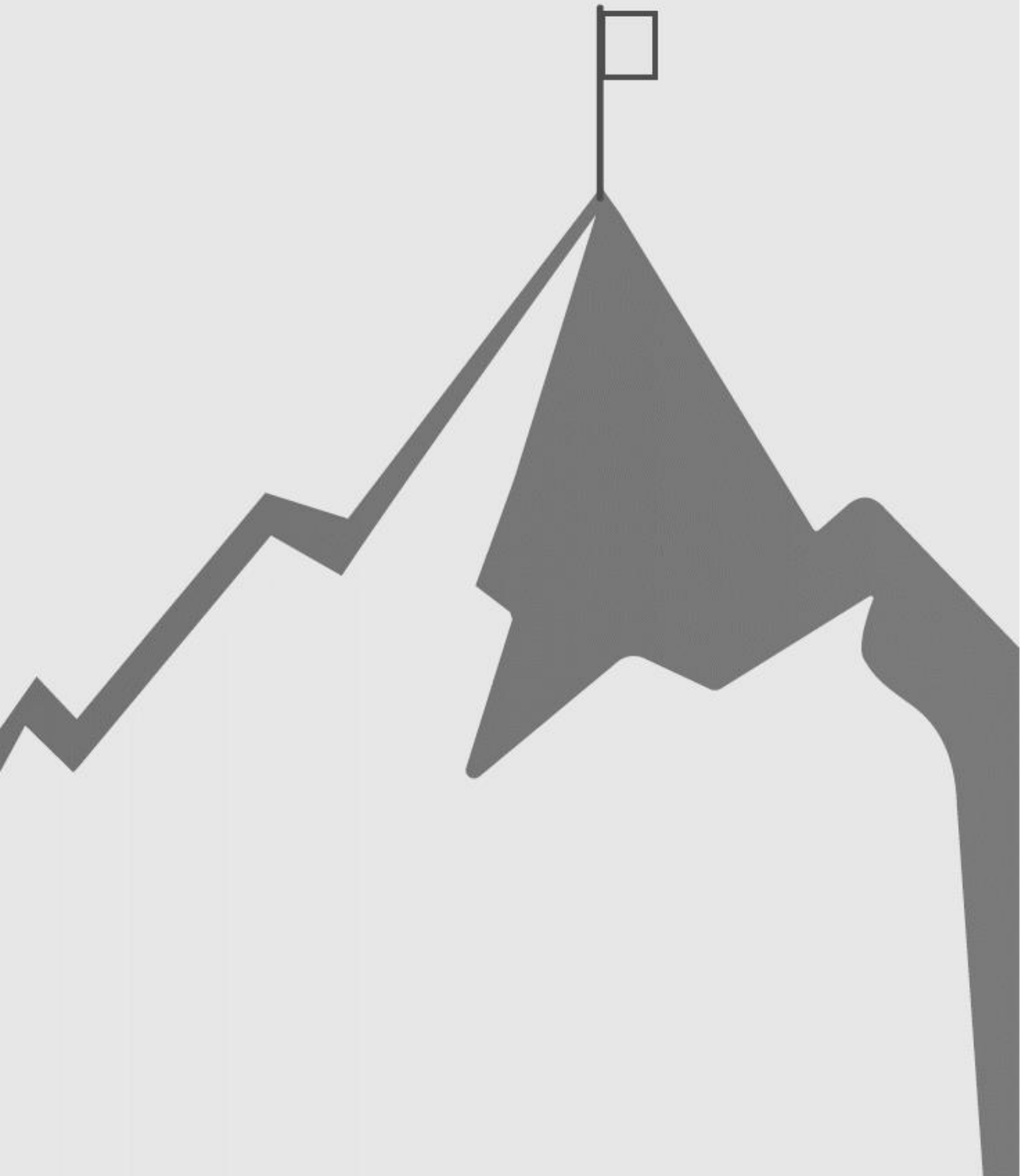

Chapter 7

Nifedipine versus placebo in the treatment of preterm prelabor rupture of membranes: a randomized controlled trial:

Assessment of perinatal outcome by use of tocolysis in early labor (APOSTEL IV trial)

Nijman TA, van Vliet EO, Naaktgeboren CA, Oude Rengerink K, de Lange TS, Bax CJ, Bloemenkamp KW, van Eyck J, Kok M, Scheepers HC, Woiski M, Franx A, Mol BW, Oudijk MA.

Eur J Obstet Gynecol Reprod Biol. 2016 Oct;205:79-84.

Abstract

Objective

Preterm birth is the most common cause of neonatal morbidity and mortality. Around one third of preterm deliveries starts with preterm prelabor rupture of membranes (PPROM). The aim of this trial was to study the effect of prolonged tocolysis with nifedipine versus placebo in women with PPROM on perinatal outcome and prolongation of pregnancy.

Study design

The Apostel IV was a nationwide multicenter randomized placebo controlled trial. We included women with PPROM without contractions between 24+0 and 33+6 weeks of gestation. Participants were randomly allocated to daily 80 mg nifedipine or placebo, until the start of labor, with a maximum of 18 days. The primary outcome measure was a composite of poor neonatal outcome, including perinatal death, bronchopulmonary dysplasia, periventricular leukomalacia > grade 1, intraventricular hemorrhage > grade 2, necrotizing enterocolitis > stage 1 and culture proven sepsis. Secondary outcomes were gestational age at delivery and prolongation of pregnancy. Analysis was by intention to treat. To detect a reduction of poor neonatal outcome from 30% to 10%, 120 women needed to be randomized. Trial registry: NTR 3363.

Results

Between October 2012 and December 2014 we randomized 25 women to nifedipine and 25 women to placebo. Due to slow recruitment the study was stopped prematurely. The median gestational age at randomization was 29.9 weeks (IQR 27.7–31.3) in the nifedipine group and 27.0 weeks (IQR 24.7–29.9) in the placebo group. Other baseline characteristics were comparable. The adverse perinatal outcome occurred in 9 neonates (33.3%) in the nifedipine group and 9 neonates (32.1%) in the placebo group (RR 1.04, 95% CI 0.49–2.2). Two perinatal deaths occurred, both in the nifedipine group. Bronchopulmonary dysplasia was seen less frequently in the nifedipine group (0% versus 17.9%; p = 0.03). Prolongation of pregnancy did not differ between the nifedipine and placebo group (median 11 versus 8 days, HR 1.02; 95% CI 0.58–1.79).

Conclusion

This randomized trial did not show a beneficial effect of prolonged tocolysis on neonatal outcomes or prolongation of pregnancy in women with PPROM without contractions. However, since results are based on a small sample size, a difference in effectiveness cannot be excluded.

Background

Preterm birth is the most common cause of neonatal morbidity and mortality worldwide and accounts for approximately 75% of all neonatal deaths and 50% of childhood neurological morbidities.[1-3] Around one third of preterm deliveries starts with preterm prelabor rupture of membranes (PPROM).[4] Despite the high prevalence of preterm birth following PPROM, the optimal management of PPROM remains a topic of debate and is hindered by a lack of evidence.

After rupture of the membranes, there is a high risk that labor will follow within days. Most women with PPROM who receive conservative management deliver within one week. Most clinical guidelines advise to administer a 48 hour course of corticosteroids and transfer to a tertiary care center to improve neonatal outcome.[5-8] One mechanism by which tocolysis might improve outcome is to delay delivery during this 48 hour period. However, the use of tocolysis in this period, but especially after 48 hours, is subject to debate. The prevalence of adverse neonatal outcome is strongly related to gestational age at delivery declining from 77% at 24-27 weeks to less than 2% from 34 weeks onwards.[9] Administration of tocolytic drugs after the 48 hour period may further increase the latency period and thereby improve gestational age at delivery. However, prolongation of pregnancy in PPROM does not automatically lead to an improvement of neonatal outcome. As infection is detected in a major part of all women with PPROM, prolongation of pregnancy may result in longer exposure of the fetus to a harmful infective environment. Therefore, the benefit of postponing delivery must be weighed against the potential harm of the increased risk on maternal and perinatal infection.

A recent Cochrane review indicated that, when compared to placebo, tocolysis in PPROM is associated with an average 73 hours longer latency of delivery (95% confidence interval (CI) 20-126; three trials, 198 women) and fewer births within 48 hours (RR 0.55; 95% CI 0.32-0.95; six trials, 354 women). However, tocolysis was also associated with an increased risk of a 5 minute Apgar score under 7 and an increased need for ventilation support. Different tocolytic drugs were compared, mostly betamimetics (ritodrine).[10] In a subgroup analysis, including three trials with 137 women with PPROM and no or minimal uterine contractions, tocolysis significantly increased the duration of pregnancy without any significant effects on maternal and neonatal outcomes. In a subgroup analysis (5 studies, 291 women) of women with PPROM before 34 weeks of gestation tocolysis increased the rate of chorioamnionitis (RR 1.79; 95% CI 1.02 - 3.14), neonatal outcome was comparable.[10]

As the goal of tocolysis is to improve neonatal outcomes, we performed a multicenter randomized trial comparing nifedipine versus placebo in women with PPROM without contractions in terms of perinatal outcomes and prolongation of pregnancy.

Methods

Trial Design

We performed a multicenter randomized placebo controlled trial, the APOSTEL IV study: Assessment of Perinatal Outcome by uSe of Tocolysis in Early Labor. It was conducted in eight Dutch perinatal centers with NICU facilities. The trial was conducted within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology. The study has been approved by the ethics committee of the Academic Medical Centre in Amsterdam (Reference number 2011-092) and by the boards of management of all participating hospitals. This trial was registered in the Netherlands Trial Register, trial number 3363. The study was not funded. The study is reported according to the CONSORT guidelines.[11]

Participants

Women, aged ≥ 18 years, with a gestational age between $24^{+0/7}$ and $33^{+6/7}$ weeks with ruptured membranes without signs of active labor were eligible for the trial. Exclusion criteria were 1) ≥ 3 contractions per 10 minutes 2) previous treatment with tocolysis in the last 7 days (tocolysis for < 6 hours for transportation was allowed) 3) symptoms justifying start of tocolysis 4) ruptured membranes ≥ 72 hours 5) signs of chorioamnionitis or intra uterine infection 6) signs of fetal distress 7) fetal major congenital anomaly 8) contraindication for the use of nifedipine 9) maternal disease as reason for delivery (such as hypertension, HELLP syndrome or preeclampsia).

Procedures, recruitment and randomization

Eligible women were identified by the staff and/or local research coordinator of the participating hospitals. After counseling and reading the patient information form, patients were asked for written informed consent. We provided patient information in Dutch and English. After informed consent, baseline demographics of the patient were entered in a web-based database. Randomization was performed per center by a web based computerized program in a 1:1 ratio, using permuted blocks of 4, rendered by an independent data manager. The study was double blind; research staff, clinicians and participants were blinded for treatment allocation.

Interventions

Study medication consisted of one tablet every six hours, administered orally, containing 20 milligrams nifedipine slow release or placebo. The medication was given until the start of active labor (>3 contractions per 30 minutes), with a maximum of 18 days or until gestational age of 34^{+0} weeks. The length of the therapy was limited to 18 days, based on the assumption that prolongation of pregnancy of more than two weeks, if clinically relevant, should show an effect on perinatal outcome. The medication package was stored

by the patient, and the administration of the study medication was noted in her medical record. Antenatal corticosteroids were administered according to national guidelines, advising antenatal corticosteroids to women in preterm labor < 34 weeks of gestation.[8] Prophylactic antibiotic therapy and magnesium sulphate were administered according to local protocol, as was maternal and fetal monitoring.

Outcome measures

Primary outcome measures

The primary outcome was a composite of adverse perinatal outcome, including perinatal death, bronchopulmonary dysplasia (BPD), periventricular leukomalacia (PVL) > grade 1, intraventricular hemorrhage > grade 2, necrotizing enterocolitis (NEC) > stage 1 and culture proven sepsis.

The diagnosis of BPD was made according to the international consensus guideline as described by Jobe and Bancalari at time of discharge to home or at 36 weeks of corrected gestational age.[12] PVL > grade 1 and IVH > grade 2 were diagnosed by repeated neonatal cranial ultrasound by the neonatologist according to the guidelines on neuroimaging described by de Vries et al. and Ment et al.[13;14] NEC was diagnosed according to Bell > stage 1.[15] Culture proven sepsis was diagnosed by the combination of clinical signs of sepsis and positive blood cultures.

Secondary outcome measures

Secondary outcomes were birth weight, gestational age at delivery, prolongation of pregnancy, number of days on ventilation support, number of days in NICU and total days in hospital. Furthermore discontinuation of study medication due to progression of labor, side effects or signs of intra uterine infection was noted.

We registered maternal morbidity, mortality or complications that might have been related to the use of tocolytics during the study. An expert panel subsequently judged whether the complication was related to the use of tocolytics or not.

Statistical analysis

Sample size

To detect a reduction in adverse perinatal outcome from 30% in the placebo group to 10% in the nifedipine group, 120 women (60 per arm) were needed (two sided test, type I error rate = 0.05, power 80%).

Data analysis

Data were analyzed according to the intention to treat principle. Continuous variables are presented as mean with standard deviation (SD) or as median with interquartile range

(IQR), depending on their distribution. Categorical and dichotomous variables are presented as a number and percentage of the total allocation group. The perinatal outcomes were assessed on child level (in case of twins both children were taken into account). The main outcome variable, 'adverse perinatal outcome', and secondary neonatal outcomes were assessed by calculating rates in the two groups, relative risks and 95% confidence intervals. The maternal outcome was assessed on maternal level.
Prolongation of pregnancy was evaluated by Cox proportional hazards regression and Kaplan-Meier estimates, and tested with the Log rank test**.**

Results

After consultation of the Data Safety Monitoring Committee, it was decided to end the study on December 10th 2014 due to slow recruitment.

Study population

Between October 2012 and December 2014 we included 50 women, of whom 25 were allocated to nifedipine and 25 to placebo (figure 1). Outcomes were available for all 25 women in both groups, corresponding with 27 children in the nifedipine group and 28 children in the placebo group. Table 1 shows that baseline characteristics of both groups were comparable, except for gestational age at study entry: median (IQR) 29.9 weeks (27.7-31.3) in the nifedipine group versus 27.0 weeks (24.7-29.9) in the placebo group.

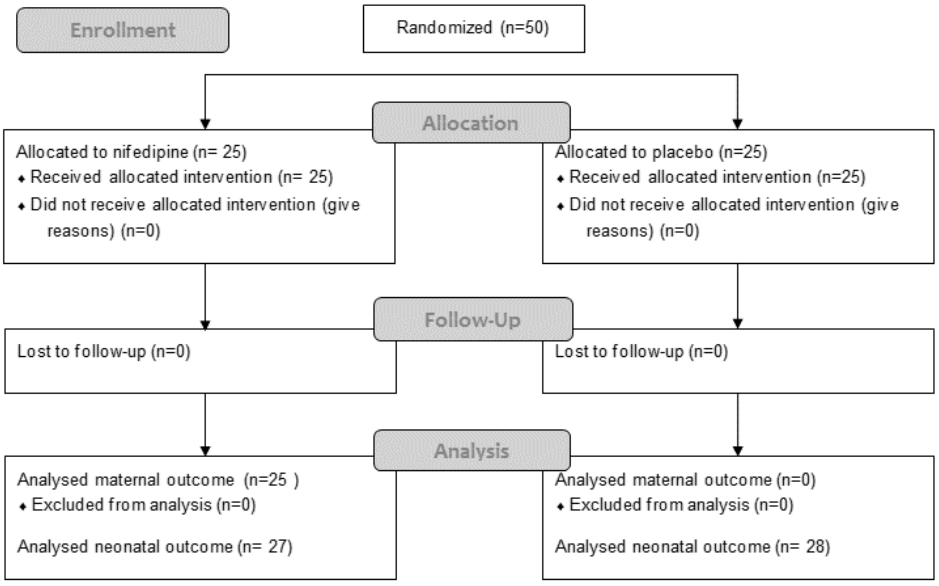

Figure 1. Flow chart

Table 1. Baseline characteristics

	Nifedipine (n = 25)	Placebo (n =25)
Gestational age at study entry, median (IQR), weeks	29.9 (27.7-31.3)	27.0 (24.7-29.9)
Maternal age, median (IQR), years	33.4 (30.3-35.7)	32.9 (27.7-36.3)
Body mass index, median (IQR)	22.7 (20.8-26.4)	23.8 (20.8-31.4)
Caucasian, n (%)	19 (76.0)	19 (76.0)
Nulliparous, n (%)	16 (64.0)	14 (56.0)
Smoking, n (%)	4 (16.0)	3 (12.0)
Prior preterm birth, n (%)	5 (20.0)	3 (12.0)
Twin gestation, n (%)	2 (8.0)	3 (12.0)
Laboratory results at entry		
Leukocytes, median (IQR), * 10^9/L	12.5 (10.4-13.3)	11.1 (9.7-12.7)
CRP, median (IQR), mg/L	7.0 (5.0-12.0)	5.0 (3.0-12.0)
Prophylactic antibiotic therapy, n (%)	15 (60.0)	14 (56.0)
Corticosteroids administered, n (%)	25 (100)	24 (96.0)

IQR: inter quartile range; CRP: c-reactive protein.

Primary outcome

Adverse perinatal outcome occurred in 9 (33.3%) children in the nifedipine group versus 9 children (32.1%) in the placebo group (RR 1.04; 95% CI 0.43-2.5). BPD occurred significantly less frequent in the nifedipine group (no children in the nifedipine group compared with five (17.9%) in the placebo group, p=0.03). Other components were not significantly different (table 2). Because there was a difference in gestational age at study entry between the arms, we performed a sensitivity analysis in which we corrected for gestational age at study entry. Results showed that the composite of adverse perinatal outcome remained comparable between the groups after adjusting for differences in gestational age at study entry (adjusted RR 1.03; 95% CI 0.51-2.1)

Perinatal deaths

Two perinatal deaths occurred, both in the nifedipine group. In the first woman, PPROM occurred at 24^{+1} weeks of gestation. Five days later a boy was born, after a vaginal breech delivery. Birth weight was 730 grams. Apgar scores after respectively 1, 5 and 10 minutes were 0, 5 and 9. After seven days the boy died of NEC followed by septic shock. In the second woman PPROM occurred at 25^{+4} weeks of gestation. After three days, an emergency Cesarean section was performed because of signs of uterine infection and suspected fetal distress. Birth weight was 900 grams. Apgar scores after respectively 1 and 5 minutes were 0 and 6. After one day he died as a result of respiratory insufficiency due to sepsis.

Secondary outcomes

Median gestational age at delivery was 32.0 weeks (IQR 29.1-33.3) in the nifedipine group compared with 30.0 weeks (IQR 26.3-32.1) in the placebo group (p = 0.15)). Prolongation of pregnancy was also comparable median 11 days (IQR 4-19) in the nifedipine group compared with 8 days (IQR 5-25) in the placebo group, HR 1.02; 95% CI 0.58-1.79). In women treated with nifedipine 92% was still pregnant 48 hours after initiation of study medication, compared with 100% in the placebo group (RR 0.92; 95% CI 0.92-1.05). After seven days 64% of the women in the nifedipine group was still pregnant, compared with 60% in women in the placebo group (RR 1.07; 95% CI 0.67-1.7). The Kaplan-Meier survival analysis on the prolongation of pregnancy revealed no differences between nifedipine and placebo (figure 2, log rank test, p = 0.94). Birth weight, number of days on ventilation support and NICU were comparable between the groups. Total days in hospital until 3 months corrected age was significantly lower in the nifedipine group (32 days vs. 48 days). Maternal mortality did not occur. Due to progression into labor within 18 days after starting treatment, study medication was discontinued in 15 women (60.0%) in the nifedipine group and in 14 women (56.0%) in the placebo group (RR 1.07; 95% CI 0.63-1.8). Two women (8.0%) in the nifedipine group discontinued study medication because of side effects, compared with no women in the placebo group (table 2). Side effects included an allergic reaction and palpitations.

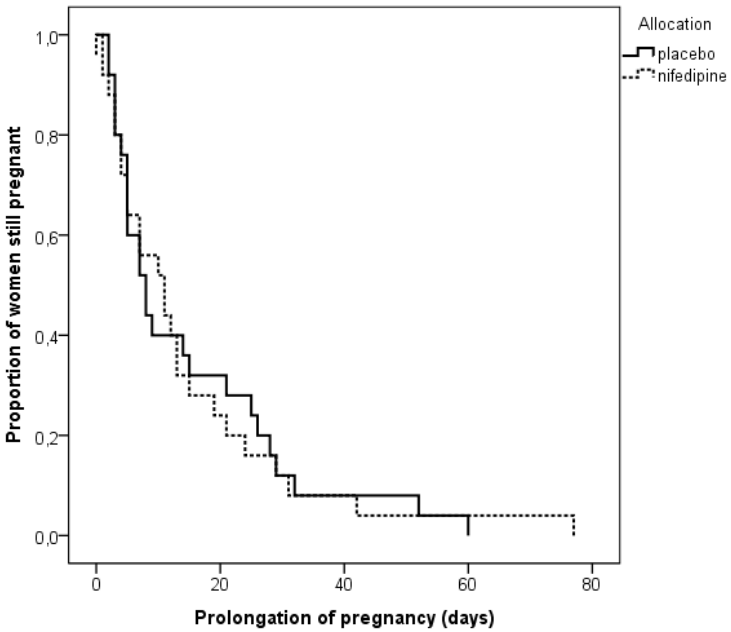

Figure 2. Kaplan-Meier curve for prolongation of pregnancy

Table 2. Primary and secondary outcomes

Primary outcome (child level)	**Nifedipine (n=27)**	**Placebo (n=28)**	**RR (95% CI)**	**p-value**
Adverse perinatal outcome, n (%)	9 (33.3)	9 (32.1)	1.04 (0.43-2.5)	0.58
Perinatal mortality, n (%)	2 (7.4)	0 (0)	NA	0.24
Broncho pulmonary dysplasia, n (%)	0 (0)	5 (17.9)	NA	**0.03**
PVL > grade I, n (%)	0 (0)	0 (0)	NA	NA
IVH > grade II, n (%)	1 (3.7)	0 (0)	NA	0.49
NEC > grade I, n (%)	3 (11.1)	0 (0)	NA	0.11
Culture proven sepsis, n (%)	6 (22.2)	7 (25.0)	0.89 (0.29-2.6)	0.53
Sensitivity analysis			**Adjusted RR (95% CI)**	**p-value**
Adverse perinatal outcome			1.03 (0.51-2.1)	0.93
Secondary outcomes (child level)	**Nifedipine (n= 27)**	**Placebo (n=28)**	**RR (95% CI)**	
Birth weight, grams median (IQR)	1745 (1250-1920)	1424 (945-1963)		0.34
NICU admittance, n (%) **Length in days, median (IQR)**	20 (74.1) 11 (3-22)	23 (82.1) 11 (5-55)	0.90 (0.69-1.2)	0.35 0.24
Ventilation support, n (%) **Length in days, median (IQR)**	5 (18.5) 1 (1-9)	6 (21.4) 4 (1-8)	0.86 (0.25-2.9)	0.53 0.93
Total days in hospital until 3 months corrected age, days, median (IQR)	32 (22-56)	48 (30-90)		**0.04**
Secondary outcomes (maternal level)	**Nifedipine (n= 25)**	**Placebo (n= 25)**	**HR (95% CI) / RR (95% CI)**	
Gestational age at delivery, mean (SD), weeks	32.0 (29.1-33.3)	30.0 (26.3-32.1)	NA	0.15
Prolongation of pregnancy				
Days, median (IQR)	11 (4-19)	8 (5-25)	1.02 (0.58-1.8)	0.92
≥48 hours, n (%)	23 (92.0)	25 (100)	0.92 (0.92-1.05)	0.25
≥7 days, n (%)	16 (64.0)	15 (60.0)	1.07 (0.67-1.7)	0.50
Maternal mortality, n (%)	0 (0)	0 (0)	NA	NA
Discontinuation of study medication, n (%)	19 (76.0)	18 (72.0)	1.06 (0.74-1.5)	0.40
Due to progression into labor, n (%)	15 (60.0)	14 (56.0)	1.07 (0.63-1.8)	0.50
Due to side effects, n (%)	2 (8.0)	0 (0)	NA	0.49
Due to signs of intra uterine infection, n (%)	6 (24.0)	8 (32.0)	0.75 (0.26-2.1)	0.38

RR: relative risk; CI: confidence interval; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; NEC: necrotizing enterocolitis; IQR: inter quartile range; NICU: neonatal intensive care unit; HR: hazard ratio.

Comment

In this randomized clinical trial among women with PPROM without contractions, we found no significant differences between treatment with nifedipine or placebo in terms of perinatal outcomes and prolongation of pregnancy. However, the trial was underpowered as only 50 of the targeted 120 women could be included.

Our results are in line with previous studies in which women with PPROM did not seem to benefit from treatment with prolonged tocolysis.[10] Our study has several strengths. The trial was a randomized, double-blind, placebo controlled trial, thereby minimizing the risk of bias. Furthermore our primary outcome was a composite of adverse perinatal outcomes, which we believe reflects the main goal of tocolysis: improving neonatal outcome. Our study has limitations as well. The most important limitation is the small sample size due to premature ending of the study. We planned to recruit 120 women, but recruitment was stopped after 50 women had been included. Our sample size only had a 45% power to detect a 20% reduction in adverse perinatal outcome. Thus, although we found a comparable rate of composite adverse perinatal outcome, arguably our small sample size indicates that we might have missed a relevant difference. Therefore, it may still be possible that use of nifedipine results in a clinically relevant difference in perinatal outcomes in women with PPROM without contractions. Other studies performed on tocolysis in women with PPROM all have small sample sizes and are mostly dated from the 1980s and 1990s. Results of a Cochrane review showed no improvement in neonatal outcomes, however not all trials used standard corticosteroid therapy and antibiotics.[10]

An additional argument against a potential effect of nifedipine in otherwise symptom free women with PPROM is that we found no effect from nifedipine on time to delivery. Furthermore the number of women that discontinued study medication because of progression into labor was high, and comparable between the groups (60% in the nifedipine group vs. 56% in the placebo group). In absence of such an effect on duration of pregnancy, it is unlikely that children born from women with PPROM will benefit directly from nifedipine. This is in line with our previous study on prolonged tocolysis in women with arrested preterm labor, the APOSTEL II study, that did not show a difference in short term perinatal outcome or at 2 year follow-up.[16;17] Two deaths occurred in the nifedipine group and although no causal relation could be determined between the two deaths and possible side effects of nifedipine, we cannot exclude an indirect effect. It may be hypothesized that the administration of nifedipine in pregnant women has an adverse effect on the fetus, for example by lowering maternal blood pressure and reducing placental perfusion. However, previous studies have shown contradictory results, thus no final conclusions can be drawn.[18-22]

Looking at separate components, we found a significantly lower rate of BPD in women treated with nifedipine (0% in the nifedipine group compared to 18% in the placebo group). This has not been reported in previous studies. A possible explanation for this

difference could be the higher gestational age at study entry and delivery in the nifedipine group, since the occurrence of BPD decreases with increasing gestational age at delivery.[12] All cases of BPD occurred in neonates born before 30 weeks of gestation. In addition there were two perinatal deaths in the nifedipine group at 24^{+1} and 25^{+4} weeks. BPD can only be diagnosed if survival occurs to a corrected age of 36 weeks of gestation.[12]

In conclusion, this randomized clinical did not show a beneficial effect of prolonged tocolysis with nifedipine on perinatal outcomes or prolongation of pregnancy in women with PPROM without contractions. Therefore we do not recommend prolonged tocolysis in women with PPROM without contractions. However, since results are based on a small sample size, a difference clinically relevant differences cannot be excluded and conclusions should be drawn with caution.

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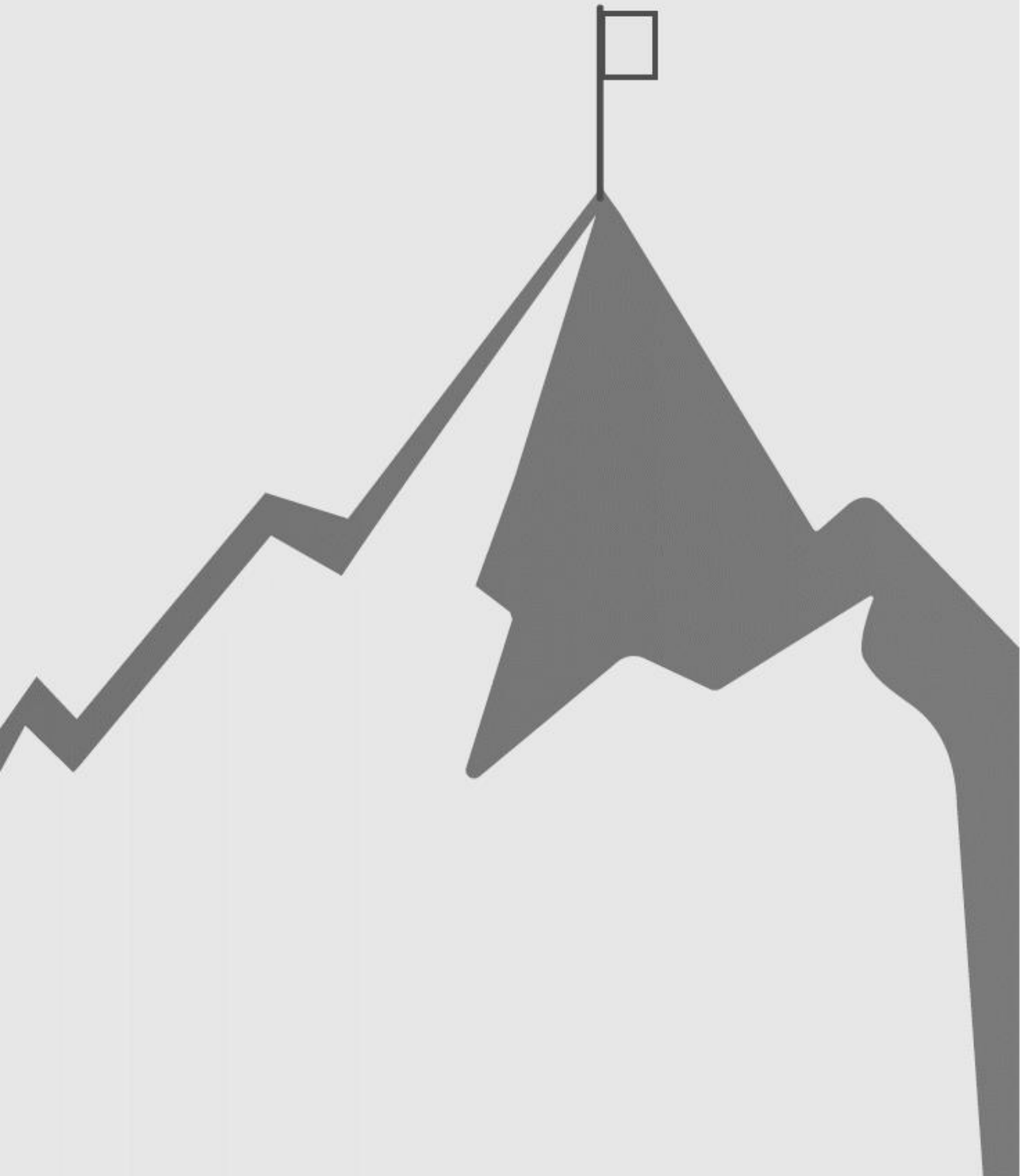

Chapter 8

A multi-country survey and review of ongoing trials on the management of women at risk of preterm birth

T.A.J. Nijman, J.P. Vogel, A. Franx, B.W. Mol, M.A. Oudijk

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Abstract

Objective

The aim of this study was to survey the current clinical recommendations of the management of threatened preterm birth around the world, as well as ongoing research on the topic.

Methods

We performed an online, multi-country survey of obstetricians, to determine what clinical practices are currently recommended in their national guidelines concerning the management of threatened preterm birth. Furthermore, we searched international trial registry databases for ongoing or planned trials in the management of preterm birth.

Results

We surveyed 24 countries, of which 18 (75%) reported having a national guideline. There was considerable variability in recommended clinical practice, mainly in the use of tocolytic drugs. There was more uniformity in the use of antenatal corticosteroids. Magnesium sulfate for fetal neuroprotection is recommended in over half of the countries. We identified 12 trials regarding tocolysis with only one trial powered for neonatal outcomes, 2 trials regarding antenatal corticosteroids and 2 regarding magnesium sulfate.

Conclusions

Considerable variation exists between countries in recommendations regarding the use of tocolytics for the management of women with threatened preterm birth. We argue that there is a need for new trials comparing tocolytic drugs with placebo, sufficiently powered for substantive neonatal outcomes.

Introduction

Preterm birth is a major health challenge. Worldwide, it is estimated that 11.1% of all children are born preterm, ranging from 5% in some European countries to 18% in African countries.[1] Preterm birth is one of the leading causes of childhood mortality, and accounts for approximately 15% of all death until five years of age.[2]

Several interventions that are administered to women at risk of preterm birth in order to improve newborn outcomes have been extensively evaluated, including antenatal corticosteroids for fetal lung development, tocolytics to delay or stop uterine contractions and magnesium sulfate for fetal neuroprotection.

A single course of corticosteroids administered over 48 hours has been shown to improve short-term neonatal outcomes such as decreased neonatal mortality, infant respiratory distress syndrome and intraventricular hemorrhage.[3] Long-term outcomes, such as cerebral palsy and poor neurological development also seem to be improved by administration of corticosteroids.[4] However one study showed that prophylactic corticosteroids before a planned term Cesarean section increases the risk of the infant to belong to the lower quartile of academic performance.[5] When pregnancy continues for seven days or more after the first administration, a repeat dose of antenatal corticosteroids can be administered, which has shown to improve short-term neonatal outcomes. However adverse long-term outcomes, such as attention disorders and problems at school might be increased too.[6]

Tocolytic drugs administered to women with threatened preterm birth, have been shown to postpone the time to delivery; this can allow transfer to a higher-level centre and administration of antenatal corticosteroids. Tocolytic drugs include calcium channel blockers (eg. nifedipine), oxytocin receptor antagonists (eg. atosiban), cyclooxygenase (COX)-inhibitors (eg. indomethacin) and β-adrenoreceptor agonists (eg. ritodrine). Most of these drugs have been shown to prolong pregnancy for at least 48 hours and in some cases up to seven days. However, when compared to placebo there is little evidence that tocolytic drugs alone improve substantive neonatal mortality and morbidity outcomes. In the latest World Health Organization (WHO) recommendations of interventions to improve preterm birth outcomes[7], tocolytic therapy is not recommended for women with threatened preterm birth to improve neonatal outcomes. However, the recommendations specify that tocolytic drugs (nifedipine as the preferred agent) can be considered to allow administration of antenatal corticosteroid, and/or facilitate in-utero fetus transfer to an appropriate neonatal health care setting.[7]

As rates of newborn morbidity and mortality are inversely related to gestational age, it has long been presumed that maintenance tocolysis could improve neonatal outcomes. However, recent research has shown that maintenance tocolysis with nifedipine, 17-alpha-hydroxyprogesterone caproate, atosiban or magnesium sulfate do not appear to improve neonatal outcomes.[8-10] Vaginal progesterone as maintenance treatment after

arrested preterm labor seems a promising treatment strategy, although this was not confirmed in large randomized clinical trials on the topic.[11,12]
In threatened preterm birth at less than 32 weeks of gestational age (GA), magnesium sulphate, as neuroprotective agent, can be administered for neuroprotection to reduce severe neurological disorders such as cerebral palsy.[13]
A major health care problem such as preterm birth requires an evidence-based approach, with clinical management according to the best available evidence. The aim of this study was to make an inventory of clinical recommendations in management of women in threatened preterm birth in multiple countries. Furthermore, we aimed to identify all ongoing and planned trials to create an overview of current and ongoing research projects in this area.

Methods

We performed a multi-country survey of obstetricians using two international research networks. The Global Obstetrics Network (GONet, http://www.globalobstetricsnetwork.org) is a group of international investigators. The GONet collaboration was initiated in 2010, bringing together research groups conducting clinical trials and observational studies in obstetrics. GONet's goal is to identify and highlight pressing issues in the fields on maternal–fetal medicine and obstetrics.[13] The WHO Multi-Country Survey on Maternal and Newborn Health Research Network (WHOMCS) is an international collaboration of researchers in obstetrics that participated in or contributed to the two recent WHO surveys on maternal and perinatal health – the WHO Global Survey on Maternal and Perinatal Health (2004-2008) and/or the WHO Multi-Country Survey on Maternal and Newborn Health (2010-2011). Both studies were facility-based, cross-sectional surveys of maternal and newborn health outcomes.

The survey (appendix 1) consisted of the following items. The first item was if there is a national guideline present; when there was no national guideline the survey ended. Furthermore it contained the assessment of threatened preterm birth. Regarding tocolysis the following items were included: the use of tocolysis: only transport or 48 hours; indication(s): threatened preterm birth, PPROM and/or multiple pregnancy ; gestational age range; drug(s) of choice; maintenance tocolysis. Furthermore the use of corticosteroids, rescue course of corticosteroids and the use of magnesium sulphate as neuroprotective agent were inquired.

Members of the GONet and WHOMCS Research Network were contacted via email and invited to participate in the survey. Reminders were sent after 2 and after 5 weeks. The survey was conducted in English. The survey contained a statement of consent for completion. As this was a survey of health professionals, and the questions related to

current practices recommended in their country, ethics approval for the survey was not sought. The survey was conducted using Google Forms.

To identifying all ongoing and planned trials, we searched the following online registers www.clinicaltrials.gov, www.clinicaltrials.nl, http://www.isrctn.com, www.who.int/ictrp, http://www.anzctr.org.au, http://www.ensaiosclinicos.gov.br, http://ctri.nic.in, http://trials.slctr.lk, http://registroclinico.sld.cu, http://www.irct.ir, http://www.pactr.org, https://www.clinicaltrialsregister.eu. For tocolysis we used the search terms "(preterm OR premature) AND (birth OR labor OR labour) AND (tocolysis OR tocolytic)" and "(pprom OR premature rupture of membranes) AND (tocolysis OR tocolytic). For antenatal corticosteroids the following search terms were used: "(preterm OR premature) AND (birth OR labor OR labour) AND corticosteroids. For magnesium sulfate the following search terms were used: (preterm OR premature) AND (birth OR labor OR labour) AND (magnesium AND (sulfate OR sulphate). The last search was conducted on November 14th 2016.

Results

Survey

Thirty-three researchers/clinicians from 33 countries were contacted from the two networks to complete the survey. Of these, 24 (73 %) respondents were from the following countries: Argentina, Australia/New Zealand, Brazil, Canada, Chile, China, Democratic Republic of the Congo, Ethiopia, France, Ghana, Guinea, Ireland, Kenia, Mongolia, Myanmar, Netherlands, Nigeria, Pakistan, Spain, Sri Lanka, Sweden, Switzerland, Thailand and the United Kingdom. Of these, 18 respondents (75%) reported that a national guideline existed regarding the management of threatened preterm birth and thus completed the survey. Australia/New Zealand, Canada, Democratic Republic of the Congo, Nigeria, Pakistan and Sweden did not have a national guideline.

Assessment of threatened preterm birth

In most countries (15/18, 83%) cervical length is recommended in the assessment of threatened preterm birth, as is digital examination (12/18, 67%). Fetal fibronectin is only recommended in 5 countries (28%). Another method used is the speculum examination (3/18, 17%).

Tocolytic therapy

Ireland was the only country in which the recommendation of the use of tocolysis was restricted to transport of women to a tertiary hospital. All other respondents reported recommendation for the administration of tocolytics for 48 hours. Indication for tocolytic therapy varied between the countries. In women with PPROM, 9 countries (50%)

recommend to administer tocolytics. For twin pregnancies, it was recommended in 10 countries (56%) to administer tocolytics. Most countries (11/18, 61%) advised administration of tocolytics with a lower limit of 24 weeks of gestation. However, in one country (France) there was no lower limit, in one country (Ghana) the lower limit was 23 weeks of gestation and in five countries (China, Ethiopia, Kenya, Mongolia and Myanmar) the lower limit was 28 weeks of gestation. The upper limit was 34 weeks of gestation in most countries. In Thailand and Guinea the upper limit was 35 weeks of gestation. In China and Myanmar this was 36 weeks of gestation. Maintenance/prolonged tocolysis is only performed in three countries (France, Guinea and Mongolia).

Preferred tocolytic drug

Respondents reported that nifedipine was the most commonly recommended tocolytic drug (16/18, 89%). Atosiban was the second most commonly recommended drug, in 8 countries (44%). The latter was mostly recommended in European countries; outside of Europe only Argentina and China reported recommendations for atosiban use. Indomethacin was recommended for use in four countries (22%). Different types of betamimetics (such as ritodrine or salbutamol) were reported being recommended for use in nine countries (50%).

Antenatal corticosteroids

All respondents reported that their national guidelines recommended administering a course of antenatal corticosteroids for women at risk of preterm birth. Respondents used either betamethasone (82%) or dexamethasone (64%). A repeated or rescue dose of antenatal corticosteroids was recommended in 9 countries (50%).

Neuroprotection

Neuroprotection with magnesium sulfate was recommended for use in 11 countries (61%). It is administered within a gestational age range of with a lower limit of 24 weeks and an upper limit up to 30 or 32 weeks of gestation.

Ongoing trials

Tocolysis

Our search for ongoing or planned trials for tocolysis revealed 12 trials (Table 1). Ongoing trials are comparing indomethacin, nifedipine, atosiban or retosiban with placebo. Most trials have prolongation of pregnancy or preterm birth as the primary outcome measure, with a sample size range of 60-330 patients. This implies that these studies were likely not powered to detect differences in important (but less frequent) adverse neonatal outcomes. Atosiban is being compared with retosiban (a new oxytocin receptor antagonist) with time to delivery as primary outcome. One study is planned to compare

retosiban with placebo, with time to delivery and a composite of adverse neonatal outcomes as primary outcome measure. This study, which aims to include 900 women, is the only trial we identified with enough power to detect differences in neonatal outcome. Indomethacin and nifedipine are being compared as well, in this trial the primary outcome is recurrent preterm labor within two weeks of randomization. One study is comparing nifedipine and atosiban in twin pregnancies, with time to delivery as primary outcome.

Antenatal corticosteroids

Two trials were found regarding antenatal corticosteroids (table 1). Both trials are comparing rescue courses of corticosteroids. Composite neonatal morbidity and length of NICU stay were the primary outcomes.

Magnesium sulfate

Two trials were found regarding magnesium sulfate (table 1). One trial is comparing magnesium sulfate to placebo, with cerebral palsy as primary outcome. The second trial is comparing magnesium sulfate to nifedipine, which is believed to have neuroprotective abilities as well. Primary outcome in the latter is difference in mean Doppler indices of middle cerebral artery.

Discussion

Main findings

We surveyed two research networks on current recommendations on the management of threatened preterm birth in 23 countries. We found a large diversity in countries across the world regarding national recommendations on the use of tocolytic drugs. In spite of the lack of evidence of benefit of tocolytic drugs alone, they are still in widespread use. This is supported by findings of a secondary analysis of the WHOMCS dataset which identified that tocolytics are often used, with beta-blockers being the most commonly prescribed agent.[15] Differences in recommended tocolytic drugs may be partly explained by different drug availability. For example, atosiban is registered in most countries in Europe, but not in the United States, Australia or many African countries. Costs may also be a factor; atosiban is much more expensive than nifedipine.[16] Differences in recommendations may be due to a lack of convincing evidence for the choice of a specific tocolytic drug. Regarding ongoing or planned trials; for tocolysis only one trial was powered for neonatal outcomes.

Table 1. Ongoing and planned trials			
Tocolysis			
Drugs compared	**Place**	**Primary outcome**	**Sample size**
Atosiban vs. placebo	Vienna, Austria[2]	Prolongation of pregnancy	60
Atosiban vs. retosiban	GlaxoSmithKline, US[1]	Time to delivery	330
Indomethacin vs. nifedipine	Stanford University, US[1]	Recurrent preterm labor within two weeks after randomization	110
Indomethacin vs. placebo	Metrohealth Medical Center Ohio, US[1]	Delivery within 48h	84
Indomethacin vs. placebo in PPROM	Thomas Jefferson University, US[1]	Prolongation of pregnancy	116
MgSO4 vs. ritodrine	Seoul National University Hospital, South Korea[1]	Ceasing of labor	50
Nifedipine vs. indomethacin	Saint Thomas Hospital, Panama[1]	Reduction of preterm birth < 48h	216
Nifedipine vs. nifedipine and indomethacin	The University of Texas Health Science Center, Houston, US[1]	Delivery within 48h	144
Nifedipine vs. nifedipine and sildenafil citrate	Al Hayat National Hospital, Saudi Arabia[1]	Time to delivery	227
Nifedipine vs. placebo	University of Texas, US[1]	Preterm birth < 37 weeks	150
Retosiban vs. placebo	GlaxoSmithKline, US[1]	Time to delivery and neonatal outcomes	900
Nifedipine vs. atosiban in twin pregnancies	Tel-Aviv Sourasky Medical Center, Israel[1]	Time to delivery	140
Antenatal corticosteroids			
Rescue course in PPROM Betamethasone/dexamethasone vs placebo	Mednax Center for Research, Education and Quality, US[1]	Composite neonatal morbidity	142
Rescue course in PPROM betamethasone vs placebo	The University of Texas Medical Branch, Galveston, US[1]	Length of NICU stay	98
Magnesium sulfate			
Magnesium sulfate vs. placebo	Hvidovre University Hospital, Denmark[1]	Cerebral palsy	500
Magnesium sulfate vs. nifedipine	Kasr El Aini Hospital, Egypt[1]	Difference in mean Doppler indices of middle cerebral artery	130
[1]www.clinicaltrials.gov; [2]www.clinicaltrialsregister.eu			

Strengths and limitations

This study has several strengths. First, we used a standard tool in a multi-country survey. Using this strategy we believe we created a wide perspective on this topic. Furthermore, we performed a comprehensive search of multiple trial registry databases, thereby covering a large part of all registered research worldwide. However a known problem with ongoing or planned trials is that many are not registered. Some limitations of or study must also be considered. We did not review the clinical guidelines from different countries directly. Thus, it is possible that respondents may not have accurately reported on their

national guidlines. However, respondents were OBGYN/researchers working in these countries, and we believe likelihood of inaccuracy is low. To validate the accuracy of the answers of the responders, national guidelines of three countries (France, Ireland and Switzerland) were checked and few irregularities were found. While the survey respondents were a convenience sample, our objective was to maximize diversity of countries represented.

Interpretation

In February 2015, GONet hosted a satellite meeting at SMFM where the issue of tocolytic drug research was discussed by GONet collaborators. It was generally agreed by the attendees that there is still no clear evidence regarding whether tocolytics improve neonatal outcomes at all, and that future research should address this uncertainty first. This argument was also supported by the guideline development group for the recent preterm birth guidelines published by WHO, which highlighted that insufficient evidence exists to recommend the routine use of tocolytics for threatened preterm labour.[7] Most tocolytic trials performed so far have not been powered for substantive neonatal outcomes, opting instead to use intermediate outcomes relating to prolongation of pregnancy. Regrettably, this appears also to be the case for the current ongoing or planned trials on tocolytic drugs - most had primary outcomes regarding prolongation of pregnancy, preterm birth or time until delivery, and are not powered for substantive neonatal outcomes (such as perinatal mortality). An appropriately powered trial would require a larger sample size, and most likely an international collaborative effort.

To establish whether tocolytics alone do improve newborn outcomes or not, we believe that further research is required. First, placebo-controlled trials of tocolytic drugs that are adequately powered for substantive newborn outcomes are needed. Proven effective strategies such as administration of corticosteroids and magnesium sulfate should also be part of the protocol in both study arms, in order to assess if there is any additional effect of tocolytic drugs. In countries where routine tocolytic drug use is the standard of care (despite the limitations of the evidence), conducting such a trial may be challenging – it may be most feasible in countries where tocolytics are currently not routinely used. Secondary analyses of observational datasets may provide clues as to whether tocolytics are beneficial, harmful or are not having an effect. In addition, knowledge synthesis activities, such as network meta-analyses or individual patient data meta-analyses (IPDMA) could provide additional information. When new trials are initiated, IPDMA's may be conducted prospectively in order to increase sample sizes and standardize outcomes across trials. Such activities are methodologically complex (requiring prior agreements on core outcomes, data sharing, oversight and analysis across trials) and also require a strong willingness to collaborate. However, such prospective meta-analyses are possible - a

prospective IPDMA, the STRIDER-trial (*Sildenafil TheRapy In Dismal prognosis Early onset fetal growth Restriction*), is currently being performed.[17] This is an international collaboration between Canada, Australia, New Zealand, the United Kingdom, Ireland and the Netherlands. In all countries, randomized clinical trials are being performed concurrently, with prior agreement that all data will be combined for analysis. Only through this international collaboration of independent research groups is it possible to warrant the sample size needed for the only relevant primary outcome (healthy perinatal survival). Prospective IPDMA's require pre-defined standard outcome measures. Recently a core outcome set was developed for the evaluation of preventive interventions for preterm birth in asymptomatic pregnant women.[18] It resulted in the following outcomes: four maternal outcomes: 1) maternal mortality, 2) maternal infection or inflammation, 3) prelabor rupture of membranes, and 4) harm to mother from intervention. Nine outcomes were related to offspring: 5) gestational age at birth, 6) offspring mortality, 7) birth weight, 8) early neurodevelopmental morbidity, 9) late neurodevelopmental morbidity, 10) gastrointestinal morbidity, 11) infection, 12) respiratory morbidity, and 13) harm to offspring from intervention. We call on researchers in any future tocolytic trials or IPD efforts to use this core outcome set.

Conclusion

There is a wide variation regarding recommendations for the management of threatened preterm birth between countries worldwide, with the largest difference in the use of tocolytic drugs. As preterm birth is an important contributor to newborn, childhood and lifelong morbidity and mortality, this variation is an undesired situation. We conclude this might be due to the lack of well-designed and adequately powered trials using adverse neonatal outcome as the primary outcome measure. We emphasize that there is a need for new trials comparing tocolytic drugs with placebo. International collaboration will be necessary to accomplish trials large enough to result in final conclusions on adverse neonatal outcomes. The use of predefined core outcome measures,could facilitate the performance of IPDMA's.

Appendix 1

Survey on management of women in threatened preterm birth

1. What is the name of your country?

2. Does your country have a national guideline relating to the management of women in preterm labour?
    a. If no or unsure, the survey is complete.

3. What methods of assessment does the guideline recommend to set the diagnosis threatened preterm birth?
    - Cervical length
    - Digital examination
    - Fetal fibronectin
    - Amniocentesis
    - Other:

4. Does the guideline recommend for the use of tocolytic therapy?
    If so:
    a. Is it recommended for:
        i. Intra uterine transfer to a center with NICU facilities only?
        ii. 48 hours administration to administer corticosteroids?
    b. Is tocolytic therapy administered in women with:
        i. Threatened preterm birth with intact membranes? Y/N
        ii. PPROM? Y/N
        iii. Twin pregnancy? Y/N
    c. What is the gestational age range in which it is performed?
    d. What is/are the drug(s) of choice?
        - Atosiban
        - Nifedipine
        - Indomethacine
        - Betamimetics
        - Other

    e. Does the guideline recommend for the use of maintenance/prolonged tocolysis?

5. Does the guideline recommend for the use of antenatal corticosteroids?
    If so:
    a. Which drug is recommended?
        - Betamethasone

- Dexamethasone
- Other:

b. Which regimen is used?
c. Does the guideline recommend for the use of a rescue/repeated course of corticosteroids?

6. Does the guideline recommend for the use of magnesium sulfate as a neuroprotective agent?

   If so

a. What is the gestational age range in which it is administered?

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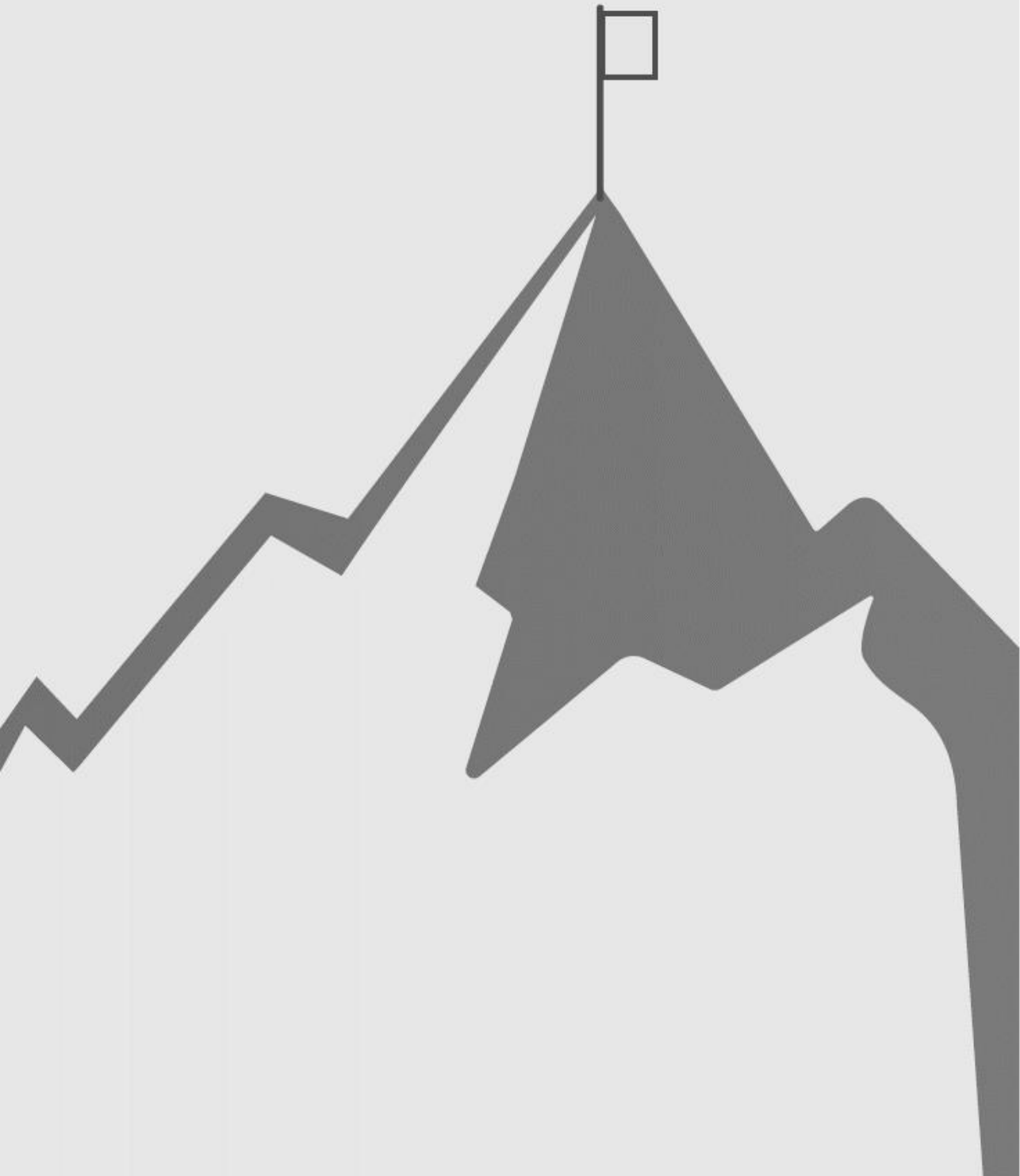

Chapter 9

Summary and general discussion

Preterm birth remains one of the most important challenges in the obstetric field. To improve neonatal outcome, many interventions have been developed and investigated. The etiology of spontaneous preterm birth is complex and many factors may play a role. Inflammation or infection has been proven to play a large role. However there is also evidence that maternal vascular malperfusion lesions have a role in spontaneous preterm birth. In indicated preterm birth, maternal vascular malperfusion lesions are very frequently seen. To investigate the possible overlap in placental pathological lesions between spontaneous and indicated preterm birth, we performed a case control study **(chapter 2)**. We classified the placentas in the presence of infectious-inflammatory lesions, maternal vascular malperfusion lesions, both lesions or no lesions. To examine the effect of gestational age, we stratified women in immature (17 - 23+6 weeks), extremely (24 - 27+6 weeks), very (28 - 31+6 weeks) and moderate/late (32 - 36+6 weeks) preterm birth. We studied 233 women, 121 women with spontaneous preterm birth and 112 women with indicated preterm birth. Among women with spontaneous extremely preterm birth, we mainly found infectious-inflammatory lesions. After 28 weeks of gestation a shift was seen from infectious-inflammatory to maternal vascular malperfusion lesions, in women with spontaneous very and moderate/late preterm birth, maternal vascular malperfusion lesions were most frequent. In women with indicated preterm birth, maternal vascular malperfusion lesions were predominantly present throughout all gestational age categories. These findings suggest an overlap in the pathological pathway between spontaneous preterm birth and indicated preterm birth (mainly preeclampsia and intra uterine growth restriction). This provides possibilities for therapeutic options in the prevention of preterm birth.

Preterm birth can have tremendous consequences for both the child and the family the child is born into. In **chapter 3** we created an overview of all current interventions to improve neonatal outcomes. The first challenge is to identify women with a high risk of delivering prematurely. Currently, the most accurate way is the combination of the cervical length and fetal fibronectin. When a woman is identified as high risk, a 48-hour course of corticosteroids has shown to improve neonatal outcomes, such as necrotizing enterocolitis, infant respiratory distress syndrome, intraventricular hemorrhage and neonatal death. To allow the administration of the corticosteroids, tocolytic drugs can be administered for 48 hours. Which tocolytic drug is the best choice has yet to be determined. The use of atosiban and nifedipine is preferred, based on the largest effectiveness in terms of prolongation of pregnancy, improving perinatal outcomes and most favorable safety profile. However, these drugs have not been compared in a large randomized clinical trial. Besides corticosteroids and tocolytic therapy, administration of magnesium sulfate at less than 32 weeks of gestation has shown to improve short-term neurologic outcomes, such as cerebral palsy and gross motor function. Antibiotic therapy

should only be administered in women with PPROM to improve short-term neonatal outcomes.

As mentioned before the preferred tocolytic drugs are nifedipine and atosiban, though they have not been compared in a large randomized clinical trial with perinatal outcomes as a primary outcome. Therefore the APOSTEL III study was performed **(chapter 4)**. In this multicenter randomized clinical trial we included women between 25 en 34 weeks of gestation with threatened preterm birth. Women were allocated for either nifedipine or atosiban. The primary outcome was a composite of adverse perinatal outcome, including perinatal mortality, bronchopulmonary dysplasia, sepsis, intraventricular haemorrhage, periventricular leukomalacia, and necrotising enterocolitis. The primary outcome occurred in 14% of the neonates in the nifedipine group, compared to 15% in the atosiban group (RR 0.91, 95% CI 0.61-1.37). Perinatal death was non-significantly higher in the nifedipine group (2% vs. 5%; RR 2.20, 95% CI 0.91-5.33). Significantly less neonates were admitted to the NICU in the nifedipine group (52.2% vs. 61.9%; RR 0.85 (0.73–0.99)). Median (IQR) prolongation of pregnancy was similar, 7 days (1.0–40.0) for nifedipine versus 4 days (1.0-38.0) for atosiban (HR 0.88 (0.72–1.07)). Maternal side effects did not differ between the groups. The study concluded that perinatal outcomes and efficacy were similar between nifedipine and atosiban, but the safety profile of nifedipine warrants further investigation. Not only clinical outcomes are important, also the costs play a role in the decision of the preferred tocolytic drug. Therefore, we performed an economic analysis alongside the APOSTEL III study **(chapter 5)**. In this analysis we assessed the costs in the time between randomization and 6 weeks postpartum, and was performed from a societal perspective. Furthermore, incremental cost-effectiveness ratios were computed, which represent the costs to prevent one adverse neonatal outcome. The mean costs per patient were €45 476 in the nifedipine group compared to €51 064 in the atosiban group (mean difference -€5 588 (95% confidence interval –13 448 to 1 618). The difference in costs was mainly driven by the lower NICU admittance rate in the nifedipine group. Regarding the incremental cost-effectiveness ratios, no differences were found in the primary outcome, however costs were higher for atosiban. The economic analysis showed that treatment with nifedipine results in lower costs when compared to treatment with atosiban, therefore atosiban does not seem to be a cost effective strategy. However, as mentioned in the original APOSTEL III study, the safety profile of nifedipine warrants further investigation.

One of the most frequent complications of preterm birth is brain injury. In **chapter 6** we performed a secondary analysis of the APOSTEL III trial. The aim of this study was to evaluate the influence of nifedipine on overall brain injury compared to atosiban. We studied all neonates born before 32 weeks of gestation in the University Medical Center Utrecht and Academic Medical Center Amsterdam. To evaluate type and severity of the

primary outcome (overall brain injury) all neonatal ultrasounds made during neonatal intensive care admission and medium care admission were analyzed. We studied 102 women, who gave birth to 117 neonates. Brain injury was found in 22 (43.1%) of the neonates exposed to nifedipine and 37 (56.1%) of the neonates exposed to atosiban (RR 0.60; 95% CI: 0.29-1.24). Since this was a secondary analysis, sensitivity analysis was performed. When corrected for maternal age and gestational age at randomization, we found no statistical difference of brain injury (OR 0.58; 95% CI 0.27-1.27). An interesting finding in this study was that cesarean section seemed protective against brain injury. In the nifedipine group more cesarean sections were performed for the indication fetal distress. Logistic regression showed significantly less brain injury in the group with a cesarean section (OR 0.32; 95% CI: 0.13-0.77). When corrected for cesarean sections, the influence of nifedipine on brain injury became smaller. The fact that more fetal distress was seen in the nifedipine group is an important note; hence the safety of nifedipine for the fetus is still not yet confirmed.

Around one third of all preterm deliveries starts with PPROM. Whether tocolysis in women with PPROM improves perinatal outcomes is unclear. Many countries do not apply tocolysis in patients with PPROM. To investigate the effectiveness of tocolysis in women with PPROM, the APOSTEL IV trial **(chapter 7)** was performed. The aim of this trial was to study the effect of prolonged tocolysis with nifedipine versus placebo in women with PPROM on perinatal outcome and prolongation of pregnancy. We included women with PPROM without contractions between 24 and 33 + 6 weeks of gestation. Women were allocated to daily 80 mg nifedipine or placebo, and treated until start of labor, 18 days of treatment or 34 weeks of gestation was reached. Due to slow recruitment the study was stopped prematurely. At the time of stopping, we included 50 women (25 in both groups). The median gestational age at randomization was 29.9 weeks (IQR 27.7-31.3) in the nifedipine group and 27.0 weeks (IQR 24.7-29.9) in the placebo group. The primary outcome was a composite of adverse perinatal outcomes. The primary outcome occurred in 9 neonates (33.3%) in the nifedipine group and 9 neonates (32.1%) in the placebo group (RR 1.04; 95% CI 0.49-2.2). Two perinatal deaths occurred, both in the nifedipine group. Prolongation of pregnancy did not differ between the nifedipine and placebo group (median 11 vs. 8 days, HR 1.02; 95% CI 0.58-1.79). In this study we could not demonstrate an advantageous effect of nifedipine on perinatal outcomes or prolongation of pregnancy. However, due to small numbers of the study, conclusions should be drawn with caution.

In the first chapters of this thesis we described and investigated many interventions to improve the perinatal and neonatal outcomes. However due to differences in availability and costs, we hypothesized that there would be large differences around the world. The aim of **chapter 8** was to survey the current clinical recommendations of the management

of threatened preterm birth around the world, as well as ongoing research on the topic. We performed an online, multi-country survey of obstetricians, to determine what clinical practices are currently recommended in their national guidelines concerning the management of threatened preterm birth. We used the Global Obstetrics Network (GONet) and the WHO Multi-Country Survey on Maternal and Newborn Health Research Network (WHOMCS). Furthermore, we searched international trial registry databases for ongoing or planned trials in the field of tocolysis, corticosteroids and magnesium sulphate. We surveyed 24 countries across the world, of which 18 (75%) reported having a national guideline. There was considerable variability in recommended clinical practice, mainly in the use of tocolytic drugs. There was more uniformity in the use of antenatal corticosteroids, all countries reported to recommend the use of corticosteroids until 34 weeks of gestation. Magnesium sulfate for fetal neuroprotection is recommended in over half of the countries. We identified 11 ongoing or planned trials that are comparing tocolytic drugs to each other or to placebo. However, only one trial is sufficiently powered to assess neonatal outcomes. Two trials are comparing a rescue course of corticosteroids to placebo. Regarding magnesium sulfate, one study is comparing magnesium sulfate to placebo and one study is comparing magnesium sulfate to nifedipine. This study showed considerable variation between countries in recommendations regarding the use of tocolytics for the management of women with threatened preterm birth. We conclude this is an undesired situation for such a big global health issue.

Implications for practice and future research

Tocolysis in threatened preterm birth

As shown in this thesis, consequences of preterm birth can be detrimental. In chapter 4 we found, respectively 15% and 14% adverse perinatal outcomes for tocolysis using nifedipine or atosiban. In chapter 6, the numbers were even higher, 33% in the nifedipine group and 32% in the placebo group. These numbers indicate the impact of being born premature. In chapter 4 over 75% of the women delivered preterm, in chapter 6, nearly all women delivered preterm, indicating that even when tocolytics are administered, many women deliver before 37 weeks of gestation. Many trials have been performed in the past, comparing different tocolytic drugs to each other or to placebo. However, no placebo-controlled trials were powered for neonatal outcomes. For most tocolytic drugs, it has been shown that they prolong pregnancy for 48 hours to 7 days, though an effect on neonatal outcomes was never found.[1] The current situation is that tocolytics are administered only to postpone delivery for 48 hours to allow administration of corticosteroids, not to improve neonatal outcome itself. However, this strategy is questionable, since there might be a pathological process behind the threatened preterm birth, and the administration of tocolytic drugs may even postpone delivery and worsen the neonatal outcome. Especially in women with PPROM administration of tocolytic drugs

is highly questionable. In chapter 4 we found that most women with PPROM and contractions deliver not long after inclusion (2 days for nifedipine versus 3 days for atosiban). For women with PPROM it can be questioned if delivery should be delayed, since the fetus might be exposed longer to a possible hostile environment, as intra-uterine infection is frequently encountered in these women. A recent Cochrane review showed more chorioamnionitis on pathological examination of placenta and membranes and lower Apgar scores in women who were treated with tocolytics. The Cochrane review showed no improvement of neonatal outcome in women treated with tocolytics.[2] Furthermore it has been shown that chorioamnionitis increases neurodevelopmental problems at child age.[3] A large placebo controlled trial should provide conclusive evidence if tocolysis leads to improvement of neonatal outcomes in women with PPROM. Until such a trial is completed, the routine administration of tocolysis in women with PPROM should be questioned by clinicians.

Future studies on tocolysis in general should be placebo-controlled trials, powered for neonatal outcomes. Furthermore, long-term outcomes are essentially the most important outcomes and future studies in obstetrics should also focus on the long-term effects of the interventions studied in the trials. Currently we are performing a long-term follow-up study of the APOSTEL-III trial. At three years of age, neurodevelopmental and behavioral outcomes will be studied. This will provide insight in the long-term effect of nifedipine and atosiban. Especially for nifedipine, the safety profile for use in pregnancy has yet to be determined. In chapter 4 we found a (non-significant) higher mortality rate, and although no direct association was made between death and use of nifedipine, these findings are of concern and warrant further investigation. Until the safety is really established, the use of nifedipine should be limited to trials.

In 2010 the Global Obstetrics Network (GONet) was formed. GONet is a collaboration between many researchers in the obstetric field from around the world; with the idea to work together in clinical trials and studies.[4] The ambition is formulated to execute large placebo controlled trials, but until now such initiatives have not been funded. Recently, a core outcome set was published for clinical trials regarding preterm birth.[5] This set is a number of outcomes, which enables, using GONet, to perform clinical trials comparing tocolytic drugs to placebo allover the world and to merge all trials in and Individual Patient Data meta-analysis. Using this method together we are able to create a very large patient population, which could never be reached in countries on their own.

Prevention of preterm birth

Once clinical signs develop, it is difficult to stop threatened preterm birth and as mentioned before, it may not even be wise to do so. The interventions discussed in this

thesis are all designed and administered with the assumption that they improve perinatal outcomes, however they do not prevent preterm birth. Therefore, prevention of the initiation of the subclinical pathway long before clinical signs of threatened preterm birth are noted, might lead to a decrease of preterm birth. Nonetheless, due to the many different causes of preterm birth this is a great challenge. First, the distinction between low-risk pregnancies and high-risk pregnancies is very important. Therefore, maternal characteristics, medical and obstetric history and the current pregnancy are crucial. Ethnicity, low socio-economic status, smoking status and low or high BMI are known maternal risk factors for preterm birth.[6-10] A history of previous preterm birth is the most important risk factor to have a recurrent preterm birth.[11] In the medical history it is important to know if women had cervical surgery.[12] Women with a multiple pregnancy are at high risk for preterm delivery.[13]

Low-risk pregnancies

Cervical length

Women with a short mid-pregnancy cervical length (< 25mm) are at increased risk of preterm delivery, with a relative risk of 4.5 (95% CI, 2.7-7.6).[14-16] A recent meta-analysis, including the results of the OPPTIMUM-study, confirmed that treatment with vaginal progesterone decreases the risk of preterm delivery < 34 weeks or fetal death in women with a short cervix and a singleton pregnancy (RR 0.66 (95% CI, 0.52-0.83).[17] Currently the Quadruple P-study compares treatment with vaginal progesterone to a cervical pessary in women with a short cervix (in both singleton and multiple pregnancies).[18] Measurement of the mid-pregnancy cervical length has not been implemented as a standard screening tool in the Netherlands. However it qualifies as an effective screening method, as it is a standardized method, not costly or too invasive, has good predictive values and the treatment is effective.

Bacterial vaginosis

As shown in chapter 2, infectious-inflammatory placental lesions are an important cause of preterm delivery, especially in early gestations. Bacterial vaginosis is a polymicrobial condition. There is a decrease in the quality or quantity of lactobacilli and a 1000-fold increase in the number of other organisms such as Mycoplasma hominis, Gardnerella vaginalis and Mobiluncus species. In pregnancy, bacterial vaginosis has been associated with early, late and recurrent miscarriage, preterm prelabor rupture of the membranes (PPROM), postpartum endometritis and preterm birth.[19] When bacterial vaginosis is detected early in pregnancy, it is even associated with a five- to sevenfold increased risk of preterm birth.[20,21] Bacterial vaginosis occurs in one third of the women.[22] Treatment with clindamycin is associated with a reduction in preterm birth.[23] The gold standard for the diagnosis bacterial vaginosis is the Nugent score.[24] However, DNA sequencing techniques

are being investigated to evaluate the vaginal microbiome. With these tests a detailed description of the microbiome can be created.[24] Wether screening all pregnant women is effective has yet to be determined. An (cheap) alternative is to perform a pH-test, and when the pH is > 4.5, further investigation should be considered.

High-risk pregnancies

Women with a previous preterm birth

Progesterone

Women with a previous preterm birth, despite of their cervical length, benefit from treatment with either vaginal progesterone or 17-alpha-hydroxyprogesterone caproate.[17,25] A recent trial comparing the two different progestagen administration found no significant differences (10% preterm birth for vaginal progesterone versus 14% for 17-alpha-hydroxyprogesterone caproate).[26] However a recent meta-analysis showed lower preterm birth rates before 32 en 34 weeks of gestation for vaginal progesterone.[27]

Cervical length

Serial cervical length measurements are recommended for women with previous preterm birth.[28] In women with preterm birth(s) before 24 weeks of gestation and a short cervical length, a cervical cerclage decreases the risk of a preterm birth.[29] Another option is a cervical pessary. Currently, the PC-study is comparing the cervical cerclage to a cervical pessary.[30] Furthermore in the United Kingdom, the SuPPoRT-trial is being performed. In this study women with a cervix < 25mm will be randomized for a cervical cerclage, a cervical pessary or vaginal progesterone.[31]

Aspirin

Chapter 2 showed that in higher gestational ages maternal vascular malperfusion lesions played a larger role than infectious or inflammatory lesions. The maternal vascular malperfusion lesions can also be found in women with preeclampsia and intra uterine growth restriction. The lesions seem to be the result of a failure of remodeling from spiral arteries in the placenta.[32] It has been shown that aspirin improves the development of the placenta, which improves pregnancy outcomes.[33] A recent re-analysis of an Individual Patient Data meta-analysis showed a reduction in spontaneous preterm birth rate when women were treated with aspirin.[33,34] This confirms the pathological findings of chapter two. To investigate this, we recently started the APRIL-study (Low dose aspirin in the Prevention of Recurrent Spontaneous Preterm Labour); a randomized placebo controlled trial, in which women with a previous spontaneous preterm birth are allocated to aspirin of placebo.[35] Results of this study will provide evidence if our theory could provide another therapeutic option for the prevention of recurrent preterm birth.

Challenges for the prevention of preterm birth

Previous and ongoing studies have focused mainly on either mechanisms behind preterm birth or interventions to prevent preterm birth. Preferably these two types of research should be combined in one study. Using both types of research might reveal more of the underlying mechanisms and the influence of the mechanism on the effect of the studied intervention. Ideally, a trial investigating both mechanisms would contain multiple arms and steps. Women with low and high risk should be included. For instance, women with history of spontaneous preterm birth, uterine anomalies, cervical surgery and twin pregnancies. All women should be informed about having a healthy lifestyle; for instance no smoking, a healthy weight and a well-balanced food pattern.

All women should be screened for bacterial vaginosis (and the vaginal microbiome) in early gestation. Women with a positive result should be randomized for metronidazole, clindamycine or placebo. After treatment, another swab should be taken to see the result of the treatment.

As shown in chapter 2 there might be an overlap in pathological mechanism between hypertensive disorders, intra uterine growth restriction and spontaneous preterm birth. Women with notches in the flow pattern of the uterine arteries early in pregnancy are known to be at risk for preeclampsia and intra uterine growth restriction.[36] Aspirin has been shown to improve these outcomes.[33] With this knowledge, the next step in the trial could be early screening for Doppler abnormalities in the uterine artery. Women with unilateral or bilateral notches in uterine artery flow would be randomized for aspirin or placebo.

For women with a previous spontaneous preterm birth progesterone improves the recurrent preterm birth rate, however the optimal way of administration (vaginal or intramuscular) has yet to be determined.[26,27] Women with a previous spontaneous preterm birth should be randomized for vaginal or intramuscular progesterone. To investigate the uptake of the progesterone and the influence of dose-response relationship, serum progesterone levels should be measured.

A midtrimester short cervix is associated with preterm birth.[6-8] An addition to cervical length could be elastography of the cervix, which is a measure of the strength of the cervix.[37] Women with less strength of the cervix could benefit from a cervical cerclage or a cervical pessary.[30,31] Furthermore, research is being performed for interventions to strengthen the cervix. When more is known about this, the methods could be compared.

In conclusion, we can only make progress if we evaluate the effectiveness of our interventions. Cerclage, cervical pessary, progestagens and aspirin are the most important candidates in the different high-risk groups. As it is unlikely that we will be completely successful in the prevention of preterm birth, management of threatened preterm birth will be a competing challenge.

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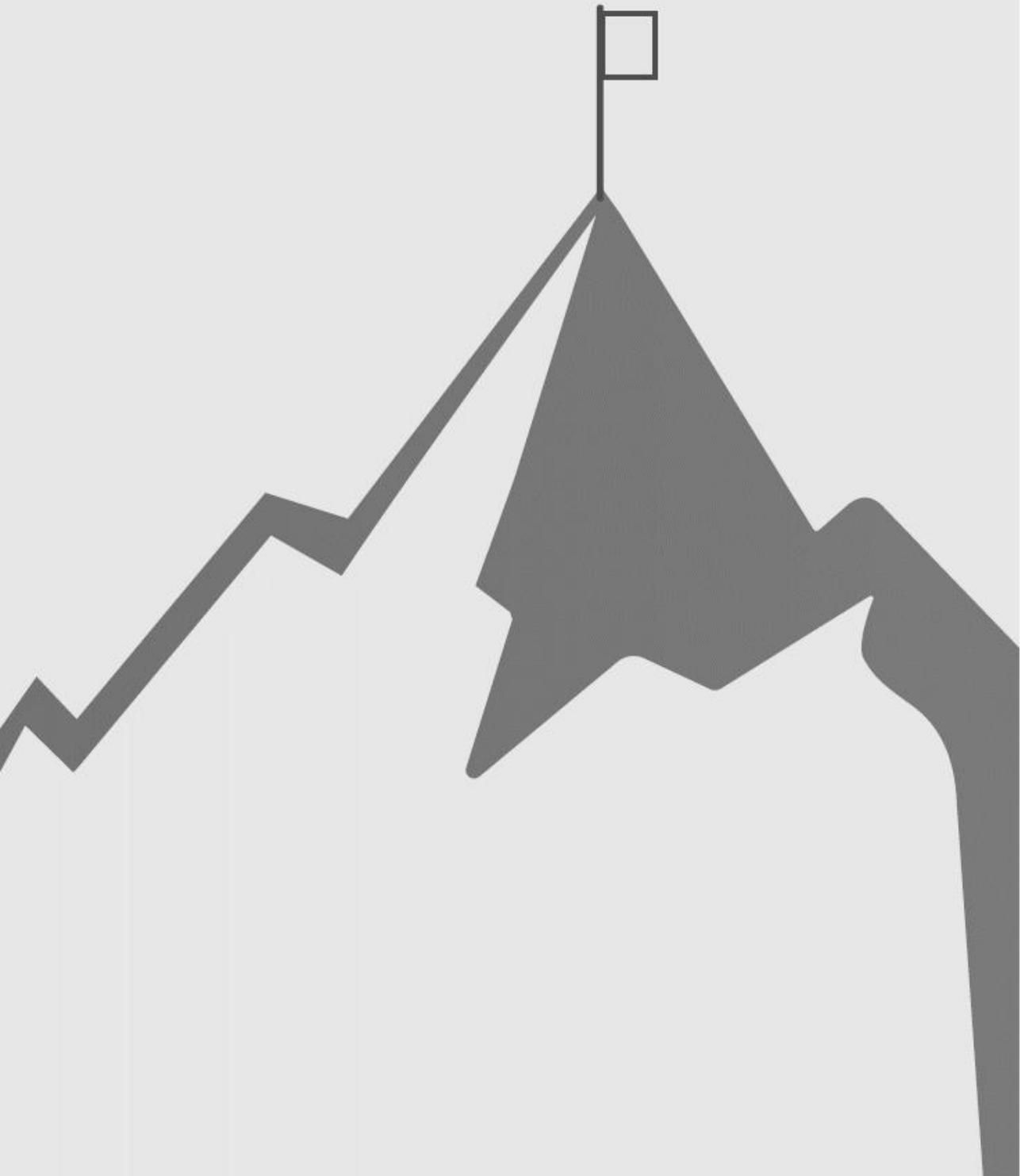


Chapter 10

Dutch summary

(Nederlandse samenvatting)

Vroeggeboorte is een van de belangrijkste problemen binnen het vakgebied van de verloskunde. Kinderen die te vroeg worden geboren hebben een sterk verhoogd risico op mortaliteit en morbiditeit, zowel op zeer jonge als latere leeftijd. Door de jaren heen zijn de uitkomsten sterk verbeterd door meerdere factoren, zoals interventies tijdens de bevalling, maar ook door transport naar gespecialiseerde ziekenhuizen waar kinderen opgevangen kunnen worden met betere faciliteiten. Ondanks deze verbeteringen blijft vroeggeboorte de belangrijkste oorzaak voor mortaliteit en morbiditeit bij pasgeborenen. De oorzaak van spontane vroeggeboorte is erg complex en nog niet geheel begrepen. Infectie en ontsteking in de placenta spelen een erg belangrijke rol. Er zijn ook aanwijzingen dat maternale vasculaire malperfusie laesies een rol hierin spelen. Deze laesies worden vaak gezien bij vrouwen met zwangerschapsvergiftiging en foetus met een groeiachterstand, die resulteren in een iatrogene vroeggeboorte. Om deze eventuele overeenkomsten tussen spontane en iatrogene vroeggeboorte te onderzoeken hebben wij een case-control studie uitgevoerd (**hoofdstuk 2**). In deze studie zijn de placenta's geclassificeerd in de aanwezigheid van infectieuze-ontstekingslaesies, maternale vasculaire malperfusie laesies, beide laesies of geen laesies. Om te bekijken wat voor invloed de zwangerschapsduur had, werden de vrouwen gestratificeerd in immature (17 - 23+6 weken), extreme (24 - 27+6 weken), ernstige (28 - 31+6 weken) en matige/late (32 - 36+6 weken) vroeggeboorte. Er werden 233 vrouwen geïncludeerd, waarvan 121 met een spontane vroeggeboorte en 112 met een iatrogene vroeggeboorte. De resultaten lieten zien dat bij vrouwen met een spontane extreme vroeggeboorte met name infectieuze-ontstekingslaesies werden gezien. Na 28 weken werd er bij spontane vroeggeboorte een shift gezien van infectieuze-ontstekingslaesies naar maternale vasculaire malperfusie laesies. In de iatrogene vroeggeboorte waren vooral de maternale vasculaire malperfusie laesies aanwezig in alle zwangerschapsduur-categorieën. De bevindingen suggereren een overlap in de pathologische cascade die leidt tot spontane vroeggeboorte en iatrogene vroeggeboorte (vooral zwangerschapsvergiftiging en intra uteriene groeivertraging). Deze informatie biedt mogelijkheden voor toetsing van mogelijke effectieve maatregelen om vroeggeboorte te voorkomen.

Vroeggeboorte kan desastreuze gevolgen hebben voor zowel het te geboren kind als de familie waarin het kind wordt geboren. In **hoofdstuk 3** hebben we een overzicht gemaakt van de huidige interventies om de uitkomsten van het kind te verbeteren. De eerste uitdaging is om vrouwen te identificeren die een hoog risico hebben om prematuur te bevallen. Op dit moment is de meest accurate manier de combinatie van cervixlengte meting en de foetale fibronectine test. Als een vrouw geïdentificeerd is als hoog risico, verbetert een kuur van corticosteroïden (48 uur) de uitkomsten van het kind, en geeft een reductie van necrotiserende enterocolitis, luchtwegproblemen, intraventriculaire bloedingen en neonatale sterfte. Om te zorgen dat de corticosteroïden hun werk kunnen

doen, kunnen 48 uur tocolytica, ofwel weeënremmers, worden toegediend. Welk tocolyticum het beste werkt is nog niet duidelijk. Uit onderzoek is gebleken dat nifedipine en atosiban de tocolytica zijn met de meest veelbelovende uitkomsten, aangaande zwangerschapsverlenging, uitkomsten van het kind en veiligheidsprofiel. Echter, deze twee soorten medicatie zijn nog nooit in een grote, gerandomiseerde studie met elkaar vergeleken, waar gekeken wordt naar de uitkomsten bij het kind. Naast corticosteroïden en tocolytica, is gebleken dat magnesiumsulfaat voor de 32 weken zwangerschapsduur de korte termijn neurologische uitkomsten, zoals cerebrale parese en grove motorische functie, verbetert. Profylactische antibiotica moeten alleen worden toegediend bij vrouwen met prematuur gebroken vliezen, in deze groep vrouwen verbetert dit de korte termijn uitkomsten van de kinderen.

Zoals eerder genoemd zijn nifedipine en atosiban de meest veelbelovende tocolytica. Er is echter nog nooit een groot gerandomiseerd onderzoek gedaan om deze twee met elkaar te vergelijken, met perinatale uitkomsten als primaire uitkomstmaat. Om deze reden is de APOSTEL III studie opgezet (**hoofdstuk 4**). In deze multicenter, gerandomiseerde trial werden vrouwen met een zwangerschapsduur tussen de 25 en 34 weken en een dreigende vroeggeboorte geïncludeerd. Vrouwen werden gerandomiseerd voor 48 uur behandeling met nifedipine of atosiban. De primaire uitkomstmaat was een samengestelde uitkomstmaat, bestaande uit perinatale sterfte, bronchopulmonale dysplasie, sepsis, intra ventriculaire bloedingen, periventriculaire leukomalacie en necrotiserende enterocolitis. De primaire uitkomstmaat kwam voor in 14% van de kinderen in de nifedipine en in 15% van de kinderen in de atosiban groep (RR 0.91, 95% CI 0.61-1.37). Perinatale sterfte was (niet significant) hoger in de nifedipine groep (2% vs. 5%; RR 2.20, 95% CI 0.91-5.33). Significant minder kinderen werden opgenomen op de NICU in de nifedipine groep (52.2% vs. 61.9%; RR 0.85, 95% CI 0.73–0.99). Mediane (IQR) zwangerschapsverlenging was vergelijkbaar tussen de groepen, 7 dagen (1.0–40.0) voor nifedipine versus 4 dagen (1.0-38.0) voor atosiban (HR 0.88, 95% CI 0.72–1.07). Maternale bijwerkingen kwamen even vaak voor in beide groepen. De studie concludeerde dat perinatale uitkomsten en effectiviteit van beide tocolytica vergelijkbaar zijn. Echter, het veiligheidsprofiel van nifedipine baart wel zorgen en moet verder onderzocht worden. Niet alleen klinische uitkomsten zijn van belang, ook kostenaspecten spelen een rol in de keuze voor een medicijn. Daarom hebben we een kosteneffectiviteitsanalyse verricht samen met de APOSTEL III studie (**hoofdstuk 5**). In deze analyse hebben we gekeken naar de kosten gemaakt tussen randomisatie en zes weken postpartum, vanuit een maatschappelijk perspectief. Daarnaast zijn stapsgewijze kosteneffectiviteitsverhoudingen berekend, welke de kosten weergeven om een slechte neonatale uitkomst (de primaire uitkomstmaat van de APOSTEL III studie) te voorkomen. De gemiddelde kosten per patiënt waren €45 476 in de nifedipine groep vergeleken met €51 064 in de atosiban groep

(gemiddeld verschil -€5 588 (95% CI –13 448 - 1 618). Het verschil in kosten werd vooral verklaard door een lager NICU-opname percentage in de nifedipine groep. In de stapsgewijze kosteneffectiviteitsverhoudingen werden geen verschillen gezien in de primaire uitkomstmaat, echter de kosten voor atosiban waren wel hoger. De kosteneffectiviteitsanalyse van de APOSTEL III studie heeft laten zien dat behandeling met nifedipine resulteert in lagere kosten dan behandeling met atosiban. Echter, zoals reeds beschreven in de APOSTEL III studie vraagt het veiligheidsprofiel van nifedipine meer onderzoek.

Een van de meest voorkomende complicaties van vroeggeboorte is hersenschade. In **hoofdstuk 6** worden de resultaten van de secundaire analyse van de APOSTEL III studie gepresenteerd. Het doel van deze studie was de invloed van nifedipine op hersenschade te vergelijken met atosiban. De hypothese was dat nifedipine de hersenen mogelijk beschermt tegen hersenschade, middels een soortgelijk werkingsmechanisme als magnesiumsulfaat. We hebben alle kinderen geboren < 32 weken in het Universitair Medisch Centrum Utrecht en het Academisch Medisch Centrum Amsterdam geïncludeerd. Om de aanwezigheid, het type en de ernst van de hersenschade te evalueren werden alle neonatale cerebrale echo's tijdens NICU of medium care opname opnieuw beoordeeld en geanalyseerd. De primaire uitkomstmaat was de aanwezigheid van hersenschade. Er werden 102 vrouwen bestudeerd, die 117 kinderen kregen. Hersenschade werd gevonden in 22 (43.1%) kinderen in de nifedipine groep en in 37 (56.1) kinderen in de atosiban groep (RR 0.60; 95% CI 0.29-1.24). Omdat het een secundaire analyse betrof, werd een sensitiviteitsanalyse uitgevoerd, waarin gecorrigeerd werd voor maternale leeftijd en zwangerschapsduur bij geboorte. Ook in de sensitiviteitsanalyse werd geen significant verschil gevonden tussen nifedipine en atosiban (OR 0.58; 95% CI 0.27-1.27). Een interessante bevinding in deze studie was dat een keizersnede beschermend leek te zijn tegen hersenschade. In de nifedipine groep werden meer keizersnedes uitgevoerd vanwege verdenking foetale nood. Logistische regressie liet significant minder hersenschade zien in kinderen geboren met een keizersnede (OR 0.32; 95% CI: 0.13-0.77). Na correctie voor keizersneden werd het effect van nifedipine op hersenschade kleiner. Het feit dat er meer keizersnedes vanwege foetale nood werden uitgevoerd in de nifedipine groep is een belangrijke bevinding, aangezien de veiligheid van nifedipine nog verder onderzocht moet worden.

Ongeveer een derde van alle vroeggeboortes begint met prematuur gebroken vliezen. Of tocolyse in vrouwen met prematuur gebroken vliezen de perinatale uitkomsten verbetert is niet duidelijk. Veel landen passen geen tocolyse toe bij vrouwen met prematuur gebroken vliezen. Om de effectiviteit van tocolyse in vrouwen met prematuur gebroken vliezen te onderzoeken is de APOSTEL IV studie opgezet (**hoofdstuk 7**). Het doel van deze

studie was het effect te onderzoeken van tocolyse met nifedipine op perinatale uitkomsten en verlenging van de zwangerschap. Vrouwen met prematuur gebroken vliezen zonder contracties met een zwangerschapsduur tussen de 24 en 33+6 weken werden geïncludeerd. Vrouwen werden gerandomiseerd voor nifedipine of placebo en behandeld tot de start van de baring, 18 dagen behandeling of 34 weken werd gehaald. Vanwege een lage inclusiesnelheid werd besloten de studie vroegtijdig te stoppen. Op dat moment waren er 50 vrouwen geïncludeerd, 25 in de nifedipine groep en 25 in de atosiban groep. De mediane zwangerschapsduur ten tijde van de randomisatie was 29.9 weken (IQR 27.7-31.3) in de nifedipine groep en 27.0 weken (IQR 24.7-29.9) in de placebo groep. De primaire uitkomstmaat was samengesteld uit slechte perinatale uitkomsten, bestaande uit perinatale sterfte, bronchopulmonale dysplasie, sepsis, intra ventriculaire bloedingen, periventriculaire leukomalacie en necrotiserende enterocolitis. De primaire uitkomstmaat kwam voor in 9 kinderen (33.3%) in de nifedipine groep en in 9 kinderen (32.1%) in de placebo groep (RR 1.04; 95% CI 0.49-2.2). Er waren twee gevallen van perinatale sterfte, beide in de nifedipine groep. Zwangerschapsverlenging was niet verschillend tussen beide groepen (mediaan 11 dagen voor nifedipine versus 8 dagen voor placebo, HR 1.02; 95% CI 0.58-1.79). In deze studie is geen gunstig effect aangetoond van nifedipine op perinatale uitkomsten en zwangerschapsduur. Echter, omdat het gebaseerd is op kleine aantallen moeten conclusies voorzichtig getrokken worden.

In de eerste hoofdstukken van dit proefschrift zijn veel interventies om de perinatale en neonatale uitkomsten te verbeteren beschreven en onderzocht. Echter, door verschillen in beschikbaarheid en kosten, werd de hypothese gesteld dat er verschillen zouden zijn wereldwijd. Het doel van **hoofdstuk 8** was de huidige klinische aanbevelingen over de behandeling van dreigende vroeggeboorte op verschillende plekken over de wereld te onderzoeken. Daarnaast werden lopende en geplande onderzoeken over het onderwerp geïnventariseerd. Er werd een online vragenlijst naar obstetrici in vele landen over de wereld gestuurd om te bekijken wat de huidige richtlijnen aangeven over de behandeling van dreigende vroeggeboorte. Hiervoor werd het Global Obstetrics Network (GONet) en WHO Multi-Country Survey on Maternal and Newborn Health Research Network (WHOMCS) gebruikt. Daarnaast werd in internationale trialregisters gezocht naar lopende of geplande studies over de tocolyse, corticosteroïden en magnesiumsulfaat. De vragenlijst werd ingevuld door 24 landen over de wereld, waarvan 18 (75%) aangaven een nationale richtlijn te hebben. Er bleken grote verschillen aanwezig te zijn in de aanbevelingen voor de praktijk, met name in het gebruik van tocolytica. In deze groep zaten de verschillen vooral in de zwangerschapsduur waarin het gegeven werd en het type tocolyticum. Meer uniformiteit werd gezien in het gebruik van corticosteroïden, alle landen gaven aan dit te gebruiken tot 34 weken zwangerschap. Magnesiumsulfaat werd in ruim de helft van de landen toegepast. Er werden 11 lopende of geplande studies

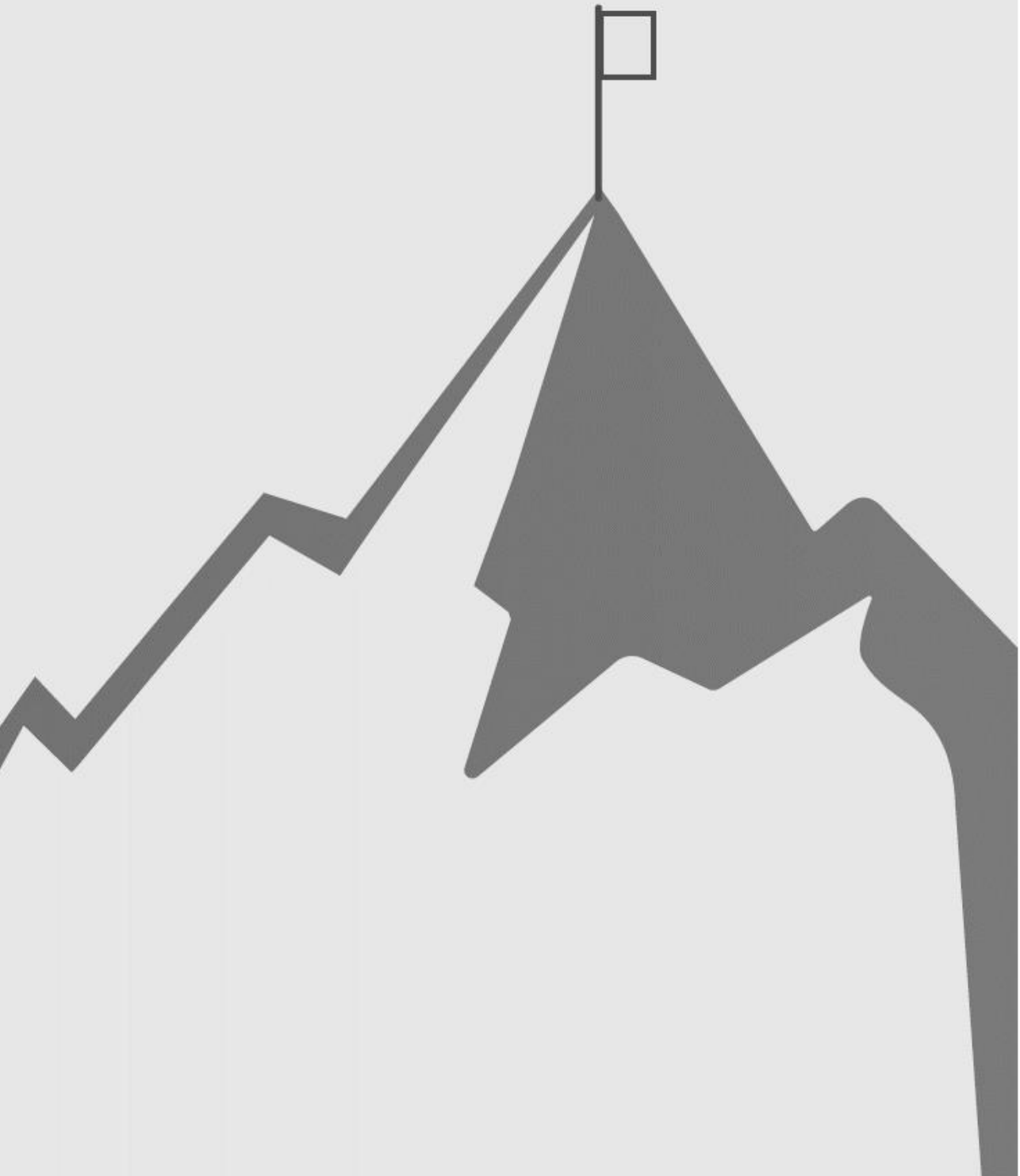
gevonden aangaande het onderwerp tocolyse. Slechts een van deze studies was gepowered op neonatale uitkomsten. Twee studies vergelijken een herhaalde kuur corticosteroïden met placebo. Naar magnesiumsulfaat lopen twee studies, een vergelijkt magnesiumsulfaat met placebo, de andere met nifedipine. Deze studie heeft laten zien dat er over de wereld grote verschillen bestaan in de behandeling van dreigende vroeggeboorte, met name in het gebruik van tocolytica. Dit zou kunnen komen door het gebrek aan duidelijk bewijs naar de effectiviteit, maar ook door verschil in beschikbaarheid. Dit is een onwenselijke situatie voor zo'n groot, wereldwijd probleem.

Conclusie

Dit proefschrift beschrijft de impact die een vroeggeboorte kan hebben. Er zijn verschillende medicamenteuze strategieën die de uitkomst van de neonaat kunnen verbeteren, zoals toediening van corticosteroïden, tocolytica, antibiotica en magnesium sulfaat. Echter deze methodes voorkomen de vroeggeboorte zelf niet.

Toekomst

De nadruk van onderzoek moet liggen in de preventie van vroeggeboorte. De winst die nog te behalen is bij een acute behandeling van een patiënt met een dreigende vroeggeboorte is waarschijnlijk beperkt op obstetrisch gebied. De complexe multifactoriële achtergrond van vroeggeboorte vereist een aanpak op verschillende punten. Primaire preventie dient zich te richten op beïnvloedbare factoren, als bijvoorbeeld roken en voedingstoestand/lichaamsgewicht. Professionals dienen hun patiënten goed voor te lichten over andere beïnvloedbare factoren, als bijvoorbeeld het niet laagdrempelig verrichten van een curettage of te adviseren een zwangerschapsinterval van meer dan 6 maanden aan te houden. Het identificeren van zwangeren met een verhoogd risico en hen een effectieve behandeling aan te bieden lijkt in het huidige Nederlandse systeem nog de grootste uitdaging. Professionals werkzaam in de geboortezorg zullen hun uiterste best moeten doen om deze uitdaging met succes aan te pakken en (nog) beter moeten samenwerken. De invoer van standaard cervixlengte metingen dient ingevoerd te worden. Potentiele effectieve behandelingen als pessarium, cerclage, progesteron en aspirine dienen verder onderzocht te worden in de verschillende groepen patiënten. Verloskundige praktijken en ziekenhuizen hebben een taak om hun patiënten deze onderzoeken aan te bieden. Vooruitgang van zorg is een taak van allen, en onderzoek is een van de manieren om verder te komen.



Chapter 11

List of publications
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List of publications

1. **Nijman TA**, Voogdt KG, Teunissen PW, van der Voorn PJ, de Groot CJ, Bakker PC. Association between infection and fever in terminations of pregnancy using misoprostol: a retrospective cohort study. BMC Pregnancy Childbirth. 2017 Jan 5;17(1):7.

2. **Nijman TA**, van Vliet EO, Benders MJ, Mol BW, Franx A, Nikkels PG, Oudijk MA. Placental histology in spontaneous and indicated preterm birth: A case control study. *Placenta. 2016 Dec; 48:56-62*

3. **Nijman TA**, van Vliet EO, Naaktgeboren CA, Oude Rengerink K, de Lange TS, Bax CJ, Bloemenkamp KW, van Eyck J, Kok M, Scheepers HC, Woiski M, Franx A, Mol BW, Oudijk MA. Nifedipine versus placebo in the treatment of preterm prelabor rupture of membranes: a randomized controlled trial: Assessment of perinatal outcome by use of tocolysis in early labor - APOSTEL IV trial. *Eur J Obstet Gynecol Reprod Biol. 2016 Oct;205:79-84*

4. **van Vliet EO**, Nijman TA, Schuit E, Heida KY, Opmeer BC, Kok M, Gyselaers W, Porath MM, Woiski M, Bax CJ, Bloemenkamp KW, Scheepers HC, Jacquemyn Y, van Beek E, Duvekot JJ, Franssen MT, Papatsonis DN, Kok JH, van der Post JA, Franx A, Mol BW, Oudijk MA. Nifedipine versus atosiban for threatened preterm birth (APOSTEL III): a multicentre, randomised controlled trial. *Lancet. 2016 May 21;387(10033):2117-24.*

5. Koullali B, Oudijk MA, **Nijman TA**, Mol BW, Pajkrt E. Risk assessment and management to prevent preterm birth. Semin Fetal Neonatal Med. 2016 Apr;21(2):80-8.

6. **Nijman TA**, van Vliet EOG, Koullali B, Mol BW, Oudijk MA. Antepartum and intrapartum interventions to prevent preterm birth and its sequelae. *Semin Fetal Neonatal Med. 2016 Apr;21(2):121-8*.

7. **Nijman TA**, Schutter EM, Amant F. Sentinel node procedure in vulvar carcinoma during pregnancy: A case report. Gynecol Oncol Case Rep. 2012 Feb 13;2(2):63-4

Dankwoord

Whoop whoop, het is af!

Dit proefschrift zou nooit tot stand gekomen zijn zonder de hulp van een groot aantal mensen. Ik wil iedereen bedanken die hierbij betrokken is geweest, maar een aantal mensen in het bijzonder.

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Curriculum Vitae

Tobias Adriaan Jules Nijman werd op 31 maart 1987 geboren in het Martini Ziekenhuis te Groningen. Hij groeide op in het Drentse dorpje Nietap. Vanaf zijn tiende wist hij dat hij dokter wilde worden, daarom was de keuze om na het gymnasium Geneeskunde te gaan studeren snel gemaakt. Hij ging studeren aan de Rijksuniversiteit Groningen. Zijn bachelor werd afgesloten met een stage in de gezondheidscentra van Campinas, Brazilië. Tijdens het tweede jaar van de master Geneeskunde werd tijdens het coschap Gynaecologie en Verloskunde in het MST, Enschede het enthousiasme voor dit vak aangewakkerd. In 2011 hij volgde een coschap sociale geneeskunde in Kumi, Uganda. Zijn laatste jaar begon met een semi-arts stage op de afdeling Gynaecologie & Verloskunde in het MST, Enschede en werd afgesloten met een wetenschappelijk stage in het VUmc, Amsterdam onder leiding van dr. P.C.A.M. Bakker. Op 12 maart 2013 behaalde hij zijn artsexamen, waarna hij startte als ANIOS Gynaecologie & Verloskunde in het Bronovo ziekenhuis, Den Haag onder leiding van dr. C.A.G. Holleboom. Na deze periode verruilde hij het Haagse voor een promotietraject in het Wilhelmina Kinderziekenhuis te Utrecht. Onder leiding van dr. M.A. Oudijk, prof. dr. A. Franx en prof.dr. B.W. Mol deed hij onderzoek naar de behandeling van dreigende vroeggeboorte. Na een periode van fulltime onderzoek, keerde hij terug naar het Bronovo Ziekenhuis, waar hij op 1 januari 2017 is begonnen met zijn opleiding tot gynaecoloog in het Leidse cluster. Tobias woont samen met Tom Winkel in de Rivierenbuurt in Amsterdam.