

## PREVENTION OF PRETERM BIRTH IN WOMEN AT RISK: SELECTED TOPICS





# PREVENTION OF PRETERM BIRTH IN WOMEN AT RISK: SELECTED TOPICS

KRISTIEN ROELEN, DOMINIQUE ROBERFROID, NADERA AHMADZAI, MOHAMMED ANSARI, KAVITA SINGH, LAURA GAUDET, SOPHIE ALEXANDER, FILIP COOLS, BÉNÉDICTE DE THYSEBAERT, PATRICK EMONTS, GILLES FARON, WILFRIED GYSELAERS, CHRISTINE KIRKPATRICK, LIESBETH LEWI, HILDE LOGGHE, ANNE NISSET, VINCENT RIGO, INGE TENCY, BART VAN OVERMEIRE, LEEN VERLEYE



## COLOPHON

Title:	Prevention of preterm birth in women at risk: selected topics
Authors:	Kristien Roelens (UZ Gent), Dominique Roberfroid (KCE), Nadera Ahmadzai (Ottawa Hospital Research Institute), Mohammed Ansari (Ottawa Hospital Research Institute), Kavita Singh (Ottawa Hospital Research Institute), Laura Gaudet (Dalhousie University, Canada), Sophie Alexander (Université Libre de Bruxelles), Filip Cools (UZ Brussel), Bénédicte de Thysebaert (Belgian Midwife Association), Patrick Emonts (CHU de Liège), Gilles Faron (UZ Brussel), Wilfried Gyselaers (Ziekenhuis Oost-Limburg), Christine Kirkpatrick (Hôpital Erasme Bruxelles), Liesbeth Lewi (UZ Leuven), Hilde Logghe (AZ St.-Lucas Brugge), Anne Niset (Belgian Midwife Association), Vincent Rigo (CHU de Liège), Inge Tency (KAHO Sint Lieven), Bart Van Overmeire (Hôpital Erasme Bruxelles), Leen Verleye (KCE)
Project coordinator	Dominique Paulus (KCE)
Reviewers:	Pascale Jonckheer (KCE), Françoise Mambourg (KCE), Raf Mertens (KCE), Dominique Paulus (KCE)
Stakeholders:	Liesbet Timmers (Belgian Midwife Association), Yannic Verhaest (VVOC), Trinette Dirickx (VVOC), Anita Verhille (VVOC)
External validators:	Gilles Kayem (CHU Louis Mourier – France), Geert Page (Jan Yperman Ziekenhuis)
CEBAM validators:	Jan Bosteels (Imelda Ziekenhuis Bonheiden), Roland Van Dijck (Heilig Hartziekenhuis Leuven), Stijn Van de Velde (CEBAM)
Acknowledgements:	We thank all participants of the LOK/GLEM groups in Bruges, Ghent, Brussels and Ixelles and the following collaborators from the Ottawa Hospital Research Institute: David Moher, Chantelle Garritty, Mark Walker, Brian Hutton, Rebecca Skidmore and Raymond Daniel.
Other reported interests:	<p>Fees or other compensation for writing a publication or participating in its development: Rebecca Skidmore (AHRQ)</p> <p>Participation in scientific or experimental research as an initiator, principal investigator or researcher: Chantelle Garritty; Laura Gaudet; Liesbeth Lewi (academic studies e.g. studies in monochorionic twins); Kristien Roelens, Geert Page</p> <p>Grants, fees or funds for a member of staff or another form of compensation for the execution of research: Wilfried Gyselaers (Promotor PHD's : IWT and LCRP-project at University Hasselt)</p> <p>Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Bart Van Overmeire (IPOKRATES courses), Geert Page (lectures on EBM for LOK's; Urology congresses), Roland Van Dijck (participation congress)</p> <p>Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Anita Verhille (board member VVOC), Trinette Dirixx (board member VVOC), Yannic Verhaest (board member VVOC), Geert Page (member of VVOG)</p>



Other possible interests that could lead to a potential or actual conflict of interest: Anita Verhille, Trinette Dirikx, Yannic Verhaest

Further, it should be noted that all experts and stakeholders, as well as the validators consulted within this report were selected because of their expertise in the field of preterm birth. Therefore, by definition, all consulted experts, stakeholders and validators have a certain degree of conflict of interest to the main topic of this report.

Layout:

Ine Verhulst

**Disclaimer:**

- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**
- **Finally, this report has been approved by common assent by the Executive Board.**
- **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

Publication date:

11 July 2014

Domain:

Good Clinical Practice (GCP)

MeSH:

Premature birth; Obstetric labor; premature; Secondary prevention; Tertiary prevention

NLM Classification:

WQ 330

Language:

English

Format:

Adobe® PDF™ (A4)

Legal depot:

D/2014/10.273/63

Copyright:

KCE reports are published under a “by/nc/nd” Creative Commons Licence

<http://kce.fgov.be/content/about-copyrights-for-kce-reports>.



How to refer to this document?

Roelens K, Roberfroid D, Ahmadzai N, Ansari M, Singh K, Gaudet L, Alexander S, Cools F, de Thysebaert B, Emonts P, Faron G, Gyselaers W, Kirkpatrick C, Lewi L, Logghe H, Niset A, Rigo V, Tency I, Van Overmeire B, Verleye L. Prevention of preterm birth in women at risk: selected topics. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2014. KCE Reports 228. D/2014/10.273/63.

This document is available on the website of the Belgian Health Care Knowledge Centre.





## ■ TABLE OF CONTENTS

LIST OF FIGURES .....	4
LIST OF TABLES .....	5
LIST OF ABBREVIATIONS .....	7
GLOSSARY .....	9
■ SCIENTIFIC REPORT .....	10
1 INTRODUCTION .....	10
1.1 BACKGROUND .....	10
1.1.1 General epidemiology .....	10
1.1.2 Preterm birth in Belgium .....	11
1.2 THE NEED FOR A GUIDELINE .....	13
1.3 SCOPE .....	13
1.4 REMIT OF THE GUIDELINE .....	14
1.4.1 Overall objectives .....	14
1.4.2 Target users of the guideline .....	14
1.5 STATEMENT OF INTENT .....	14
1.6 FUNDING AND DECLARATION OF INTEREST .....	14
2 METHODOLOGY .....	15
2.1 INTRODUCTION .....	15
2.2 THE GUIDELINE DEVELOPMENT GROUP .....	15
2.3 CLINICAL RESEARCH QUESTIONS .....	15
2.4 OUTCOMES .....	17
2.5 LITERATURE SEARCH AND STUDY SELECTION .....	17
2.5.1 Research questions and PICOT .....	18
2.5.2 Study design .....	23
2.5.3 Search methods .....	24
2.5.4 Study screening and selection .....	24
2.5.5 Quality appraisal .....	24



2.6	DATA EXTRACTION.....	25
2.7	ANALYSIS .....	25
2.7.1	Diagnostic test performance .....	25
2.7.2	Effectiveness of diagnostic and therapeutic interventions .....	25
2.8	GRADING OF EVIDENCE .....	26
2.9	FORMULATION OF RECOMMENDATIONS.....	28
2.10	REVIEW BY STAKEHOLDERS .....	30
2.10.1	Healthcare professionals.....	30
2.10.2	Patient representatives .....	31
2.11	CEBAM VALIDATION .....	31
<b>3</b>	<b>RECOMMENDATIONS.....</b>	<b>31</b>
3.1	IDENTIFICATION OF WOMEN AT RISK.....	31
3.1.1	Foetal fibronectin (fFN) test.....	31
3.1.2	phIGFBP test.....	38
3.1.3	Transvaginal ultrasound.....	43
3.2	SECONDARY PREVENTION .....	55
3.2.1	Progesterone for women at risk .....	55
3.2.2	Cerclage .....	61
3.3	TERTIARY PREVENTION .....	68
3.3.1	Decision to treat .....	68
3.3.2	Type of tocolytic therapy .....	69
3.3.3	Repeated dose(s) of corticosteroid therapy .....	72
3.3.4	Duration of therapy.....	74
3.3.5	Mg(SO4) for neuroprotection .....	87
<b>4</b>	<b>DISCUSSION .....</b>	<b>91</b>
<b>5</b>	<b>IMPLEMENTATION AND UPDATING OF THE GUIDELINE .....</b>	<b>92</b>
5.1	IMPLEMENTATION.....	92
5.1.1	Multidisciplinary approach.....	92
5.1.2	Patient-centred care.....	92
5.1.3	Barriers and facilitators for implementation of this guideline .....	92



	5.1.4	Actors of the implementation of this guideline .....	92
5.2		MONITORING THE QUALITY OF CARE .....	93
5.3		GUIDELINE UPDATE.....	93
■		<b>REFERENCES .....</b>	<b>94</b>



## LIST OF FIGURES

Figure 1 – Fetal fibronectin test for guiding treatment of threatened preterm labour versus clinical assessment: forest plot outcome preterm birth before 34 weeks of pregnancy .....	33
Figure 2 – Fetal fibronectin test for guiding treatment of threatened preterm labour versus clinical assessment: forest plot outcome preterm birth before 37 weeks of pregnancy .....	34
Figure 3 – Coupled sensitivity and specificity plots for pHIGFBP test for PTD <48 h in symptomatic singleton pregnancy .....	39
Figure 4 – Coupled sensitivity and specificity plots for pHIGFBP test for PTD within 7 days in symptomatic singleton pregnancy .....	41
Figure 5 – Coupled sensitivity and specificity plots for ultrasound cervical length (various cut-offs) for PTD <48 h in symptomatic singleton pregnancy in both old and new studies .....	45
Figure 6 – Coupled sensitivity and specificity plots for ultrasound cervical length test (15mm cut-off) for PTD <7days in symptomatic singleton pregnancy .....	47
Figure 7 – Coupled sensitivity and specificity plots for ultrasound cervical length (30mm cut-off) for PTD <7days in symptomatic singleton pregnancy .....	48
Figure 8 – Management of threatened preterm labour in singleton pregnancies.....	51
Figure 9 – Coupled sensitivity and specificity plots of ultrasound cervical length (20-22mm cut-off) for PTD < 34 weeks in asymptomatic pregnant women with singleton gestation in both old and new studies ..	53
Figure 10 – Coupled sensitivity and specificity plots of ultrasound cervical length (various thresholds) for PTD < 37 weeks in asymptomatic pregnant women with singleton gestation in both old and new studies ..	53



## LIST OF TABLES

Table 1 – Incidence of preterm births in single pregnancies in 2011 in Belgium .....	12
Table 2 – Proportion of preterm births after induced preterm labour or planned caesarean section in 2011 in Belgium .....	12
Table 3 – Perinatal mortality rates in preterm births in 2011 in Belgium .....	13
Table 4 – A summary of the GRADE approach to grading the quality of evidence for each outcome .....	26
Table 5 – Levels of evidence according to the GRADE system .....	27
Table 6 – Downgrading the quality rating of evidence using GRADE .....	27
Table 7 – Strength of recommendations according to the GRADE system .....	29
Table 8 – Factors that influence the strength of a recommendation .....	29
Table 9 – Interpretation of strong and conditional (weak)* recommendations .....	30
Table 10 – Clinical effectiveness of fFN testing: RCT results.....	32
Table 11 – Test accuracy of fFN testing: summary of results .....	35
Table 12 – Calculated post-test probabilities for fFN testing in different populations .....	36
Table 13 – pHIGFBP test: pooled results and subgroup analysis by pre-specified covariates (PTD within 7 days).....	40
Table 14 – Summary of the systematic review on clinical effectiveness of vaginal ultrasound (cervical length measurement) .....	43
Table 15 – Cervical length measurement to predict preterm birth within 7 days: results per threshold.....	46
Table 16 – Calculated post-test probabilities for cervical length measurements in symptomatic women, by threshold .....	48
Table 17 – Cervical length measurement to predict preterm birth before 34 weeks of pregnancy: results per threshold .....	49
Table 18 – Summary results test accuracy pHIGFBP test, fetal fibronectin test and transvaginal ultrasound to predict delivery at 7 days <sup>1</sup> .....	52
Table 19 – Calculated post-test probabilities for cervical length measurements in asymptomatic, high risk women, by threshold .....	54
Table 20 – Progesterone in asymptomatic women with history of spontaneous preterm birth: summary of results.....	56
Table 21 – Progesterone in asymptomatic women with a short cervix on ultrasound: summary of results.....	59
Table 22 – Efficacy and safety of cerclage versus no cerclage in asymptomatic women at high risk based on women's history .....	62



Table 23 – Efficacy and safety of cerclage versus no cerclage in asymptomatic, high risk women with a short cervix on ultrasound .....	64
Table 24 – Efficacy and safety of cerclage versus no cerclage in asymptomatic singleton women with short cervix or previous spontaneous preterm birth <37 weeks.....	66
Table 25 – Efficacy of repeated dose antenatal corticosteroids versus single dose in pregnant women with threatened preterm labour .....	73
Table 26 – Efficacy and safety of magnesium maintenance tocolytic treatment versus placebo/ no treatment in women after threatened preterm labour: results.....	75
Table 27 – Efficacy and safety of nifedipine maintenance tocolytic treatment versus placebo/ no treatment in women after threatened preterm labour: results.....	77
Table 28 – Efficacy and safety of oral betamimetics maintenance tocolytic treatment versus placebo/ no treatment in women after threatened preterm labour: results.....	80
Table 29 – Efficacy and safety of oxytocin antagonist maintenance tocolytic treatment versus placebo/ no treatment in women after threatened preterm labour: results.....	83
Table 30 – Efficacy and safety of progesterone maintenance tocolytic treatment versus placebo/ no treatment in women after threatened preterm labour or PPROM: results .....	85
Table 31 – Efficacy and safety of vaginal progesterone maintenance tocolytic treatment versus placebo/ no treatment in women after threatened preterm labour or PPROM: updated results .....	86
Table 32 – Efficacy and safety of magnesium sulphate neuroprotection versus no treatment in women at risk of preterm birth before 34 weeks: results .....	88



## LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AMSTAR	A MeaSurement Tool to Assess Reviews
ARDS	Acute respiratory distress syndrome
AUC	Area Under the Curve
BPD	Bronchopulmonary dysplasia
CI	Confidence interval
CL	Cervical length
CDT	Clinical decision threshold
INAMI	Institut national d'assurance maladie-invalidité
IUT	In utero transfer
IVH	Intraventricular hemorrhage
FDA	Food and Drug administration
FN	False negative
fFN	Fetal fibronectin
FP	False positive
GA	Gestational age
KCE	Belgian Health Care Knowledge Centre
LR-	Negative likelihood ratio
LR+	Positive likelihood ratio
Mg	Magnesium
Mg Cl	Magnesium Chloride
Mg(SO) <sub>4</sub>	Magnesium Sulphate
NA	Not applicable
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NNP	Number needed to protect
NNTB	Number needed to treat to benefit
NPV	Negative predictive value
NR	Not reported



OHRI	Ottawa Hospital Research Institute
OIS	Optimal information size
phIGFBP	Phosphorylated insulin-like growth factor-binding protein
PTB	Preterm birth
PPROM	Preterm premature rupture of the membranes
PPV	Positive predictive value
PTD	Preterm delivery
PVL	Periventricular leukomalacia
RCT	Randomized controlled trial
RDS	Respiratory distress syndrome
RIZIV	Rijksinstituut voor ziekte- en invaliditeitsverzekering
RR	Relative risk
RRR	Relative risk reduction
SAE	Serious adverse event
SR	Systematic review
sROC	Summary receiver operating curve
SPE	Studiecentrum voor perinatale epidemiologie
TN	True negative
TP	True positive
TVU	Transvaginal ultrasound
US	United States
VVOC	Vlaamse vereniging voor ouders van couveusekinderen



## GLOSSARY

### **Preterm birth**

Preterm births are those that occur at less than 37 weeks' gestational age (or fewer than 259 days since the first day of a woman's last menstrual period). This can be further subdivided on the basis of gestational age:

- extreme preterm: less than 28 weeks
- very preterm: 28-32 weeks
- moderately preterm: 32-33 weeks
- late preterm: 34-36 weeks

### **Secondary prevention**

These interventions happen after an illness or serious risk factors have already been diagnosed. Secondary prevention aims at detecting and addressing an existing disease prior to the appearance of symptoms

### **Tertiary prevention**

Tertiary prevention targets the person who already has symptoms of the disease.

### **Threatened or suspected preterm labour**

Threatened or suspected preterm labour means the presence of uterine activity (contractions) after 20 weeks and before 37 weeks gestation, but no clear evidence of cervical change.

### **Cerclage**

A cervical cerclage or cervical stitch consists of a strong suture being inserted into and around the cervix early in the pregnancy to reduce the risk for preterm birth and its sequelae. A primary cerclage is put in place early in pregnancy (usually between 12 and 14 weeks), before any changes of the cervix occur.



## ■ SCIENTIFIC REPORT

### 1 INTRODUCTION

#### 1.1 Background

Preterm deliveries are those that occur at less than 37 weeks' gestational age (or fewer than 259 days since the first day of the women's last menstrual period). According to gestational age, preterm birth (PTB) can be classified in four categories:

- extreme preterm (less than 28 weeks),
- very preterm (between 28 and 31 + 6/7 weeks),
- moderate preterm (between 32 and 33 + 6/7 weeks) or
- late preterm (between 34 and 36 + 6/7 completed weeks of gestation).

The obstetric precursors leading to preterm birth are: delivery for maternal or fetal indications (by induction of labour or pre-labour caesarean section); spontaneous preterm labour with intact membranes; and preterm premature rupture of the membranes (PPROM).<sup>1</sup>

##### 1.1.1 General epidemiology

Preterm birth complications are the second most common cause of death in children under 5 years worldwide, and the leading cause of child deaths in most high-income countries.<sup>2</sup> Preterm birth accounts for 60–80% of neonatal mortalities and 75% of morbidities in most developed countries. PTB can cause severe morbidities such as bronchopulmonary dysplasia, respiratory distress syndrome (RDS), necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), retinopathy of prematurity, and sepsis. Moreover, preterm birth can have lifelong effects on neurodevelopmental functioning such as increased risk of cerebral palsy, impaired learning and visual disorders, and is associated with an increased risk of chronic disease in adulthood.<sup>3–6</sup> The economic cost is high in terms of neonatal intensive care and ongoing health-care and educational needs. The social, psychological and financial burden is very high for families. Also the economic cost is high in terms of neonatal intensive care and ongoing health-care and educational needs.<sup>7</sup>



Spontaneous preterm birth is a multi-factorial process, resulting from the interplay of factors causing the uterus to change from quiescence to active contractions and to birth before 37 completed weeks of gestation. The precursors to spontaneous preterm birth vary by gestational age, and social and environmental factors, but the cause of spontaneous preterm labour remains unidentified in up to half of all cases.<sup>8</sup> The most significant and consistently identified risk factor for preterm birth, is a woman's history of previous preterm birth.<sup>9</sup> Estimates suggest the rate of recurrent preterm birth in this group of women to be 22.5%<sup>10</sup>, a 2.5 times increased risk ratio when compared with women with no previous spontaneous preterm birth. The risk increases with more than 1 preterm birth. For women with a history of a single preterm birth, the recurrence risk in a subsequent pregnancy is approximately 15%, increasing to 32% where there have been two previous preterm births.<sup>11</sup> The risk is also inversely proportional to the gestational age of the previous preterm birth.<sup>12</sup> In up to 50% of cases of preterm birth, the cause is spontaneous onset of labour or preterm premature rupture of membranes (PPROM). The identification of a short cervix (considered to be less than 25mm) on ultrasound examination has been associated with an increased likelihood of preterm birth before 34 weeks' gestation.<sup>12</sup> Multiple pregnancy is also a strong risk factor for preterm birth although the mechanisms may be different to those operating in women with a singleton pregnancy. Multiple pregnancies (twins, triplets, etc.) carry nearly 10 times the risk of preterm birth compared to singleton births.<sup>13</sup> Up to 50% of women with a twin pregnancy will give birth prior to 37 weeks' gestation.

Infection plays an important role in preterm birth. Intrauterine infections might account for 25-40% of preterm births.<sup>1</sup> Lifestyle factors such as low pre-pregnancy weight, cigarette smoking or substance abuse during pregnancy also are important factors.<sup>1</sup> Stress and excessive physical work or long times spent standing may also play a possible role.

The natural history of (threatened) preterm labour is not very well known. A recent systematic review including 1383 women over 26 studies reported that 52.2% of women (median) with (threatened) preterm labour were still undelivered at 7 days, with large variations across studies (range: 0%-84%) and little indication on the source of such variations.<sup>14</sup> A cohort study not included in that systematic review also reported that among 234 women hospitalized for threatened preterm labour, only 38% delivered during that admission (56% delivered at term).<sup>15</sup>

Many countries have reported increased preterm birth rates over the past two decades.<sup>1,7</sup> There are three main reasons to expect preterm birth rates to rise.<sup>16</sup> First, multiple pregnancy rates, associated with the use of subfertility treatments and later maternal age at childbirth, are increasing, and the associated risk of preterm delivery is much higher in these pregnancies. Second, the survival of very preterm infants has improved markedly over recent decades because of medical advances in neonatal care, such as antenatal corticosteroids and surfactants, and their improved prognosis has changed perceptions of the risk associated with preterm birth versus other pregnancy complications. This has lowered the threshold for indicated (provider-initiated) preterm births, and has led to the rise in number of these births. Lastly, other risk factors for spontaneous and non-spontaneous preterm birth, such as in vitro fertilization (IVF), older maternal age, and higher maternal body mass index (BMI), have also become more prevalent among childbearing women.<sup>16</sup> A comparison of 19 countries reported contrasting trends, though. For multiple pregnancies, rates have generally increased between 1996 and 2008, although the range was wide. For singletons, the direction of change differed across countries.<sup>16</sup>

### 1.1.2 Preterm birth in Belgium

There are 106 maternity units in Belgium and 19 recognised Neonatal Intensive Care Units (NICUs).

The Studiecentrum voor Perinatale Epidemiologie (SPE) was created in Flanders in 1987. The Walloon Centre of Perinatal Epidemiology was created in 2007 by the Groupement des Gynécologues Obstétriciens de Langue Française de Belgique (GGOLF) with the collaboration of the Belgian Society of Paediatrics.

Incidence of preterm births in single pregnancies in year 2011 is presented in Table 1. The overall incidence was 6.61% (8442/127 775), with a notable difference between regions, the lowest incidence being observed in Flanders (6.26%; 4198/67098) ( $p < 0.0001$ ). However, the incidence in Flanders was 7.57% (5112/67 493) in 2012 (personal communication from Evelyn Martens; Kind en Gezin), and the differences between regions observed in 2011 are likely due to time variations. In Flanders, where the statistics have been available for years, the incidence of preterm birth has remained stable since 2002 at around 7.3%.<sup>17</sup>


**Table 1 – Incidence of preterm births in single pregnancies in 2011 in Belgium**

Gestational age	Wallonia <sup>18</sup> N=37 006		Flanders <sup>17</sup> N=67 098		Brussels <sup>19</sup> N=23 671		TOTAL N=127 775	
	n	%	n	%	n	%	n	%
<b>&lt;28 w</b>	166	0.40%	240	0.40%	163	0.70%	<b>569</b>	<b>0.44%</b>
<b>28w-31w</b>	217	0.60%	386	0.60%	173	0.70%	<b>776</b>	<b>0.61%</b>
<b>32w -36 w</b>	2252	6.10%	3572	5.30%	1273	5.40%	<b>7097</b>	<b>5.55%</b>
<b>TOTAL</b>	<b>2635</b>	<b>7.10%</b>	<b>4198</b>	<b>6.26%</b>	<b>1609</b>	<b>6.80%</b>	<b>8442</b>	<b>6.61%</b>

Up to 15% of preterm deliveries occurred after induction of labour or planned caesarean section countrywide, and up to one quarter in Brussels (Table 2). The perinatal mortality rate in preterm births is elevated, even in late preterm babies, when compared to the rate observed in term babies (0.15% in Wallonia, 0.14% in Flanders, and 0.23% in Brussels) (Table 2). In Brussels, the perinatal mortality rate in late preterm babies is as high as 3.22%. The presence of many university hospitals in Brussels, which receive referred neonates who may have poorer outcomes, and the socio-economic status of the population could explain some of this inter-regional variability. In the absence of more detailed data, it is however difficult to enlighten such differences.

Risk factors of giving birth before week 37 are young age (8.2% in the 1140 15-19 years), old age (8.4% in the 2231 35-44 years), being unemployed (15.0% of the 5 344 deliveries) and being lowly educated (probably confounded by young age). A foreign nationality is not a risk factor.<sup>19</sup>

**Table 2 – Proportion of preterm births after induced preterm labour or planned caesarean section in 2011 in Belgium**

Gestational age	Wallonia <sup>18</sup>		Flanders <sup>17*</sup>		Brussels <sup>19</sup>		TOTAL	
	n (N)	%	n (N)	%	n (N)	%	n (N)	%
<b>&lt;28 w</b>	54 (185)	29.19%	71 (281)	25.27%	89 (179)	49.72%	<b>214(645)</b>	<b>33.18%</b>
<b>28w-31w</b>	46 (256)	17.97%	60 (485)	12.37%	50 (218)	22.94%	<b>195 (959)</b>	<b>20.33%</b>
<b>32w -36 w</b>	383 (2536)	15.10%	597 (4127)	14.47%	331 (1472)	22.50%	<b>1030 (9135)</b>	<b>12.66%</b>
<b>TOTAL</b>	<b>483 (2977)</b>	<b>16.22%</b>	<b>728 (4893)</b>	<b>14.88%</b>	<b>470 (1869)</b>	<b>25.15%</b>	<b>1439 (9559)</b>	<b>15.05%</b>

\* data complemented by personal communication from Evelyn Martens (Kind en Gezin)


**Table 3 – Perinatal mortality rates in preterm births in 2011 in Belgium**

Gestational age	Wallonia <sup>18</sup>		Flanders <sup>17*</sup>		Brussels <sup>19</sup>		TOTAL	
	n (N)	%	n (N)	%	n (N)	%	n (N)	%
<b>&lt;28 w</b>	124 (206)	60.19%	182 (325)	56.00%	140 (199)	70.35%	446 (730)	61.10%
<b>28w-31w</b>	55 (298)	18.46%	76 (585)	12.99%	41 (266)	15.41%	172 (1149)	14.97%
<b>32w -36 w</b>	52 (2828)	1.84%	106 (4686)	2.26%	54 (1677)	3.22%	212 (9191)	2.31%
<b>TOTAL</b>	231 (3332)	6.93%	364 (5596)	6.50%	235/2142	10.97%	830 (11070)	7.50%

\* data complemented by personal communication from Evelyn Martens (Kind en Gezin)

## 1.2 The need for a guideline

Given the high number of individuals involved and the deleterious consequences of the condition, preventing preterm birth is of the utmost importance. The College of physicians of Mother and Newborn, an advisory committee of the Federal Public Service, has underlined the lack of clear guidelines as regards perinatal referral in Belgium.<sup>20</sup> Approximately 90/10 000 pregnant women are transferred to specialised intensive care units (in utero transfer, IUT), but one third of the IUT mothers are retransferred back to the original maternity service.<sup>20</sup>

There is no official screening and prevention program in place on a national level in Belgium or country-wide education or support measures in place to help families at risk of having a preterm infant. Different guidance on prevention and healthcare during pregnancy exists at community level (the Flemish Kind and Gezin, the German Dienst für Kind und Familie and the Walloon Office de la Naissance et de l'Enfance). Each hospital also has its own guidelines on prevention and screening. This said, the Belgian Health Care Knowledge Centre issued general recommendations on antenatal and intrapartum care for all women in 2004 and 2010, and professional organizations such as the College of Physicians for Mothers and Newborns and the Flemish Association for Obstetrics and Gynaecology issue guidelines on care and treatment.

## 1.3 Scope

Preterm birth prevention can be classified as primary (directed to all women before or during pregnancy to prevent and reduce risk), secondary (aimed at women at increased risk of preterm delivery on the basis of either obstetric history or present pregnancy risk factors) and tertiary (initiated after the parturitional process has begun, with a goal of preventing delivery or improving outcomes for preterm infants).<sup>21</sup>

For feasibility reasons, the scope of the guideline was kept limited to specific topics of special interest to the stakeholders and members of the guideline development group.

This guideline concerns only secondary and tertiary prevention of spontaneous preterm birth. Primary prevention of preterm birth will be the subject of another report (update of KCE report 6).<sup>22</sup>

### Included:

- Secondary prevention in asymptomatic women at risk with:
  - History of preterm birth or surgery to the uterine cervix
  - Short cervix measured by ultrasound
  - Asymptomatic changes of cervix (e.g. funneling, effacement, dilatation)
- Tertiary prevention in symptomatic women (treatment of preterm labour)

**Not included:**

- Primary prevention (will be included in the updated guideline ‘antenatal care for the healthy pregnant woman’)
- Twin pregnancy / multiple pregnancies
- Iatrogenic preterm birth
- Preterm premature rupture of membranes (PPROM)

## 1.4 Remit of the guideline

### 1.4.1 Overall objectives

This guideline provides recommendations based on current scientific evidence for the secondary and tertiary prevention of preterm birth. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences.

The guidelines are based on clinical evidence and may not always be in line with the current criteria for RIZIV/INAMI reimbursement of diagnostic and therapeutic interventions. The RIZIV/INAMI may consider adaptation of reimbursement/funding criteria based on these guidelines.

### 1.4.2 Target users of the guideline

This guideline is intended to be used by all care providers involved in the management of pregnant women at high risk for preterm birth, including midwives and gynaecologists working on a secondary or tertiary care level. It can also be of interest for pregnant women and their partners, general practitioners, hospital managers and policy makers.

## 1.5 Statement of intent

Clinical Guidelines are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding the care and management of pregnant women at risk for preterm birth.

The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all the available clinical data for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, clinical judgement and patient choice, may also be appropriate. The information in this guideline is not a substitute for proper diagnosis, treatment or the provision of advice by an appropriate health professional. It is advised, however, that significant deviations from strong recommendations in the national guideline are fully documented in the patient's file at the time the relevant decision is taken.

## 1.6 Funding and declaration of interest

KCE is a federal institution funded for the largest part by INAMI/RIZIV, but also by the Federal Public Service of Health, Food chain Safety and Environment, and the Federal Public Service of Social Security. The development of clinical practice guidelines is part of the legal mission of the KCE. Although the development of guidelines is paid by KCE's budget, the sole mission of the KCE is providing scientifically valid information. KCE has no interest in companies (commercial or non-commercial i.e. hospitals and universities), associations (e.g. professional associations, unions), individuals or organisations (e.g. lobby groups) that could be positively or negatively affected (financially or in any other way) by the implementation of these guidelines. All clinicians involved in the Guideline Development Group (GDG) or the peer-review process completed a declaration of interest form. Information on potential conflicts of interest is published in the colophon of this report. All members of the KCE Expert Team make yearly declarations of interest and further details of these are available upon request.



## 2 METHODOLOGY

### 2.1 Introduction

The KCE guideline is produced according to highly codified principles, based on scientific information regularly updated from the international literature. This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at <https://kce.fgov.be/content/kce-processes>.

Several steps were followed to elaborate this guideline. Firstly, clinical questions were developed and the inclusion and exclusion criteria were defined in collaboration with the members of the Guideline Development Group. Secondly a systematic literature review was performed and the identified body of evidence was critically appraised. Thirdly, on the basis of the results of the literature review, recommendations were formulated and graded according to the GRADE approach.

As a preliminary review of the literature did not identify a recent, evidence-based guideline on the secondary and tertiary prevention of preterm birth, no ADAPTE procedure was followed.

### 2.2 The Guideline Development Group

This guideline was developed as a result of a collaboration between representatives of health professionals involved in the care for women at risk of preterm birth (GDG) and KCE.

The composition of the Guideline Development Group (GDG) is documented in Appendix.

The roles assigned to the GDG were:

- To define the clinical questions, in close collaboration with the KCE Expert Team and stakeholders;
- To identify critical and important outcomes;
- To provide feedback on the selection of studies and identify further relevant manuscripts which may have been missed;
- To provide feedback on the content of the guideline;
- To provide judgement about indirectness of evidence;

- To provide feedback on the draft recommendations;
- To address additional concerns to be reported under a section on 'other considerations'.

Guideline development and systematic literature review expertise, support and facilitation were provided by the KCE Expert Team and researchers from the Ottawa Hospital Research Institute (OHRI).

### 2.3 Clinical research questions

Timely intervention (e.g. the use of antenatal steroids) can significantly reduce the rate of neonatal mortality and morbidities in symptomatic women. To maximise the effectiveness of antenatal therapy and to plan other necessary management strategies (e.g. in utero transfer to neonatal intensive care facilities), it is therefore important to determine the likelihood of a preterm birth at an early stage after the appearance of signs and symptoms.

The inclusion of fetal fibronectin (fFN), Actim Plus, or transvaginal cervical ultrasound testing in the diagnostic workup may help to predict which women displaying symptoms of premature labour will progress to preterm delivery and which do not require active intervention. fFN is an extracellular matrix glycoprotein produced by amniocytes and by cytotrophoblast and can be found in cervicovaginal secretions because of the mechanical damage caused to fetal membrane. It can be predictive of preterm delivery when elevated levels ( $\geq 50$  ng/ml) are found in a cervicovaginal swab after 22 weeks gestation. The Actim Plus test measures the level of the phosphorylated insulin-like growth factor binding protein-1 (pHIGFBP-1) which is secreted by decidual cells and leaks into cervical secretions when fetal membranes detach from decidua. Hence, inclusion of fFN or pHIGFBP testing in the diagnostic workup may help to predict which women displaying the symptoms of preterm labour will actually have a preterm delivery. Similarly, the identification of a short cervix (considered to be less than 2.5cm) on transvaginal ultrasound examination has been associated with an increased likelihood of preterm birth before 34 weeks' gestation.<sup>23</sup> However, not only the accuracy of these tests need to be assessed on the basis of available evidence, but also their clinical effectiveness, i.e. how testing actually results in preterm birth prevention must be established.

A proportion of pregnant women bear an increased risk of preterm delivery not because they present with uterine contraction but because of a history



of fetal loss and/or preterm delivery or because their cervix is prematurely shortened and/or dilated during pregnancy. It has been proposed that (vaginal or oral) progesterone until birth or 37 weeks of pregnancy could prevent usefully premature delivery in such women,<sup>24</sup> as progesterone might suppress smooth muscle activity in the uterus. Cerclage could also be an appropriate intervention in such cases.<sup>25</sup> However, the use and efficacy of cerclage is highly controversial because of the absence of a well-defined population for whom there is clear evidence of benefit.

In case of preterm labour, interventions to optimize newborn health are crucial. Administering magnesium sulfate might prevent cerebral palsy (neuroprotection) in the newborn<sup>26</sup>, but this intervention must be weighed against its potential adverse events. It is also of utmost importance to administer corticosteroids during 48h before delivery for accelerating fetal lung maturation and in reducing other complications of preterm birth such as intraventricular haemorrhage. Corticosteroids have become the standard of care for women at risk of preterm birth before 32 to 34 weeks' gestation in many countries. To make sure that enough time is available for a standard 24-hour dosing regimen corticosteroids, a tocolysis could be started for 48 hours. However, many tocolytic agents are available and their respective risk-benefit balance must be compared.<sup>27</sup> Moreover, it needs to be assessed if there is any benefit of giving tocolysis longer than 48 hours and if additional benefits can be expected of a longer course of treatment (maintenance tocolysis). Repeated tocolysis could also allow administering repeated courses of antenatal corticosteroids as a single dose of antenatal corticosteroid might have a lesser preventative effect on respiratory distress syndrome if it is administered seven days or more prior to birth.<sup>28</sup> Whether antenatal corticosteroids for women who remain at risk of preterm birth need to be repeated seven days after the initial course needs to be assessed.

The selection of priority research questions was made by the members of the GDG and representatives of professional organizations during an initial stakeholder meeting at KCE on 04 February 2013. Participants were asked to select priority research questions from a list of possible diagnostic and therapeutic interventions, grouped in the following three chapters: identification of patients at risk, secondary prevention of preterm birth (in women at risk) and tertiary prevention of preterm birth (treatment of preterm labour). Listed interventions were selected from a quick review of the existing literature and could be supplemented with other suggestions by the

participants. The list with proposed interventions and interventions selected by the group can be found in appendix.

The following six priority questions were selected:

1. What is the predictive value and effectiveness of performing a fetal fibronectin test or a pHIGFBP-test in pregnant women presenting with symptomatic uterine contractions?
2. What is the predictive value and effectiveness of vaginal ultrasound and cervical length measurement in
  - asymptomatic pregnant women with a history of preterm birth?
  - pregnant women presenting with signs of suspected preterm labour?
3. What is the efficacy and safety of progesterone as secondary prevention in
  - asymptomatic pregnant women with a history of preterm birth?
  - asymptomatic pregnant women with a short cervix on ultrasound at 20-22 weeks of pregnancy?
4. What is the efficacy and safety of cerclage in asymptomatic pregnant women with
  - a history of second trimester preterm birth?
  - a short cervix on ultrasound?
  - premature dilatation of the cervix early in pregnancy?
5. (a) What is the efficacy and safety of continuing tocolytic therapy after 48 hours, i.e. the time needed for corticosteroid administration, in
  - pregnant women with preterm labour before 32 weeks?
  - pregnant women with preterm labour after 32 weeks?

(b) What is the efficacy and safety of maintenance tocolytic therapy after arrested preterm labour in

  - pregnant women with preterm labour before 32 weeks?
  - pregnant women with preterm labour after 32 weeks?



6. What is the efficacy and safety of antenatal magnesium sulphate as neuroprotective agent in women with preterm labour before 30-32 weeks?

Details of the research questions in PICOT format can be found in the scientific report of the guideline.

After this initial selection of research questions, the GDG decided to add 2 questions:

7. What is the tocolytic agent of choice?
8. What is the risk-benefit of repetitive courses of steroids to enhance lung maturity in the newborn?

## 2.4 Outcomes

Critical and important outcomes were defined by the members of the GDG, based on consensus reached during the meeting on 04 February 2013.

Critical outcomes are:

- Neonatal and perinatal survival
- Neonatal survival without morbidities (e.g. intraventricular hemorrhage (IVH), cerebral palsy, periventricular leukomalacia, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), retinopathy, patent ductus arteriosus)
- Neurological outcomes at age 18-24 months
- Serious maternal side effects (serious adverse events)
- Maternal mortality

Important outcomes are:

- Preterm delivery
- Overall maternal side effects

## 2.5 Literature search and study selection

Priority research questions were translated into in- and exclusion criteria using the PICOT (Participants–Interventions–Comparator–Outcomes–Timing) framework.



### 2.5.1 Research questions and PICOT

Domain	Description
<b>Population</b>	Pregnant women presenting with symptomatic uterine contractions
<b>Intervention or Index test</b>	fFN or pHIGFBP testing
<b>Comparator or Reference test</b>	Clinical assessment (i.e. standard care measures such as assessment of contractions, digital vaginal examination for cervical changes, digital examination, and abdominal palpation) or the outcome of preterm birth
<b>Outcomes</b>	Diagnostic outcomes: Sensitivity and specificity NPV and PPV LR+ and LR- Prognostic performance (for outcome of preterm birth only, not the sequelae of preterm birth): Calibration (e.g. calibration plots, observed versus predicted tests, goodness-of-fit tests) Discrimination (e.g. sensitivity, specificity, AUC or c-index, integrated discrimination index, measures of reclassification such as net reclassification index, integrated discrimination index) Odds ratio, risk ratio, hazards ratio Effectiveness Odds ratio, risk ratio, hazards ratio for preterm birth outcome
<b>Timing</b>	Prediction of spontaneous preterm birth within and beyond 7 days Note: Prediction of preterm birth within 7 days is of utmost clinical importance

Abbreviations: AUC = area under the curve; fFN = fetal fibronectin; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value



Domain	Description
<b>Population</b>	Asymptomatic pregnant women with history of preterm birth or symptomatic pregnant women presenting with uterine contractions
<b>Intervention or Index test</b>	Transvaginal cervical ultrasound +/- fFN (both combination therapy or add on, irrespective of administration order)
<b>Comparator or Reference standard</b>	Clinical assessment (i.e. standard care measures such as assessment of contractions, digital vaginal examination for cervical changes, digital examination, and abdominal palpation) or the outcome of preterm birth
<b>Outcomes</b>	<p>Diagnostic outcomes:</p> <ul style="list-style-type: none"><li>• Sensitivity and specificity</li><li>• NPV and PPV</li><li>• LR+ and LR-</li></ul> <p>Prognostic performance (for outcome of preterm birth only, not the sequelae of preterm birth):</p> <ul style="list-style-type: none"><li>• Calibration (e.g. calibration plots, observed versus predicted tests, goodness-of-fit tests)</li><li>• Discrimination (e.g. sensitivity, specificity, AUC or c-index, integrated discrimination index, measures of reclassification such as net reclassification index, integrated discrimination index)</li><li>• Odds ratio, risk ratio, hazards ratio</li></ul> <p>Effectiveness</p> <ul style="list-style-type: none"><li>• Odds ratio, risk ratio, hazards ratio of preterm birth outcome</li></ul>
<b>Timing</b>	<p>Prediction of spontaneous preterm birth within and beyond 7 days</p> <p>Note: Prediction of preterm birth within 7 days is of most clinical importance</p>

Abbreviations: AUC = area under the curve; fFN = fetal fibronectin; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NPV = negative predictive value; PPV = positive predictive value



Domain	Description
<b>Population</b>	<ul style="list-style-type: none"><li>• Women with short cervix (&lt; 25mm) at mid-trimester of pregnancy, and/or</li><li>• Women with history of (unexplained) early fetal loss or PTB , and/or</li><li>• Women with mid-trimester cervical changes – cervical dilatation and/or membranes showing</li></ul> <p><i>Note:</i> We will include both symptomatic and asymptomatic women at risk for PTB but will conduct subgroup analysis for each population listed above</p> <p>The following were excluded:</p> <ul style="list-style-type: none"><li>• Progesterone administered to prevent miscarriage in the current pregnancy</li><li>• Multiple gestations</li></ul>
<b>Intervention</b>	Oral or vaginal progesterone in addition to routine care
<b>Comparator</b>	<ul style="list-style-type: none"><li>• No progesterone (i.e. placebo and/or routine care*)</li></ul> <p>* (E.g. as needed tocolytics, bed rest...).</p> <p>Co-interventions (e.g. cerclage) must not confound the studies, i.e. they should be balanced between two arms when employed.</p>
<b>Outcomes</b>	<p><i>Neonatal</i></p> <ul style="list-style-type: none"><li>• Survival without sequelae</li><li>• Neonatal morbidity: BPD, NEC, significant IVH (grade III/IV), PVL, seizures, sepsis, retinopathy of prematurity, ARDS, congenital heart defects, and long-term morbidity of neurological deficit</li><li>• <i>Note:</i> We extracted need for assisted ventilation and need for oxygen per nasal canula as surrogate outcomes for ARDS and congenital heart defects, if there was insufficient data for these outcomes.</li><li>• Frequency of PTB (extremely: &lt; 28 weeks , very : 28 to &lt; 32 weeks, moderately: 32 to &lt; 33weeks, or late: 34-36 weeks)</li><li>• survival</li></ul> <p><i>Maternal</i></p> <ul style="list-style-type: none"><li>• Maternal mortality</li><li>• Maternal morbidity/side effects - important harms</li><li>•</li></ul>
<b>Timing</b>	Until birth
<b>Abbreviations:</b> ARDS = acute respiratory distress syndrome; BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; NEC = necrotizing; enterocolitis; PTB = preterm birth; PVL = periventricular leucomalacia	



Domain	Description
Population	<ul style="list-style-type: none"><li>• Women with history of fetal loss early in pregnancy</li><li>• Women with history of PTB and/or cervix &lt; 25mm at mid-trimester of pregnancy</li><li>• Women with premature dilatation of cervix early in pregnancy</li></ul> <i>Note: We included asymptomatic populations only.</i>
Intervention	<p>Cerclage:</p> <ul style="list-style-type: none"><li>• Primary (no dilatation of cervix and at the beginning of pregnancy)</li><li>• Secondary (asymptomatic mid-trimester shortening of cervix)</li><li>• Emergency (dilatation of cervix has occurred already)</li></ul> <i>Note: We considered both abdominal and vaginal cerclage.</i>
Comparator	<ul style="list-style-type: none"><li>• No cerclage, routine care*</li><li>• Progesterone</li></ul> <p>* (E.g. as needed tocolytics, bed rest)</p> <p>Co-interventions (e.g. progesterone) must not confound the studies, i.e. they should be balanced between two arms when employed.</p>
Outcomes	<ul style="list-style-type: none"><li>• Neonatal/long-term survival with or without sequelae<ul style="list-style-type: none"><li>Fetal loss</li></ul></li><li>• Neonatal morbidity: BPD, NEC, significant IVH (grade III/IV), PVL, seizures, sepsis, retinopathy of prematurity, ARDS, congenital heart defects, and long-term morbidity of neurological deficit<ul style="list-style-type: none"><li><i>Note: We extracted need for assisted ventilation and need for oxygen per nasal canula as surrogate outcomes for ARDS and congenital heart defects, if there was insufficient data for these outcomes.</i></li></ul></li><li>• Frequency of PTB (extremely: &lt; 28 weeks , very : 28 to &lt; 32 weeks, moderately: 32 to &lt; 33 weeks, or late: 34-36 weeks)<ul style="list-style-type: none"><li><i>Maternal</i></li><li>• Maternal mortality</li><li>• Maternal morbidity/side effects - e.g. infection; number of caesareans; cervical trauma; haemorrhage</li></ul></li></ul>
Timing	Until birth
<b>Abbreviations:</b> ARDS = acute respiratory distress syndrome; BPD = bronchopulmonary dysplasia; IVH = intraventricular haemorrhage; NEC = necrotizing; enterocolitis; PTB = preterm birth; PVL = periventricular leucomalacia	



Domain	Description
Population	Pregnant women with preterm labour < 32 weeks or > 32 weeks
Intervention	Antenatal corticosteroids + tocolysis > 48 hours or antenatal corticosteroids + 48 hours tocolysis + maintenance tocolytic therapy (e.g. progesterone, nifedipine)
Comparator	Antenatal steroids + 48 hours tocolysis (i.e. no maintenance tocolysis)
Outcomes	<i>Neonatal</i> <ul style="list-style-type: none"><li>• Neonatal/long-term survival</li><li>• Neonatal morbidity: bronchopulmonary dysplasia (BPD), necrotizing; enterocolitis (NEC), significant intraventricular haemorrhage (IVH) (grade III/IV), periventricular leukomalacia (PVL), seizures, sepsis, retinopathy of prematurity, acute respiratory distress syndrome (ARDS), congenital heart defects, and long-term morbidities of neurological deficit. (Note: We will extract need for assisted ventilation and need for oxygen per nasal canula as surrogate outcomes for ARDS and congenital heart defects, if there is insufficient data for these outcomes.)</li><li>• Frequency of preterm birth (extremely: &lt; 28 weeks , very : 28 to &lt; 32 weeks, moderately: 32 to &lt; 37 weeks, or late: 34-36 weeks) as proxies for short and/or long-term neonatal morbidity and mortality</li><li>• Gain in duration of pregnancy in days (for extremely preterm birth)</li></ul> <i>Maternal</i> <ul style="list-style-type: none"><li>• Maternal mortality</li><li>• Maternal morbidity/side effects – important harms</li></ul>
Timing	Until birth
<b>Abbreviations:</b> ARDS = acute respiratory distress syndrome; BPD = bronchopulmonary dysplasia; IVH = intraventricular haemorrhage; NEC = necrotizing; enterocolitis; PTB = preterm birth; PVL = periventricular leucomalacia	



Domain	Description
<b>Population</b>	Children born to women with preterm labour < 30-32 weeks (i.e. very preterm newborns) and pregnant women with preterm labour < 30-32 weeks
<b>Intervention</b>	Magnesium sulphate (administered as a neuroprotective agent, not as a tocolytic) + standard care (including tocolytic therapy)
<b>Comparator</b>	No magnesium sulphate or standard care (including tocolytic therapy)
<b>Outcomes</b>	<i>Neonatal</i> <ul style="list-style-type: none"><li>• Neonatal/long-term survival</li><li>• Childhood morbidity – cerebral palsy (surrogates of cerebral palsy – neonatal convulsions, neonatal hypotonia, use of respiratory support, Apgar score)</li></ul> <i>Maternal</i> <ul style="list-style-type: none"><li>• Maternal mortality</li><li>• Maternal side effects - any reported in the literature, including serious adverse events (SAEs)</li></ul>
<b>Timing</b>	Until birth
<b>Abbreviations:</b> SAEs= serious adverse events	

### 2.5.2 Study design

We screened for relevant published and unpublished recent, high-quality systematic reviews from 2008 onwards. For fFN test, pHIGFBP test, and transvaginal ultrasound, we searched for reviews of both test performance and test effectiveness.

To be classified as a systematic review, a publication must have met all of the following criteria:

1. At least one database was searched with a specified search date
2. At least one clinically relevant eligibility criterion was reported
3. The included studies were quality assessed in a systematic manner

Once identified, the systematic reviews were categorized according to their publication and search dates. We then quality appraised the systematic reviews in chronological order using AMSTAR (A MeaSurement Tool to Assess Reviews) until 2-4 reviews scored high quality (score of 8-11).<sup>29</sup> We

selected reviews for updating based on quality, publication date, and gestation type.

The selected reviews were then updated with primary studies from the last search date. We identified relevant observational cohort studies and randomized-controlled trials (RCTs) for test performance evaluation, and RCTs only for test effectiveness. We did not consider other types of observational designs, such as case-control, as per recommended guidance.<sup>30</sup>

If a review was not identified for a specific test, we attempted a de novo synthesis of the primary studies without restricting literature search to 2008 onwards.



### 2.5.3 Search methods

An experienced Information Specialist conducted comprehensive literature searches, using high recall subject searches. To identify systematic reviews and primary studies from 2008 onwards, search strategies were developed for Medline, Embase, and the Cochrane Library (CDSR, CENTRAL, DARE, HTA database). Search strategies can be found in appendix.

Search concepts were first explored vis-a-vis existing key studies. Concepts were defined and not limited to Medical Subject Headings (MeSH); non-thesaurus terms (i.e. text words) were also included as search terms. Searches were tailored to account for the inconsistent use of controlled vocabulary and indexing procedures across the different databases. No limitations (aside from the year restriction of  $\geq 2008$  for all searches except when de novo synthesis was attempted) were placed on search terms in order to maximize sensitivity.

The search strategies were peer reviewed by another experienced Information Specialist using the PRESS guideline,<sup>31</sup> which has become standard practice in our systematic review procedures.

In addition, we conducted a grey literature search of key organizational websites as identified by the guideline development group, KCE experts, and Grey matters: a practical search tool for evidence-based medicine<sup>32</sup> to identify relevant unpublished materials.

### 2.5.4 Study screening and selection

De-duplicated citations were uploaded into an online systematic review software (Distiller Systematic Review (DSR) Software©)<sup>33</sup> to facilitate title/abstract screening (Level 1) and full-text screening (Level 2). At Level 1 screening, titles and abstracts were assessed for eligibility using a liberal accelerated method, which means that one reviewer was needed to pass a record on to Level 2 but two reviewers were needed to exclude a record. At Level 2 screening, full-texts were assessed for eligibility by two reviewers. Disagreements among reviewers were resolved through consensus or third party adjudication. Reports that were companions or co-publications of studies were identified as such.

Systematic reviews and primary studies were selected according to the inclusion and exclusion criteria specified in the PICOT frameworks. We did not distinguish between unassisted or assisted (e.g. Caesarean delivery) spontaneous delivery. We focused on singleton gestation and excluded studies that were exclusively in multiple gestations. We included studies that did not report gestation, but that otherwise met all other eligibility criteria, with the assumption that the majority of participants would likely be singletons.

At the abstract level, citations were not excluded based on language. However, for systematic reviews, we considered including papers only in English, French or Dutch. At the primary study level, we included relevant studies of any language as long as an English abstract was available from which we could assess eligibility. French or Dutch papers were translated (DR-LV).

### 2.5.5 Quality appraisal

Two reviewers independently assessed the quality of the selected systematic reviews using the 11-point validated AMSTAR tool.<sup>29</sup> Based on guidance from the Canadian Agency for Drugs and Technology in Health (CADTH), we categorized systematic reviews as: Low Quality (score 0 to 3 AMSTAR), Medium Quality (score 4 to 7 AMSTAR), and High Quality (score 8 to 11 AMSTAR).<sup>34</sup> Discrepancies were resolved through discussion or third party adjudication.

To assess the quality of primary diagnostic accuracy studies we used the QUADAS-2 tool<sup>30</sup> and to assess the quality of primary test effectiveness studies we used the Cochrane Risk of Bias Tool.<sup>35</sup> The Cochrane Risk of Bias assessments were done by two reviewers and discrepancies resolved through discussion or third party adjudication. Given a large number of new primary studies investigating test performance, risk of bias was assessed by a single reviewer after pilot testing for consistency across reviewers.



## 2.6 Data extraction

Qualitative data was extracted by one reviewer and a second reviewer verified the extractions for a 10% random sample of primary studies (see Evidence Tables in appendix). Given the large number of primary studies identified for the test performance of transvaginal ultrasound, we presented numerical study data by summary population and test characteristics (i.e. symptomatic vs. asymptomatic, reference standard, and cervical length threshold) in evidence tables. One reviewer extracted numerical data from relevant primary studies for participants with singleton or unclassified gestation meeting pre-specified population criteria reported above. One reviewer also extracted numerical data from the newer primary studies and this data was verified by a second reviewer. If a study did not report estimates for sensitivity, specificity, likelihood ratios, or their confidence intervals, but reported a 2 x 2 table of true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN), then we used an online calculator to obtain those estimates.<sup>36</sup>

## 2.7 Analysis

### 2.7.1 Diagnostic test performance

Using recommendations of the Cochrane Handbook of Diagnostic Test Accuracy, the selected systematic reviews were updated with primary studies published after the search dates of the reviews.<sup>37</sup> We meta-analysed studies using a hierarchical bivariate model if there were 3 or more studies and if the studies used the same or similar diagnostic threshold values.<sup>38</sup>

Because inadequate data did not permit exploration of between study heterogeneity in a multiple regression model, we evaluated effect modification with subgroup analyses according to the following covariates: publication year, prevalence of preterm birth, quality, blinding, and timing of testing (mid-trimester, third trimester, or spanning mid and third trimester). In the reviews that we updated, quality was dichotomized as “High” or “Low”. In our QUADAS-2 assessments, we categorized overall quality as “High”, “Low”, or “Unclear”. To follow the dichotomization of the original reviews, we coded studies of “Unclear” quality as Low quality or High quality and conducted a sensitivity analysis (specified as Methodologic Quality v1 and Methodologic Quality v2 in heterogeneity tables). Heterogeneity for

continuous or dichotomous covariates was assessed only if there were 10 or more studies.

For pooled analyses we present coupled sensitivity and specificity plots, summary receiver operating curves (sROC) with 95% confidence intervals and prediction region, and average (i.e. pooled) sensitivity, specificity, LR+, and LR- with 95% confidence intervals. All sROC plots present study level estimates using points sized according to study sample size. We also present results of subgroup analyses in tabular format. If studies were not pooled, we present coupled sensitivity and specificity plots and synthesizing evidence qualitatively.

We ran the bivariate models in SAS 9.2 software according to the methods of Reitsma et al. using NLMIXED procedure,<sup>38</sup> as described in the Cochrane Handbook for Diagnostic Test Accuracy Reviews. Grid searching techniques were used to choose starting values for all analyses. When model convergence was not achieved, we either do not report the pooled estimates, or report them as “interim” results if the estimates appeared to be expected based on an approximate averaging of individual study estimates. For interpretation, such estimates should be considered fragile.

We used RevMan 5 to generate coupled forest plots for sensitivity and specificity.

### 2.7.2 Effectiveness of diagnostic and therapeutic interventions

Following recommendations of the Cochrane Handbook for Systematic Reviews of Interventions, the selected systematic reviews were updated with primary studies published after the search dates of the reviews.<sup>35</sup> All meta-analyses were based on the DerSimonian's and Laird's random effects approach with the following reported exception.<sup>39</sup> Statistical heterogeneity between studies was quantified with I-squared statistics and the P value from the chi squared test (a P-value of ~0.10 determined statistical significance). Sparse data was not meta-analysed but was described qualitatively. Relative risk for dichotomous outcomes, mean difference/standardized mean difference/ratio of means for continuous, and rate ratios for count data were planned measures of analysis. When event rates were less than 5%, Mantel-Haenszel, and when less than 1%, Peto Odds methods were planned for use without continuity correction as per previous guidance<sup>35</sup> Studies with zero events in one arm were to be meta-



analysed without continuity correction with either Peto method or the Mantel-Haenszel method.<sup>35</sup> We used RevMan 5 to generate updated forest plots.

## 2.8 Grading of evidence

For each recommendation, we provided its strength and the quality of the supporting evidence. According to GRADE, we classified the quality of evidence into 4 categories: high, moderate, low, and very low (Table 4 and Table 5). The quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect was adequate to support a particular recommendation.

GRADE for guidelines was used, meaning that the evidence across all outcomes and across studies for a particular recommendation was assessed. The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

For RCTs, quality rating was initially considered to be of high level (Table 4 and Table 6). The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down 1 or 2 levels respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a

continuum and the final rating of confidence could differ from that suggested by each separate domain.<sup>40</sup>

Observational studies were by default considered low level of evidence (Table 4 and Table 5). However, the level of evidence of observational studies with no threats to validity can be upgraded for a number of reasons:

1. Large magnitude of effects;
2. All plausible confounders: all plausible confounding from observational studies or randomized trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed;
3. Dose-response gradient: the presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence.

The general principles used in this report to downgrade the quality rating are summarized in Table 6. Decisions on downgrading 1 or 2 levels were based on the judgement of the assessors. Reasons for (no) downgrading were summarized in the GRADE profiles.

Due to current methodological limitations of the GRADE system for diagnostic tests, GRADE was not applied to the recommendations on diagnosis. As such, optional upgrading GRADE domains could not be invoked for any outcome.

**Table 4 – A summary of the GRADE approach to grading the quality of evidence for each outcome**

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency	1. Large effect 2. Dose-response	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖)
Observational studies	Low	3. Indirectness 4. Imprecision 5. Publication bias	3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. *J Clin Epidemiol.* 2011;64(12):1311-6.

**Table 5 – Levels of evidence according to the GRADE system**

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011;64(4):401-6.

**Table 6 – Downgrading the quality rating of evidence using GRADE**

Quality element	Reasons for downgrading
<b>Limitations</b>	<p>For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of unvalidated outcome measures were taken into consideration.</p> <p>In general, we did not down grade evidence when risk was reported as unclear – any exceptions are footnoted with accompanying explanation. A high risk of performance, attrition, or “other bias” even in only one of the several data contributing studies was considered to be a serious risk if we judged substantive impact on the pooled estimate (e.g. higher weight of the study in a meta-analysis). Detection and selective reporting biases were deemed unimportant given our outcomes of interest.</p>
<b>Inconsistency</b>	<p>Our judgement of inconsistency was guided by visual assessment of forest plot confidence interval overlap, and statistical test for heterogeneity (I-squared and P-value). We ensured that we did not double downgrade heterogeneity in the evidence both for inconsistency and imprecision.</p>
<b>Indirectness</b>	<p>Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.</p> <p>We graded the outcomes of preterm birth and Caesarean section as seriously indirect because they are intermediates for short and long-term neonatal and maternal health outcomes. In other words, we felt that even though birth at &lt;28 weeks gestation is likely to be associated with more neonatal mortality and morbidity than birth &lt;37 or &lt;34 weeks, there is still some uncertainty that treatment induced</p>



pregnancy prolongation of what was naturally destined to deliver at <28 weeks to <34-37 weeks or even full term would result in improved short and long-term neonatal/infant health outcomes.

**Imprecision**

Evaluation of the imprecision of results was primarily based on examination of the 95%CI. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 20% was defined as CDT by default unless otherwise stated.

If 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a meta-analysis was less than the calculated OIS, rating down for imprecision was considered.

When both factors were present, we considered imprecision to be very serious.

**Reporting bias**

We considered publication bias as undetected because the systematic reviews that we updated could not detect signs of publication bias or because few studies contributed to meta-analyses.

We used GRADEpro software (version: 3.6) to grade our confidence in estimates of effects for the outcomes of interest. Outcome effect estimates were obtained from selected high quality systematic reviews or our updates of review meta-analyses when new trials were found. For each outcome, we used information reported in the selected systematic reviews to assess the domains of risk of bias, consistency, imprecision, and publication bias.

## 2.9 Formulation of recommendations

Based on the retrieved evidence, the first draft of recommendations was prepared by a small working group (*KCE experts and GDG members*). This first draft was, together with the evidence tables, circulated to the guideline development group one week prior to the face-to-face meetings (held on 4 November 2013, 25 February and 25 March 2014). Based on the discussion meetings a second draft of recommendations was prepared and once more circulated to the guideline development group for final approval. During the final GDG meeting, all recommendations were accepted by general consensus.

The strength of each recommendation was assigned using the GRADE system (Table 7). The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), quality of available evidence, values and preferences, and estimated cost (resource utilization). For this guideline, no formal cost-effectiveness study was conducted. Factors that influence the strength of a recommendation are reported in Table 8.

**Table 7 – Strength of recommendations according to the GRADE system**

Grade	Definition
<b>Strong</b>	The desirable effects of an intervention clearly outweigh the undesirable effects ( <i>the intervention is to be put into practice</i> ), or the undesirable effects of an intervention clearly outweigh the desirable effects ( <i>the intervention is not to be put into practice</i> )
<b>Weak</b>	The desirable effects of an intervention probably outweigh the undesirable effects ( <i>the intervention probably is to be put into practice</i> ), or the undesirable effects of an intervention probably outweigh the desirable effects ( <i>the intervention probably is not to be put into practice</i> )

Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol.* 2013;66(7):726-35.

**Table 8 – Factors that influence the strength of a recommendation**

Factor	Comment
<b>Balance between desirable and undesirable effects</b>	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
<b>Quality of evidence</b>	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
<b>Values and preferences</b>	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
<b>Costs (resource allocation)</b>	The higher the costs of an intervention, i.e. the greater the resources consumed, the lower the likelihood that a strong recommendation is warranted

Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol.* 2013;66(7):726-35.

A strong recommendation implies that most patients would want the recommended course of action. A weak recommendation implies that the majority of informed patients would want the intervention, but many would not.<sup>41</sup> Specifically, a strong negative recommendation means the harms of the recommended approach clearly exceed the benefits whereas a weak negative recommendation implies that the majority of patients would not want the intervention, but many would. In the case of a weak recommendation, clinicians are especially required to spend adequate time with patients to discuss patients' values and preferences. Such an in-depth discussion is necessary for the patient to make an informed decision. This may lead a significant proportion of patients to choose an alternative approach. Fully informed patients are in the best position to make decisions that are consistent with the best evidence and patients' values and preferences.

For policy-makers, a strong recommendation implies that variability in clinical practice between individuals or regions would likely be inappropriate whereas a weak recommendation implies that variability between individuals or regions may be appropriate, and use as a quality of care criterion is inappropriate<sup>41</sup>.

We offer the suggested interpretation of "strong" and "weak" recommendations in Table 9.

**Table 9 – Interpretation of strong and conditional (weak)\* recommendations**

Implications	Strong recommendation	Conditional or weak recommendation
<b>For patients</b>	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
<b>For clinicians</b>	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
<b>For policy makers</b>	The recommendation can be adapted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

\* The terms “conditional” and “weak” can be used synonymously.

Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol.* 2013;66(7):726-35.

## 2.10 Review by stakeholders

### 2.10.1 Healthcare professionals

The recommendations prepared by the guideline development group were circulated to midwives, gynaecologists and neonatologists working on secondary and tertiary care level, who participated in one of the LOK/GLEM group meetings organized in Bruges, Ghent, Ixelles and Brussels.

All invited panellists received the guideline summary and were asked to score the each recommendation for clarity and completeness on a 5-point Likert scale indicating their level of agreement with the recommendation, with a score of ‘1’ indicating ‘completely disagree’, ‘2’ ‘somewhat disagree’, ‘3’ ‘unsure’, ‘4’ ‘somewhat agree’, and ‘5’ ‘completely agree’ (the panellists were also able to answer ‘not applicable’ if they were not familiar with the

underlying evidence). If panellists disagreed with the recommendation (score ‘1’ or ‘2’), they were asked to provide an explanation supported by appropriate evidence. Scientific arguments reported by these experts were used to adapt the formulation or the strength of the clinical recommendations. In Appendix, an overview is provided of how their comments were taken into account.

Furthermore, clinicians were asked to score each recommendation for feasibility and provide comments on which factors could be a barrier for implementation of the guideline. A 5-point Likert scale indicating the feasibility of implementing the recommendation, with a score of ‘1’ ‘very low’, ‘2’ ‘low’, ‘3’ ‘average’, ‘4’ ‘high’, and ‘5’ ‘very high’.



### 2.10.2 Patient representatives

De Vlaamse Vereniging voor Ouders van Couveusekinderen (VVOC) was contacted to invite representatives to review the draft recommendations from a patient perspective.

The patient representatives were asked the following questions:

- Have important considerations from a patients' perspective been missed in the formulation of our recommendations?
- Do we need to add information that could assist patients in making clear choices when doctors discuss treatment options with them?

Patient views and concerns were discussed during a meeting using skype on 2 April 2014.

Concerns raised by the patient representatives are summarized in the "patient values and preferences" for each recommendation.

### 2.11 CEBAM validation

As part of the standard KCE procedures, an external scientific validation of the report was conducted prior to its publication. This validation was done in two phases. First, the content was evaluated by two clinicians on 20 May 2014. Second, the methodology was validated making use of the AGREE II checklist. This validation process was chaired by CEBAM on 27 May 2014.

## 3 RECOMMENDATIONS

### 3.1 Identification of women at risk

#### 3.1.1 Fetal fibronectin (fFN) test

Details on search strategy, study selection and critical appraisal can be found in appendix.

##### 3.1.1.1 Clinical effectiveness of Fetal Fibronectin test for guiding treatment of symptomatic women with a singleton gestation

A systematic review by Berghella et al.<sup>42</sup> was selected for assessing the clinical effectiveness of fFN for predicting preterm delivery in symptomatic pregnant women with singleton gestation. This review compared treatment based on knowledge of fFN test results versus treatment selection without knowledge of test results for the outcomes of preterm delivery before 28 weeks, 32 weeks, 34 weeks and 37 weeks. The relevant analyses in the systematic review included 3 RCTs in 275 to 284 women depending on outcome. The review was rated as high quality (AMSTAR score: 8).<sup>42</sup>

A total of 4 primary RCTs, published after the search date of the review (January 2008), were eligible for the update.<sup>43-46</sup> The primary studies were carried out in the United States, Scotland, and Portugal. Random sequence generation and allocation concealment were unclear in most of the primary studies. Dutta et al. did not provide extractable outcome data,<sup>44</sup> the trial by Burwick et al. did not report relevant outcome data,<sup>45</sup> and Osorio et al. just reported narratively that no significant differences were found in neonatal outcomes at birth.<sup>46</sup> Therefore, only one small trial was added to earlier meta-analyses on outcomes of preterm birth before 37 or 34 weeks. Updated meta-analyses did not demonstrate any meaningfully changed results (Figure 1 and Figure 2).



Results are summarized in Table 10. While the pooled effect estimate for preterm birth before 34 weeks was wide and statistically non-significant, for preterm birth before 37 weeks, the pooled relative risk ratio was 0.62 (95%CI 0.40, 0.95), a substantial risk reduction although the confidence interval around the point estimate was wide. In the review of Berghella et al. (no data in more recent studies), no significant differences were seen for preterm birth before 28 weeks of pregnancy (RR 1.0; 95%CI 0.15-6.82) or for delivery before 32 weeks of pregnancy (RR 0.85; 95%CI 0.28-2.58).

There were no data from RCTs on neonatal short-term or long-term outcomes. Also data on maternal side effects were not available.

For all outcomes, studies were generally underpowered (low number of events). Interpretation of the RCTs is further hampered by the absence of fixed management protocols based on fFN test results and the possible limited effect of tocolytic therapy on the occurrence of preterm birth.<sup>47, 48</sup> Effect of fFN testing and subsequent use of steroids and Mg(SO) 4 or transfer on clinical neonatal outcomes is unclear as these outcomes were not reported.

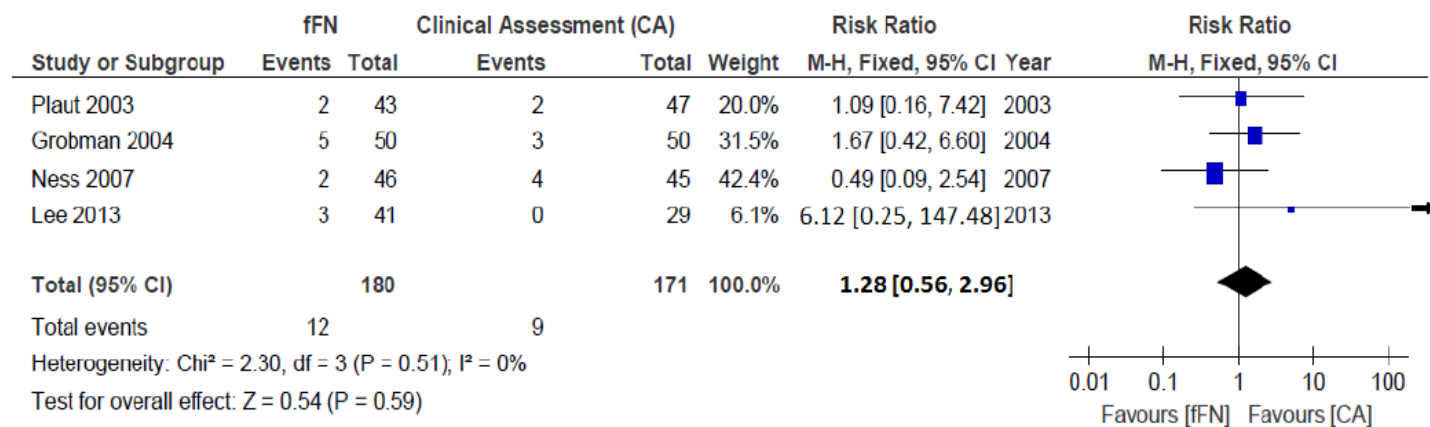
**Table 10 – Clinical effectiveness of fFN testing: RCT results**

fFN testing versus no testing in symptomatic singleton pregnancy			
Outcome	RR (95%CI)	Number of studies	Comments
<b>PTB&lt;28 weeks</b>	1.00 (0.15-6.82)	3	Inconclusive results
<b>PTB&lt;32weeks</b>	0.85 (0.28-2.58)	3	Estimates of test effectiveness are imprecise incorporating all possibilities of clinically meaningful improvement in the outcome of preterm birth, clinically insignificant effect, and/or even substantial harms of testing
<b>PTB&lt;34 weeks</b>	1.28 (0.56-2.96)	4	
<b>PTB&lt;37 weeks</b>	0.62 (0.40-0.98)	4	



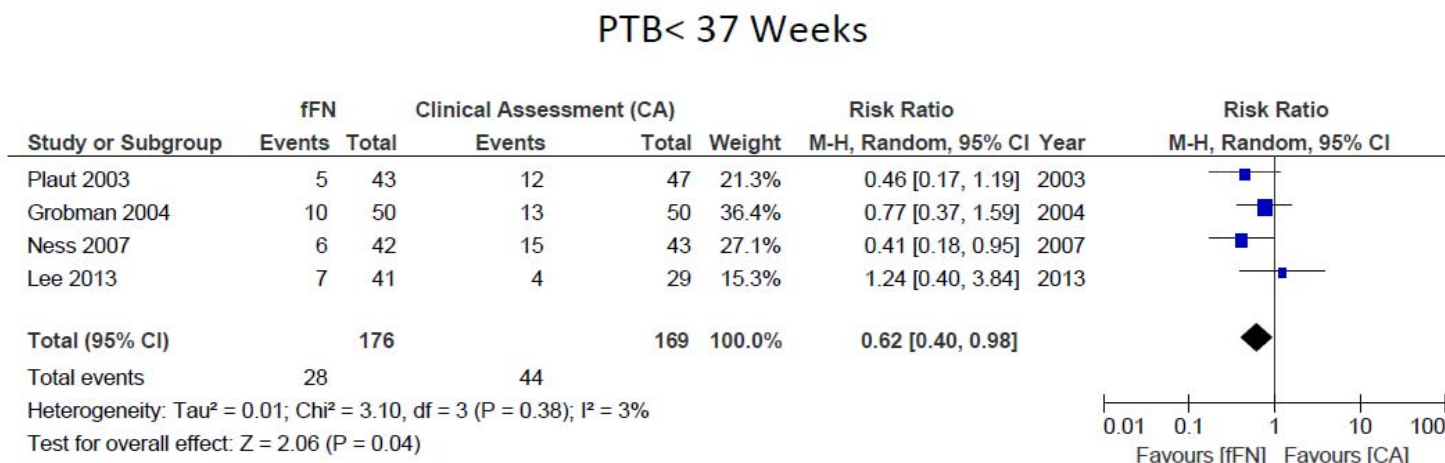
**Figure 1 – Fetal fibronectin test for guiding treatment of threatened preterm labour versus clinical assessment: forest plot outcome preterm birth before 34 weeks of pregnancy**

### PTB < 34 Weeks





**Figure 2 – Fetal fibronectin test for guiding treatment of threatened preterm labour versus clinical assessment: forest plot outcome preterm birth before 37 weeks of pregnancy**



### 3.1.1.2 Performance of the fetal fibronectin test for predicting preterm delivery in symptomatic women with singleton gestation

Sanchez-Ramos et al. conducted a systematic review to assess the predictive value of fFN for preterm delivery within 7 days of testing.<sup>49</sup> The review included studies of women with singleton, multiple, and unknown gestation. We extracted data only from those studies that reported data on women with singleton and unknown gestation ( $n=27$  studies). The review was rated as high quality (AMSTAR score: 9).

Eleven new primary studies, all observational cohorts, met the eligibility criteria for the review.<sup>50-60</sup> Three studies were not included in meta-analyses because they reported no useful numerical data.<sup>51, 53, 57</sup> The studies originated from various countries, including Japan, Turkey, United States, Korea, Italy, the Netherlands, Canada, and Ecuador. Most studies were rated unclear risk of bias, and most were not blinded or blinding was not reported.

In keeping with the original review, preterm birth within 7 days of testing was considered as the reference standard. The updated meta-analysis showed an overall pooled sensitivity of 0.73 (95%CI 0.67-0.80) and a pooled specificity of 0.81 (95%CI 0.77-0.84) (with no specification of gestational age at time of test). The corresponding estimates for the LR+ and LR- are 3.79 (95%CI 3.10-4.49) and 0.33 (95%CI 0.25-0.41) respectively. Compared with estimates of specificity, substantial heterogeneity was observed across studies in test sensitivity (see appendix). Subgroup analyses for publication year, methodological quality, prevalence, blinding or gestation (singleton versus unknown) did not show obvious effect modification except that lower quality studies slightly underestimated test performance (see appendix). The original review did not report gestational age at testing and, therefore, we could not assess heterogeneity for this covariate. Furthermore, as for the randomized controlled trials, it is unclear which treatment was offered to the patients and how this influenced the occurrence of delivery within 7 days.

We found no information on calibration or reclassification index of the test.

**Table 11 – Test accuracy of fFN testing: summary of results**

TEST PERFORMANCE – SUMMARY RESULTS							
Threshold	Outcome/Reference standard	Sensitivity (95%CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)	N of studies	Comments
fFN – symptomatic with singleton gestation							
50 ng/mL	PTB ≤7days	0.73 (0.67-0.80)	0.81 (0.77-0.84)	3.79 (3.10-4.49)	0.33 (0.25-0.41)	35	Unexplained heterogeneity

### Discussion

Only a minority of women who present with signs of threatened preterm labour deliver within 48 hours after the occurrence of symptoms. Clinical judgement alone is unable to appropriately predict delivery within 48h or 7 days leading to important overuse of tocolytic therapy and steroids and unnecessary hospitalisations and transfers to tertiary level obstetric care.<sup>47</sup> Hence, the possible added value of tests such as fFN lies particularly in the identification of women who will not deliver in the short term and so avoid overtreatment and its side effects and cost.

For diagnostic tests, a high sensitivity (or a low negative likelihood ratio) is desirable to rule out a disease or condition. To rule in a condition, a high specificity (or high positive likelihood ratio) is required. As a rough guide, for a positive test, LR+ > 10 generally indicates good performance for predicting preterm birth and moderate performance when 5-10 based on the routinely observed change in magnitude from pre- to post-test probability. For a negative test, LR- < 0.1 generally indicates good performance in predicting non-occurrence of preterm birth and moderate performance when between 0.1-0.2.

When interpreting the results of test performance studies for fFN test, the sensitivity (0.73; 95%CI 0.67-0.80) and negative likelihood ratio (0.33; 95%CI 0.25-0.41) are thus of most importance. Given a pre-test probability of preterm birth in a patient, the post-test probabilities (positive and negative) can be calculated and it can be judged whether post-test probabilities vary substantially from pre-test probabilities and if performing the test would influence decision-making.

In Table 12, we calculated post-test probabilities using the meta-analytic estimates from our updated review for three possible pre-test probabilities: the median, the highest and the lowest prevalence observed in the body of evidence.

Given a pre-test probability of 8.9% and considering all patients would be treated based on clinical judgement alone, the calculated number needed to test to avoid 1 unnecessary treatment (NNP) is 1.36. If we account for patients deprived of a needed treatment (false negative test), the corrected NNP is 1.40.



Table 12 – Calculated post-test probabilities for fFN testing in different populations

Population Threshold	/ Reference Standard	Analysis	Pre-test Probability (%)	Post-test probability +ve test (%)	As Low as	As High as	Post-test probability –ve test (%)	As Low as	As High as
Singleton, symptomatic	7 days	Bivariate threshold specific meta-analysis	8.9 [median prevalence across studies]	27.0	23.2	30.5	3.1	2.4	3.9
Singleton, symptomatic	7 days	Bivariate threshold specific meta-analysis	29.7 (highest prevalence across studies)	61.6	56.7	65.5	12.0	10	15
Singleton, symptomatic	7 days	Bivariate threshold specific meta-analysis	0.7% (lowest prevalence across studies)	2.6	2.1	3.1	0.2	0.2	0.3

-ve test: negative test. +ve test: positive test

#### Other considerations

Factor	Comment
<b>Balance between benefits and harms</b>	<p><b>clinical</b> RCTs show a possible beneficial effect on the number of preterm births before 37 weeks of pregnancy. However, the RCTs are flawed with serious shortcomings, most importantly the lack of standardized treatment protocols depending on test result. Benefit for other outcomes could not be proven, due to small sample sizes. In particular, there was no evidence on pre-defined critical outcomes.</p> <p>This said, the fFN test may be of value, not in preventing PTB, but in reducing overtreatment of women presenting with signs of PTB. As discussed in the introduction, only a minority of the latter will give birth within 7 days and is in need of immediate treatment. In spite of this, current practice is to give tocolytics to any woman presenting with signs of PTB. As tocolytic therapy can have serious side effects (see chapter 3.3) and supporting evidence for its benefit is limited, careful assessment of women with PTB is warranted before starting treatment.</p> <p>Although the negative LR(-) of fFN testing is only moderate (0.33), observational studies show that, given a pre-test probability of 9% in symptomatic women with less than 3cm dilation of the cervix, a negative test result leads to a post-test probability of 3 to 4%. As the prevalence of preterm birth within 7 days in selected women (based on clinical judgement and vaginal ultrasound, see below) is low, the NPV of fFN testing is high in this group of women. Assuming</p>



	<p>that, based on clinical judgement, the vast majority of patients would be treated, fFN could reduce overtreatment and its associated side effects and cost: approximately for each 1.4 tests performed, one unnecessary treatment can be avoided. Furthermore, using fFN testing on a secondary care level may possibly reduce the number of unnecessary transfers to tertiary care.<sup>61-63</sup></p> <p>For patients with a higher pre-test probability e.g. imminent labour, fFN testing is not useful. Also if pre-test probability is very low, fFN testing is not helpful. Cervical length measurement can be considered to assess pre-test probability in symptomatic women as will be discussed below.</p> <p>As the test is performed on a routine vaginal swab, there are no significant test-specific maternal side effects related to the test itself.</p>
<b>Quality of evidence</b>	<p>Due to current methodological limitations of the GRADE system for diagnostic tests, GRADE was not applied to the recommendations on diagnosis.</p> <p><u>Effectiveness</u>: the RCTs testing the clinical effectiveness of fFN testing to guide treatment decisions have several limitations, most importantly the lack of standardized treatment policy depending on test results and lack of sufficient statistical power. Furthermore, the RCTs do not report on avoiding overtreatment as a possible benefit of the test.</p> <p><u>Test performance</u>: observational studies may have underestimated test performance as the majority of studies did not report on blinding of care providers for test results. The observational studies were also at risk for spectrum bias, as in most studies the sampling method was not random or consecutive or both.</p>
<b>Costs (resource allocation)</b>	<p>fFN tests are currently not reimbursed in Belgium. The GDG estimates that one test costs the hospital or the patient between 25 and 70 euros. Unpublished data from the Hospital in Genk show that for each 4 fFN tests performed, one tocolytic treatment is avoided. The cost of one course of atosiban equals approximately the cost of 6 fFN tests (personal communication W. Gyselaers).</p> <p>The use of fFN tests to avoid overtreatment can be cost-effective if hospitalisation of women is prevented, as shown in a recent HTA by Deshpande et al.<sup>61</sup></p> <p>No formal cost-effectiveness study based on Belgian data was performed.</p>
<b>Patients values and preferences</b>	See recommendation on vaginal ultrasound in symptomatic women.

Recommendations	Strength of Recommendation	Level of Evidence
In women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation, consider further assessment using a fetal fibronectin test if measured cervical length is between 16 and 29mm. If test result is negative, no treatment is indicated as there is insufficient evidence.	Weak	NA



### 3.1.2 *phIGFBP test*

#### 3.1.2.1 *Clinical effectiveness of phIGFBP test for predicting preterm delivery in symptomatic women with singleton gestation*

No systematic review was identified for effectiveness of phIGFBP test. Also, no relevant randomised controlled trial or comparative observational study were found when we attempted to undertake a de novo synthesis of primary literature with no date restrictions applied to a separate search strategy. The decision to include comparative observational evidence was made *post hoc* when no trials were found.

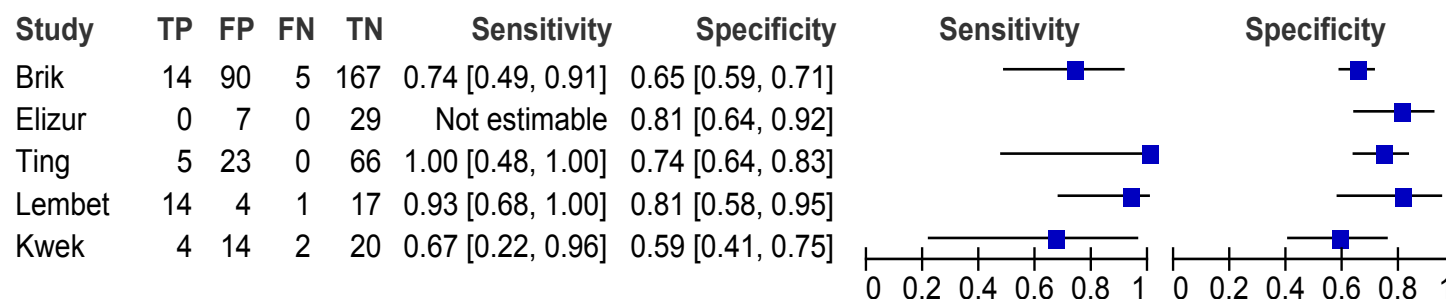
#### 3.1.2.2 *Performance of phIGFBP test for predicting preterm delivery in women with singleton gestation*

A systematic review by Honest et al. assessed the value of several testing strategies for preterm birth, including Actim Partus (phIGFBP-1).<sup>64</sup> The review included both asymptomatic and symptomatic pregnant women. For updating, we focused only on those studies in symptomatic populations. Reference standards were preterm delivery within 48 hours or 7 days of testing, preterm birth before 34 weeks, and before 37 weeks. The search date of this review ended September 2005. Therefore, we screened for primary studies from 2005 onwards. The review was rated as high quality (AMSTAR score: 8).

Fifteen primary studies met eligibility for updating the review.<sup>53, 58, 60, 65-76</sup> All studies, except one,<sup>53</sup> presented numerical data that could be used in quantitative syntheses. The studies took place in various countries, including Canada, Italy, Malaysia, Spain, Turkey, Finland, Bosnia and Herzegovina, Japan, and Singapore. Most studies were of unclear risk of bias and about half were blinded. Studies were considered to use common thresholds of approximately 10 µg/L or 30+ µg/L. In keeping with the original review, preterm birth within 48 hours and 7 days, and < 34 weeks and < 37 weeks of gestation were considered as separate reference standards.

#### **Reference Standard: Preterm Delivery within 48 hours**

A total of 5 studies (2 new) contributed to evidence synthesis. All studies employed a test cut-off of 30 µg/L. Given the data, substantial imprecision in test sensitivity (anywhere between 0.22 to approaching 1.00) and specificity estimates (0.41 to 0.95) were noted. Sparse data precluded exploration of heterogeneity and summary operating point estimation.

**Figure 3 – Coupled sensitivity and specificity plots for phIGFBP test for PTD <48 h in symptomatic singleton pregnancy****Reference Standard: Preterm Delivery within 7 days**

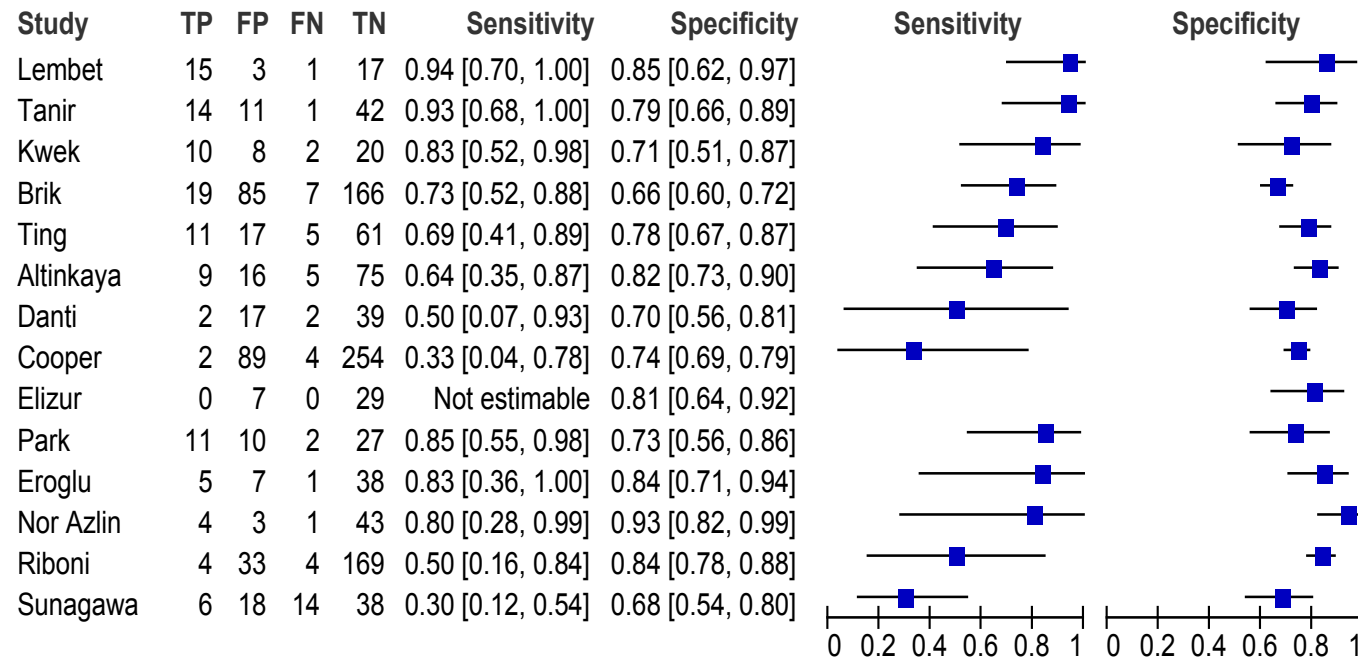
A total of 14 studies (10 new) contributed to evidence synthesis. Three studies employed a test cut-off of 10 µg/L. In keeping with the original review, our updated meta-analysis yielded evidence of test performance unlikely to yield substantial changes between pre- and post-test probabilities (see overall pooled estimates of sensitivity, specificity and likelihood ratios in Table 13). Compared with estimates of specificity, substantial heterogeneity was observed across studies in estimates of test sensitivity (Figure 4). No meaningful effect modification was observed in subgroup analyses (Table 13). Also, because of the limitation in the number of data contributing studies, threshold related effect modification in effect estimates could not be explored.

The calculated number of tests needed to prevent one course of unneeded treatment is 1.47. Accounted for patients deprived of a needed treatment, the corrected NNP is 1.57. Summary results of phIGFBP test and fFN test are listed in Table 18.

Results for preterm birth before 34 weeks and 37 weeks as a reference standard can be found in appendix.

**Table 13 – pHIGFBP test: pooled results and subgroup analysis by pre-specified covariates (PTD within 7 days)**

Characteristic	Sensitivity (95%CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)
All studies	0.73 (0.59-0.86)	0.78 (0.73-0.83)	3.33 (95%CI 2.24-4.41)	0.35 (95%CI 0.17-0.53)
Publication year				
Before 2008	Convergence issues	Convergence issues	Convergence issues	Convergence issues
After 2008	0.63 (0.40-0.85)	0.78 (0.70-0.85)	2.80 (1.21-4.38)	0.48 (0.17-0.79)
Methodologic quality (v1)				
High quality	0.73 (0.58-0.90)	0.80 (0.75-0.84)	3.60 (2.37-4.82)	0.33 (0.13-0.53)
Low quality	0.70 (0.13-1.00)	0.76 (0.48-1.00)	2.91 (0-7.74)	0.40 (0-1.21)
Methodologic quality (v2)				
High quality	Convergence issues	Convergence issues	Convergence issues	Convergence issues
Low quality	0.72 (0.55-0.89)	0.79 (0.73-0.86)	3.45 (1.92-4.98)	0.36 (0.14-0.58)
Prevalence (%)				
<=13	0.65 (0.47-0.84)	0.79 (0.70-0.88)	3.09 (1.50-4.69)	0.44 (0.20-0.68)
>13	Convergence issues	Convergence issues	Convergence issues	Convergence issues
Blinded				
Yes	Convergence issues	Convergence issues	Convergence issues	Convergence issues
no	0.67 (0.46-0.88)	0.78 (0.68-0.87)	3.06 (1.34-4.78)	0.42 (0.14-0.70)
Threshold				
10 ug	Convergence issues	Convergence issues	Convergence issues	Convergence issues
30+ug	Convergence issues	Convergence issues	Convergence issues	Convergence issues
Abbreviations: CI = confidence interval; LR+ = positive likelihood ratio; LR- = negative likelihood ratio				

**Figure 4 – Coupled sensitivity and specificity plots for phIGFBP test for PTD within 7 days in symptomatic singleton pregnancy**

Given a pre-test probability of 8.9% and considering all patients would be treated based on clinical judgement alone, the calculated number needed to test to avoid 1 unnecessary treatment (NNP) is 1.36. If we account for patients deprived of a needed treatment (false negative test), the corrected NNP is 1.40.

Summary results of phIGFBP test and fFN test are listed in Table 18.

**Other considerations**

Factor	Comments
<b>Balance between clinical benefits and harms</b>	<p>There are no data from randomized trials on the clinical effectiveness of pHIGFBP testing.</p> <p>Only few studies compared the two tests directly in the same population (results in appendix). When compared indirectly, the test accuracy parameters of pHIGFBP test seem similar to the fetal fibronectin test, although the fFN test has been studied more extensively.</p> <p>The choice between the pHIGFBP test and the fFN test will depend on other factors such as availability, user friendliness and price. An advantage of the pHIGFBP test is its generalized applicability, also e.g. in case of vaginal blood loss. According to the experiences of the GDG, a possible disadvantage of the pHIGFBP test can be the occurrence of unclear test results that are difficult to interpret.</p>
<b>Quality of evidence</b>	<p>Due to current methodological limitations of the GRADE system for diagnostic tests, GRADE was not applied to the recommendations on diagnosis.</p> <p>Test performance: observational studies may have underestimated test performance as the majority of studies did not report on blinding of care providers for test results. The observational studies were also at risk for spectrum bias, as in most studies the sampling method was not random or consecutive or both.</p>
<b>Costs (resource allocation)</b>	The pHIGFBP test is cheaper than the fibronectin test, its price estimated around 12 euro.
<b>Patients values and preferences</b>	See recommendation on vaginal ultrasound in symptomatic women.

Recommendations	Strength of Recommendation	Level of Evidence
In women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation, consider further assessment using a fetal fibronectin test or pHIGFBP test if measured cervical length is between 16 and 29mm. If test result is negative, no treatment is indicated as there is insufficient evidence.	Weak	NA



### 3.1.3 Transvaginal ultrasound

#### 3.1.3.1 Clinical effectiveness of transvaginal ultrasound (cervical length) for guiding treatment of symptomatic women with a singleton gestation

Similar to the fFN test effectiveness review, Berghella et al. compared treatment based on knowledge of transvaginal ultrasound results with treatment selected without knowledge of ultrasound results on the outcomes of preterm delivery before 28 weeks, 34 weeks, and 37 weeks.<sup>77</sup> The review planned to include trials of asymptomatic women in addition to symptomatic women with singleton gestation. However, no trials were identified in the asymptomatic population and therefore, all relevant analyses were based on a symptomatic, singleton, population. Relevant analyses in their systematic review pooled data from 3 RCTs. The review was rated as high quality (AMSTAR score: 9).

One record was identified in the update search, which was available in abstract form only.<sup>78</sup> No usable numerical data was presented in the abstract. Therefore, we could not use this study to update the review.

RCTs did not report on neonatal outcomes and maternal side effects.

**Table 14 – Summary of the systematic review on clinical effectiveness of vaginal ultrasound (cervical length measurement)**

Population	Intervention	Comparator	Pooled Estimate (95%CI)	Number of Patients	Number of Studies	Quality (AMSTAR)
Symptomatic pregnant women with singleton gestation between GA 14-34 weeks	Knowledge of TVU CL test results	No knowledge of TVU CL test results	<b>Preterm birth &lt; 28 weeks</b>	137	2	9
			No events			
			<b>Preterm birth &lt; 34 weeks</b>	256	3	
			RR = 0.55 (95%CI: 0.25, 1.20)			
			<b>Preterm birth &lt; 37 weeks</b>	242	2	
			RR = 0.59 (95%CI: 0.26, 1.32)			

Abbreviations: CI = confidence interval; CL = cervical length; GA = gestational age; RR = relative risk; TVU = transvaginal ultrasound



### 3.1.3.2 *Performance of vaginal ultrasound (cervical length measurement) for predicting preterm delivery in women with singleton gestation*

The systematic review by Honest et al. was updated for cervical assessment by ultrasound.<sup>64</sup> This review evaluated studies of both asymptomatic and symptomatic pregnant women. Although the review included 13 studies in the asymptomatic population, we extracted data for only 2 of these studies which explicitly reported participants as asymptomatic women with history of preterm delivery. For symptomatic women there were 19 included studies and we included all in updated meta-analyses. The review examined both cervical length measurement and cervical funneling – our focus was on the former only. Reference standards were delivery within 48 hours or 7 days of testing and preterm birth before 34 weeks or 37 weeks. The review was rated as high quality (AMSTAR score: 8).

The search date of this review ended September 2005. Therefore, we screened for primary studies from 2005 onwards. We identified a total of 44 new primary studies, all observational cohorts that met eligibility criteria for updating Honest et al.'s review.<sup>51, 52, 54, 65, 66, 69, 70, 72, 74, 79-83</sup> The new studies originated from several countries, such as India, Japan, Turkey, Australia, Brazil, United States, Mexico, Korea, Denmark, Spain, France, Italy, Finland, Sweden, Ireland, United Kingdom, Thailand, and Germany. Most studies were of unclear risk of bias and the majority were not blinded or blinding status was not reported. Aside from 4 studies with no extractable numerical data,<sup>51, 79, 84, 85</sup> all other studies were incorporated into updated meta-analyses.

#### 3.1.3.2.1 Symptomatic Pregnant Women

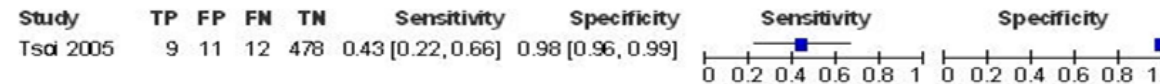
##### **Reference Standard: Preterm Delivery within 48 Hours of Testing (Figure 5)**

Few studies contributed to the evidence for predicting preterm birth within 48 hours with cervical length measurement in this patient population. Several different thresholds for cervical length were employed. Given sparse data, we could not estimate the average operating sensitivity and specificity for specific test thresholds. Variability in test performance was more pronounced for test sensitivity than specificity as previously observed in the original review. Specifically for testing thresholds of cervical length between 15-25mm, imprecise and heterogeneous sensitivity data from occasional studies precluded meaningful and reliable conclusions and exploration of heterogeneity. Our qualitative synthesis shows that test sensitivity estimates could be as low as 0.38 and as high as 1.00, while test specificity estimates as low as 0.43 and as high as 0.95.

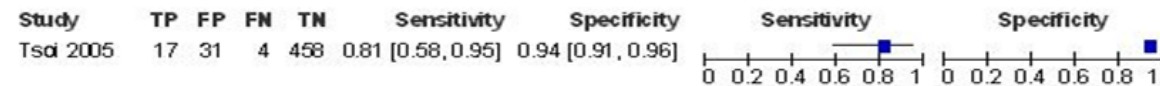


**Figure 5 – Coupled sensitivity and specificity plots for ultrasound cervical length (various cut-offs) for PTD <48 h in symptomatic singleton pregnancy in both old and new studies**

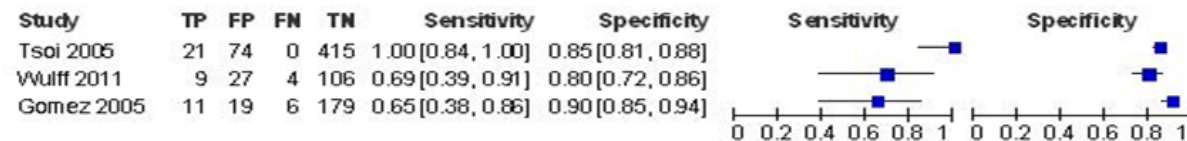
**Symptomatic 48hrs 5mm:**



**Symptomatic 48hrs 10mm:**



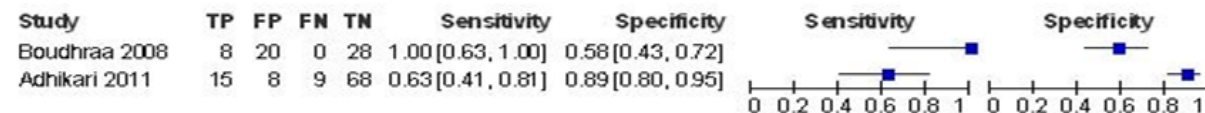
**Symptomatic 48hrs 15mm:**



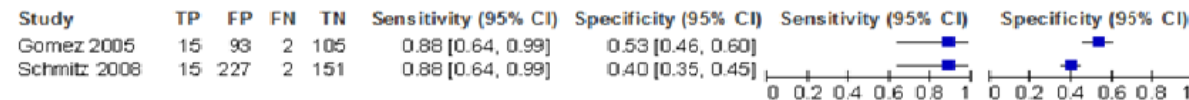
**Symptomatic 48hrs 20mm:**



**Symptomatic 48hrs 25mm:**



**Symptomatic 48hrs 30mm:**



**Reference Standard: Preterm Delivery within 7 days of Testing**

Pooled results for each threshold (15mm, 25mm and 30mm) is summarized in Table 15.

**Table 15 – Cervical length measurement to predict preterm birth within 7 days: results per threshold**

Threshold	Pooled sensitivity	Pooled specificity	LR+	LR-
15mm	0.77 (95%CI 0.59-0.94)	0.90 (95%CI 0.88-0.93)	7.57 (95%CI 5.34-9.79)	0.26 (95%CI 0.07-0.45)
25mm	0.75 (95%CI 0.63-0.88)	0.74 (95%CI 0.59-0.89)	2.87 (95%CI 1.33-4.40)	0.33 (95%CI 0.17-0.50)
30mm	0.94 (95%CI 0.87-1.01)	0.66 (95%CI 0.59-0.73)	2.75 (95%CI 2.16-3.34)	0.09 (95%CI 0.02-0.19)

**15mm Threshold:** A total of 17 studies (10 new) contributed to evidence synthesis. In keeping with the original review, our updated meta-analysis yielded imprecise evidence of test performance incorporating both possibilities of yielding important changes between pre- and post-test probabilities and lack thereof. The pooled sensitivity was 0.77 (95%CI 0.59-0.94) and specificity 0.90 (95%CI 0.88-0.93); corresponding estimates for LR+ and LR- were 7.57 (95%CI 5.34-9.79) and 0.26 (95%CI 0.07-0.45) respectively. Compared with estimates of specificity, substantial heterogeneity was observed across studies in estimates of test sensitivity. This heterogeneity is reflected both in the imprecise pooled sensitivity and LR- estimates, as well in a vertically elongated prediction ellipse around the summary point. Model non-convergence precluded exploration of heterogeneity in subgroup analyses. In a qualitative exploration, no obvious explanation was found for the variability in test performance estimates across studies.

**30mm Threshold:** A total of 7 studies (5 new) contributed to evidence synthesis. The bivariate model did not converge to elicit a reliable estimate of test accuracy because of inadequate power in the evidence base and

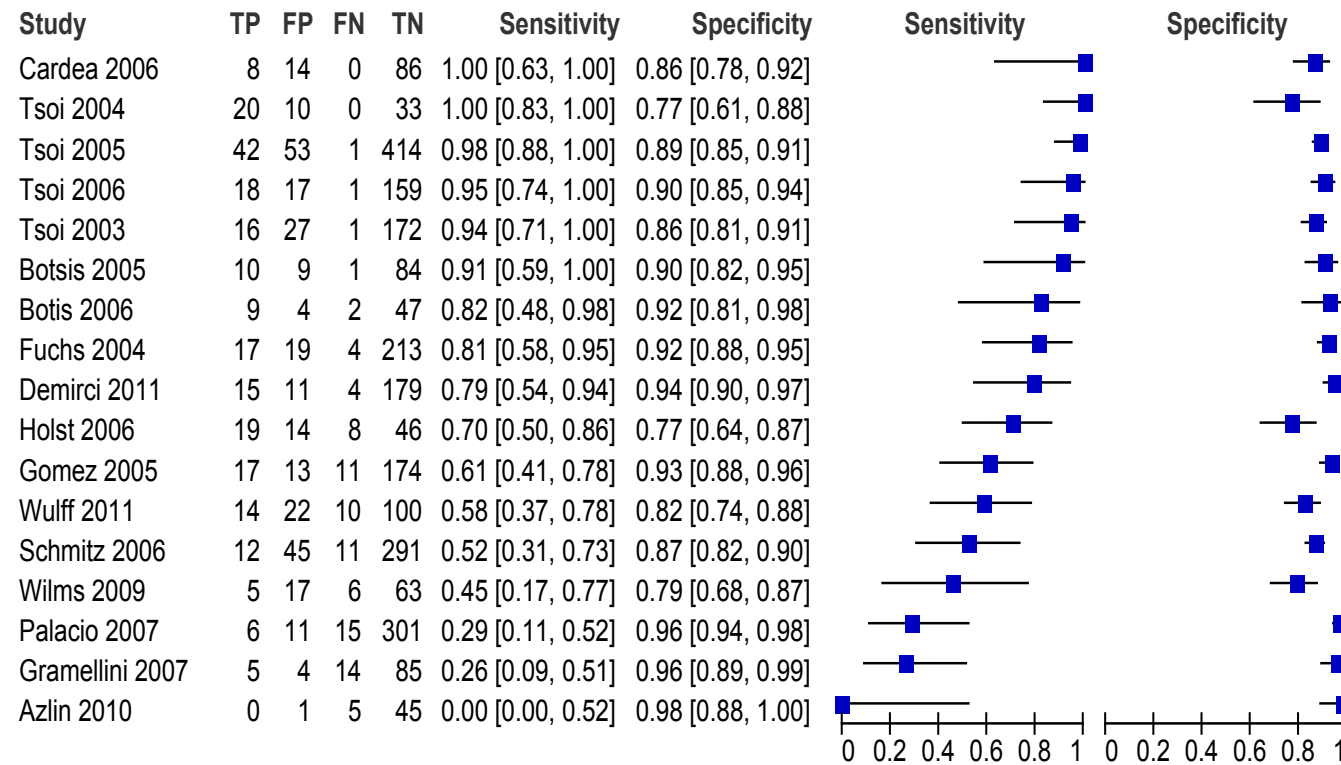
heterogeneity in the body of evidence. However, we observed relatively consistent good test sensitivity for predicting preterm birth within 7 days of testing. Heterogeneity in test specificity was substantial. The pooled estimates were: sensitivity = 0.94 (95%CI 0.87-1.01); specificity = 0.66 (95%CI 0.59-0.73); LR+ = 2.75 (95%CI 2.16-3.34); LR- = 0.09 (95%CI 0.02-0.19). Across the studies, the extreme values of confidence interval were LR+ 1.12 and 9.01; and LR- 0.00 and 3.26. In a qualitative investigation of heterogeneity we found no obvious explanation that could be explained by publication year, blinding status, overall study risk of bias, or prevalence of preterm birth. Given the fragility of the pooled estimates, existing evidence is best characterized as imprecise for test performance as it also incorporates the possibility of yielding no important changes between pre- and post-test probabilities.

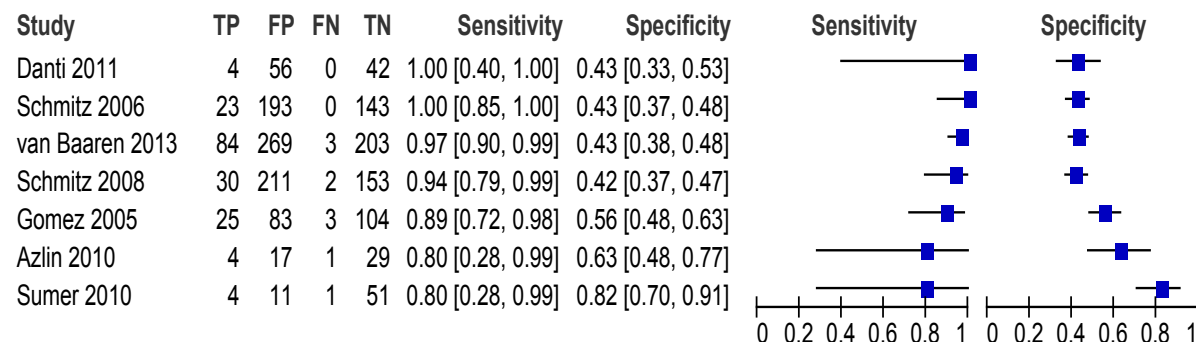
Results for other thresholds are summarized in appendix.

As for the fFN test, post-test probabilities were calculated for cervical length measurement given a pre-test probability, for different thresholds used, as summarized in Table 16.



**Figure 6 – Coupled sensitivity and specificity plots for ultrasound cervical length test (15mm cut-off) for PTD <7days in symptomatic singleton pregnancy**



**Figure 7 – Coupled sensitivity and specificity plots for ultrasound cervical length (30mm cut-off) for PTD <7days in symptomatic singleton pregnancy****Table 16 – Calculated post-test probabilities for cervical length measurements in symptomatic women, by threshold**

Population / Threshold	Reference Standard	Analysis	Pre-test Probability (%) [median prevalence across studies]	Post-test probability +ve test (%)	As Low as	As High as	Post-test probability -ve test (%)	As Low as	As High as
15mm	7 days	Bivariate threshold specific meta-analysis	9.8	45.1	36.7	51.5	2.7	0.8	4.7
30mm	7 days	Fragile pooled estimates from meta-analysis, so extreme CIs in the body of evidence used	8.1	NA	9.0	44.3	NA	0.0	22.3

-ve test: negative test. +ve test: positive test

#### Reference Standard: Preterm Delivery before 34 weeks

Pooled results for each threshold are summarized in Table 17. More details can be found in appendix.

**Table 17 – Cervical length measurement to predict preterm birth before 34 weeks of pregnancy: results per threshold**

threshold	Pooled sensitivity	Pooled specificity	LR+	LR-
15mm	0.51 (95%CI 0.32-0.70)	0.91 (95%CI 0.85-0.96)	5.44 (95%CI 2.92-7.95)	0.54 (95%CI 0.35-0.73)
20mm	0.63 (95%CI 0.54-0.70)	0.82 (95%CI 0.79-0.85)	3.41 (95%CI 2.67-4.15)	0.46 (95%CI 0.37-0.56)
25mm	0.69 (95%CI 0.62-0.76)	0.72 (95%CI 0.69-0.75)	2.49 (95%CI 2.12-2.87)	0.43 (95%CI 0.32-0.53)
30mm	0.93 (95%CI 0.80-1.06)	0.55 (95%CI 0.46-0.63)	2.05 (95%CI 1.53-2.58)	0.14 (95%CI 0.11-0.38)

**Reference Standard: Preterm Delivery before 37 weeks**

A total of 21 studies (12 new) investigated the accuracy of cervical length measurement using transvaginal ultrasound for prediction of birth before 37 weeks of gestation. Various testing thresholds were examined. For all thresholds, few underpowered evidence yielding imprecise estimates of test performance precluded meaningful conclusions – meta-analyses could not be performed. In general, wide confidence intervals ranged from low to substantial test performance. For test threshold of 25mm we attempted to meta-analyse 7 studies (2 new), but studies were mostly small not permitting convergence of the bivariate model. Pooled results for 25mm threshold reported below suggest low test performance of cervical length measurement in predicting the preterm birth before 37 weeks of gestation. The results, however, are fragile. Sensitivity was 0.64 (95%CI 0.053-0.74); specificity 0.71 (95%CI 0.65-0.78); LR+ 2.20 (95%CI 1.59-2.81); LR- 0.51 (95%CI 0.36-0.67). Across the studies, the extreme values of confidence interval were LR+ 1.08 and 302.59; and LR- 0.13 and 1.07. These results are best considered imprecise.

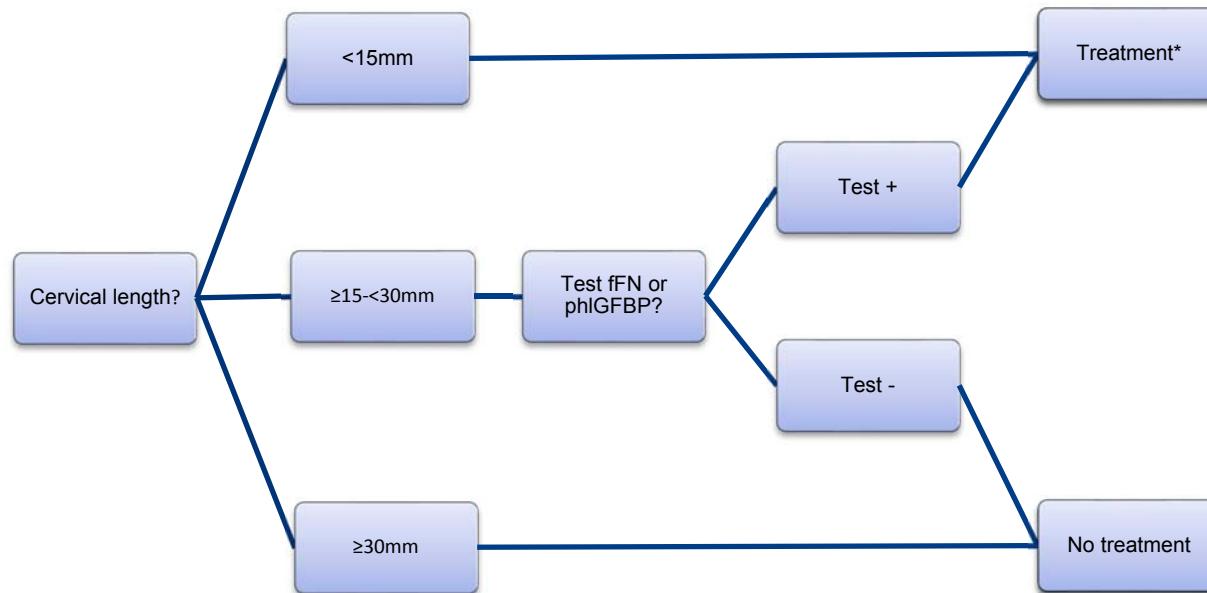
**Other considerations**

Factor	Comment
<b>Balance between benefits and harms</b>	<p>Three RCTs investigated the effectiveness of transvaginal ultrasound to prevent preterm birth before 28, 34 or 37 weeks, showing no proof of a beneficial effect. However number of events in the trials is low.</p> <p>As for the fFN test, the most important possible advantage of vaginal ultrasound is that unnecessary hospital admission and treatment can be avoided. With a threshold of 15mm and a LR(-) of 2.6 (95%CI 0.07-0.45), an acceptable post-test probability can be achieved given a pre-test probability of 10%. However, confidence in the pooled results is undermined due to heterogeneous sensitivity between studies and inconsistent results for other thresholds (higher LR(-) for the 20mm threshold). When a threshold of 30mm is used, the rate of false negative results is consistently low, pooled LR(-) is 0.09 (95%CI 0.02-0.19).</p> <p>The accuracy of diagnosing preterm labour can be improved by combining vaginal ultrasound with fFN testing. Based on a review by DeFranco et al.<sup>86</sup> the following schedule can be proposed:</p> <ul style="list-style-type: none"> <li>cervical length on vaginal ultrasound <math>\geq</math> 30mm: no treatment</li> </ul>



Factor	Comment
	<ul style="list-style-type: none"> <li>cervical length on vaginal ultrasound 16-29mm: perform fFN test               <ul style="list-style-type: none"> <li>fFN test negative: no treatment</li> <li>fFN test positive: steroids, tocolytic therapy, transfer to tertiary level if indicated</li> </ul> </li> <li>cervical length on vaginal ultrasound <math>\leq 15</math>mm: steroids, tocolytic therapy, transfer to tertiary level if indicated</li> </ul> <p>Although vaginal ultrasound can be uncomfortable, no serious side effects are noted.</p>
Quality of evidence	<p>RCTs testing the clinical effectiveness of cervical length measurement by vaginal ultrasound are underpowered to show proof of clinical benefit.</p> <p>Observational studies show heterogeneous results and are subject to spectrum bias.</p>
Costs (resource allocation)	<p>Cervical length measurement is currently not reimbursed in Belgium. A cost-effectiveness analysis based on Dutch data found that additional fFN testing in the case of cervical length between 15 and 30mm is cost-saving without compromising neonatal health outcomes compared to a treat-all strategy or measuring cervical length only.<sup>63</sup> No formal cost-effectiveness study based on Belgian data was performed.</p>
Patients values and preferences	<p>Patients stress that women who present with symptoms of possible preterm labour should be taken seriously and that their concerns should not be minimized or simply dismissed in case of a negative test. Women should also be reassured that they can always return if new symptoms occur, especially as the post-test risk is not zero percent.</p>

Recommendation	Strength of Recommendation	Level of Evidence
<p>Consider performing cervical length measurement in women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation to avoid overtreatment (avoid unnecessary admissions to hospital, transfer to tertiary level and administration of tocolytic therapy), using a threshold of <math>\geq 30</math>mm to decline treatment. Consider further assessment using a fetal fibronectin test or pHIGFBP test if measured cervical length is between 16 and 29mm. If cervical length is <math>&lt; 15</math>mm, consider treatment (Figure 8).</p>	Weak	NA

**Figure 8 – Management of threatened preterm labour in singleton pregnancies**

\* steroids, tocolytic therapy, transfer to tertiary level if indicated

**Table 18 – Summary results test accuracy pHIGFBP test, fetal fibronectin test and transvaginal ultrasound to predict delivery at 7 days<sup>1</sup>**

	Fetal fibronectin test (95%CI)	pHIGFBP test (95%CI)	Cervical length ≤ 30mm (95%CI)
<b>Specificity</b>	0.81 (0.77-0.84)	0.78 (0.73-0.83)	0.66 (0.59-0.73)
<b>Sensitivity</b>	0.73 (0.67-0.80)	0.73 (0.59-0.86)	0.94 (0.87-1.00)
<b>Pre-test probability of condition</b>	0.089	0.089	0.089
<b>Pre-test probability of being treated</b>	1	1	1
<b>NNP<sup>2</sup></b>	1.36 (1.31-1.43)	1.41 (1.32-1.50)	1.66 (1.50-1.86)
<b>Corrected NNP<sup>3</sup></b>	1.40 (1.34-1.49)	1.46 (1.34-1.59)	1.68 (1.50-1.90)
<b>NRI<sup>4</sup></b>	0.78 (0.67-0.75)	0.75 (0.63-0.74)	0.68 (0.53-0.67)
<b>LR+</b>	3.84 (2.91-5.00)	3.33 (2.24-4.41)	2.76 (2.12-3.70)
<b>LR-</b>	0.33 (0.24-0.43)	0.35 (0.17-0.53)	0.09 (0.00-0.22)
<b>PPV</b>	0.27 (0.22-0.33)	0.24 (0.18-0.33)	0.21 (0.17-0.27)
<b>NPV</b>	0.97 (0.96-0.98)	0.97 (0.95-0.98)	0.99 (0.98-1.00)

1: Indirect comparison based on the meta-analyses of studies on diagnosis performance of fFN and pHIGFBP test.

2: NNP Number Needed to Protect

3: The corrected NNP accounts for false negative tests

4: NRI=Net Reclassification Index

### 3.1.3.2.2 Asymptomatic pregnant women with history of preterm delivery

#### **Reference Standard: Preterm Delivery before 34 weeks**

Sparse data precluded quantitative or qualitative synthesis of cervical length diagnostic test performance for predicting preterm birth across various thresholds, ranging from 15-30mm. Results for a 20-22mm cut-off are summarized in Figure 9. Other results are summarized in appendix.

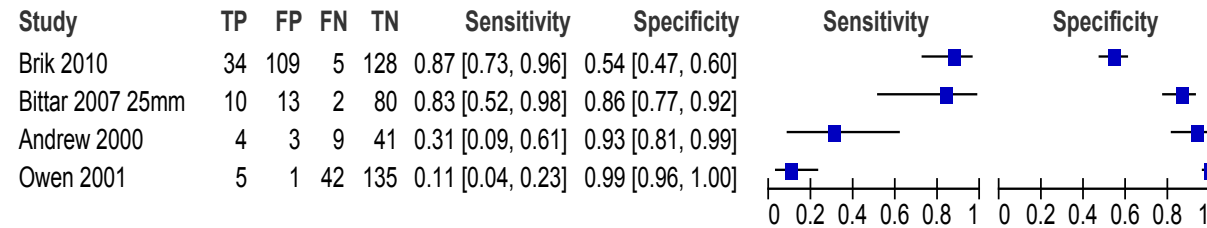
#### **Reference Standard: Preterm Delivery before 37 weeks**

*Various Thresholds:* Three studies evaluated cervical length measurement by ultrasound to predict preterm delivery < 37 weeks. Cervical length thresholds varied from 20-29.5mm. Sensitivity ranged from 0.43 to 0.90 and specificity from 0.54 to 0.96. Results are summarized in Figure 10.

Post-test probabilities were calculated for cervical length measurement given a pre-test probability, for different thresholds used, as summarized in Table 19.



**Figure 9 – Coupled sensitivity and specificity plots of ultrasound cervical length (20-22mm cut-off) for PTD < 34 weeks in asymptomatic pregnant women with singleton gestation in both old and new studies**



**Figure 10 – Coupled sensitivity and specificity plots of ultrasound cervical length (various thresholds) for PTD < 37 weeks in asymptomatic pregnant women with singleton gestation in both old and new studies**

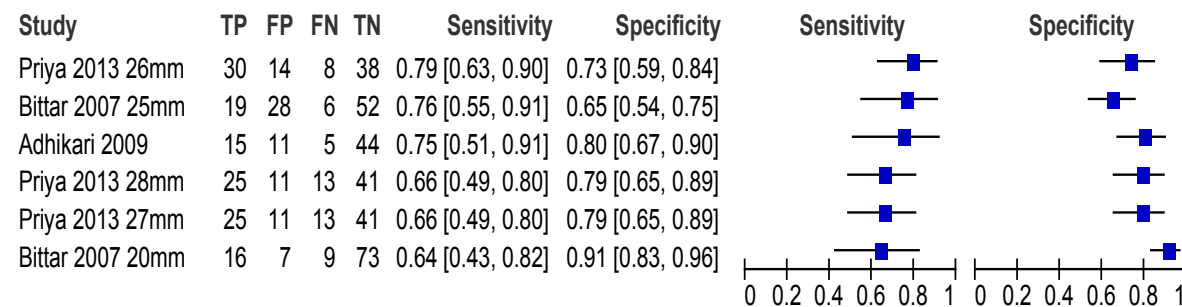




Table 19 – Calculated post-test probabilities for cervical length measurements in asymptomatic, high risk women, by threshold

Population / Threshold	Reference Standard	Analysis	Pre-test Probability (%) [median prevalence across studies]	Post-test probability +ve test (%)	As Low as	As High as	Post-test probability –ve test (%)	As Low as	As High as
15-25mm	34 weeks	Data not pooled, extreme CIs in the body of evidence used	20.0	NA	24.5	99.4	NA	1.5	25.0
20-25mm	37 weeks	Data not pooled, extreme CIs in the body of evidence used	23.8	NA	31.9	83.1	NA	5.3	19.1

+ve test: positive test. –ve test: negative test.

Factor	Comment
<b>Balance between benefits and harms</b>	<p>clinical Only sparse data are available. In the four studies investigating the value of cervical length to predict preterm delivery before 34 weeks in high risk women with a history of preterm birth, sensitivity ranged from 0.43 to 0.90 and specificity from 0.54 to 0.96.</p> <p>However, as shown in trials investigating the use of cerclage, ultrasound can be used to limit the number of cerclage procedures, if cerclage is omitted in high risk women with a cervical length before 24 weeks remaining longer than 25mm. This way, the number of cerclage procedures and associated morbidity can be limited (see below, recommendation on cerclage).<sup>87, 88</sup></p>
<b>Quality of evidence</b>	Due to current methodological limitations of the GRADE system for diagnostic tests, GRADE was not applied to the recommendations on diagnosis.
<b>Costs (resource allocation)</b>	Cervical length measurement is currently not reimbursed in Belgium.
<b>Patients values and preferences</b>	Pregnant women experience the disadvantages associated with vaginal ultrasound as only minor. Follow-up of cervical length can give reassurance and support women to be in control of the further preventative measures during pregnancy. To avoid inducing additional fear of poor prognosis, it is important to provide sufficient information about the preventative nature of the test and subsequent measures and start follow-up of cervical length only in close discussion with the women.



Recommendations	Strength of Recommendation	Level of Evidence
Consider performing cervical length measurement during the second trimester (14-24 weeks) in women with a history of spontaneous preterm birth prior to 32 weeks, to select women eligible for cerclage for secondary prevention.	Weak	NA

### 3.2 Secondary prevention

Secondary prevention refers to prevention of preterm birth in pregnant women at risk for preterm delivery e.g. women with a history of preterm birth or a history of surgery to the uterine cervix.

Many different strategies to prevent preterm birth in women at risk have been proposed, such as screening for and treatment of periodontal disease, smoking cessation, cervical cerclage or pessary, reduction of physical activity or bed rest, antibiotic treatment of vaginal vaginosis and asymptomatic bacteriuria etc.

As prioritized by the members of the GDG, only progesterone and cerclage as secondary prevention of preterm birth are discussed in this guideline.

#### 3.2.1 Progesterone for women at risk

Four hundred sixty two bibliographic records were identified (MEDLINE=118, EMBASE=179, Cochrane Library=116, Grey Literature=2). Additionally, we brought in 47 records flagged relevant for this question from searches undertaken for other research questions. After de-duplicating and consideration of companion articles, 370 records remained for title/abstract screening. Of these, 119 (107 reviews, and 12 primary studies) met the eligibility criteria based on title and abstract, and 12 (9 systematic reviews and 3 primary studies) based on full-text. Of the 9 included systematic reviews, 2 were eventually selected for updating based on quality and publication year (see appendix).

- One systematic review (Dodd et al. 2013)<sup>24</sup> on **progesterone** versus **placebo/no treatment** in women with short cervix, or past history of spontaneous preterm birth, or following presentation of threatened preterm birth. This section is also relevant to the question on progesterone maintenance therapy for women with threatened preterm labour as discussed in section 3.3.4.2.5
- One systematic review (Conde-Agudelo et al. 2013)<sup>89</sup> on **progesterone** versus **placebo**, and **progesterone** versus **cerclage** (indirect comparison) in asymptomatic women with short cervix a and past history of preterm birth with a companion paper<sup>14</sup>

Three primary studies were retrieved for updating the review by Dodd et al.<sup>90-92</sup> Bimbashi et al. performed a trial including women with a short cervix on ultrasound measurement. Results were available in abstract form only and did not provide any numerical data to update the meta-analysis.<sup>90</sup> Palacio et al. was also an abstract that evaluated singleton pregnancies with successfully arrested preterm labour, cervical length of < 25mm, and gestational age between 24-34 weeks.<sup>91</sup> Saleh Gargari et al., studied singleton pregnant women with successfully arrested preterm labour, short cervix (<15mm), and gestational age of ≥ 24 and < 34 weeks.<sup>92</sup> These two studies contributed data that was used to update the review by Dodd et al. (see 3.3.4.2.5)

No relevant primary studies were identified for updating the review by Conde-Agudelo et al.

The PRISMA diagram providing further detail on the identified records is presented in appendix.



### 3.2.1.1 Progesterone for asymptomatic women with a history of spontaneous preterm delivery

Results for asymptomatic women with a history of spontaneous preterm delivery are summarized in Table 20. Although intramuscular progesterone was not of primary interest, overall results including oral, vaginal or intramuscular progesterone were added to the summary posthoc for additional information. GRADE evidence profiles for vaginal and oral progesterone can be found in appendix.

In the majority of trials, progesterone was started between 16 and 24 weeks of pregnancy. Progesterone during pregnancy reduces the risk for preterm birth before 34 weeks of pregnancy and perinatal death without a significant increase in adverse events for the mother. Also the use of assisted ventilation, the occurrence of NEC and neonatal and perinatal death appear to be reduced. The 95%CI for the number of patients needed to treat to prevent one case of RDS ranged from 2 to 3.

There is no proof that progesterone during pregnancy has a beneficial or detrimental effect on long term outcomes such as developmental delay and learning difficulties, but as only one RCT, with 274 patients, reports long term outcomes, evidence is still seriously underpowered.

**Table 20 – Progesterone in asymptomatic women with history of spontaneous preterm birth: summary of results**

Intervention	Comparator	Outcomes by subgroups	Pooled estimate RR [95%CI]	Number of events / number participants	Number of studies
Progesterone (oral or vaginal or intramuscular)	Placebo or no treatment	<b>Asymptomatic women with history of spontaneous preterm delivery</b>			
		PTB < 34 weeks	0.31 [0.14-0.69]	108/602	5
		Vaginal progesterone	0.21 [0.10-0.44]	49/454	4
		Oral progesterone	0.59 [0.39-0.90]	59/148	1
		PTB < 37 weeks	0.55 [0.42-0.74]	653/1750	10
		Vaginal progesterone	0.52 [0.29-0.92]	364/1065	5
		Oral progesterone	0.46 [0.19-1.11]	13/33	1



Intervention	Comparator	Outcomes by subgroups	Pooled estimate RR [95%CI]	Number of events / number of participants	Number of studies
		RDS	0.45 [0.17, 1.16]	156/1217	3
		Vaginal progesterone	0.92 [0.59, 1.43]	70/611	1
		Oral progesterone	0.10 [0.03, 0.30]	34/148	1
		Use of assisted ventilation	0.40 [0.18, 0.90]	67/633	3
		Vaginal progesterone	0.24 [0.07, 0.81]	16/141	1
		Oral progesterone	0.11 [0.01, 1.92]	3/33	1
		NEC	0.30 [0.10, 0.89]	12/1170	3
		Vaginal progesterone	0.53 [0.15, 1.92]	8/711	2
		Neonatal sepsis	0.42 [0.08, 2.23]	20/700	3
		Vaginal progesterone	0.13 [0.02, 1.01]	7/241	2
		Neonatal death	0.45 [0.27, 0.76]	60/1456	6
		Vaginal progesterone	0.53 [0.24, 1.18]	26/752	2
		Oral progesterone	0.43 [0.12, 1.59]	10/148	1
		Perinatal death	0.50 [0.33-0.75]	49/1453	6
		Vaginal progesterone	0.67 [0.34-1.29]	35/753	2
		Oral progesterone	0.43[0.12-1.29]	10/148	1
		IVH grade III-IV	1.59 [0.21, 11.75]	4/1069	2
		Vaginal progesterone	0.98 [0.06, 15.55]	2/611	1
		PVL	3.13 [0.13, 75.52]	1/141	1
		Vaginal progesterone	3.13 [0.13, 75.52]	1/141	1



## Conclusions

- There are indications that secondary prevention with progesterone reduces the use of assisted ventilation, the occurrence of NEC in the newborn and neonatal and perinatal death.
- There are indications that progesterone reduces the risk for preterm birth before 34 and 37 weeks of pregnancy in asymptomatic pregnant women with a history of preterm birth.
- There is insufficient evidence to judge the effect of secondary prevention with progesterone on the long-term outcome of neonates in pregnant women with a history of preterm birth.

## Other considerations

Factor	Comments
<b>Balance between clinical benefits and harms</b>	<p>Progesterone during pregnancy reduces the risk of perinatal death, of preterm birth before 34 weeks and of preterm birth before 37 weeks of pregnancy, without a significant increase in adverse events for the mother. Also the use of assisted ventilation, the occurrence of NEC, admissions to the neonatal intensive care unit and neonatal death are reduced. There is no proof of benefit for long term outcomes; available evidence is underpowered. No differential effects in terms of route of administration, time of commencing therapy and dose of progesterone were observed.</p> <p>There are no indications that progesterone during pregnancy has serious adverse events.</p> <p><b>Dosage</b></p> <p>To limit side effects, it is suggested to use vaginal administration at the lowest dose tested in clinical trials (200mg once daily).</p>
<b>Quality of evidence</b>	Low level of evidence
<b>Costs (resource allocation)</b>	No formal cost-effectiveness analysis is performed.
<b>Patients values and preferences</b>	Women with a history of preterm birth feel reassured that something can be done before any symptoms of preterm birth occur and that progesterone is a safe intervention. Again, it is important to stress the preventative nature of the intervention.

NB included studies: (Akbari 2009; Cetingo 2011; da Fonseca 2003; Glover 2011; Johnson 1975; Ibrahim 2010; Majhi 2009; Meis 2003; O'Brien 2007; Rai 2009; Saghafi 2011a)

Recommendations	Strength of Recommendation	Level of Evidence
Offer vaginal progesterone to asymptomatic pregnant women with a history of spontaneous preterm birth, from the start of the second trimester onwards until at least 34 weeks.	Strong	Low



### 3.2.1.2 Progesterone for asymptomatic women with a short cervix identified on ultrasound

Results for women with a short cervix on ultrasound are summarized in Table 21. A short cervix was defined as less than 15mm, 25mm or 30mm or between 10 and 20mm.

There is moderate level of evidence that vaginal progesterone reduces the risk of respiratory distress syndrome by 50% (RR 0.49; 95%CI 0.29-0.85). The corresponding 95%CI for the number of patients needed to treat (NNT) to prevent one case of RDS ranged from 13 to 63.

**Table 21 – Progesterone in asymptomatic women with a short cervix on ultrasound: summary of results**

Intervention	comparator	Outcomes by subgroups	Pooled estimate RR [95%CI]	Number of events / number of participants	Number of studies
Progesterone (Oral or vaginal or intramuscular)	Placebo or no treatment	<b>Asymptomatic women with a short cervix on ultrasound</b>			
		PTB < 34 weeks	0.64 [0.45, 0.90]	105/438	2
		Vaginal progesterone	0.58 [0.38, 0.87]	71/250	1
		PTB < 37 weeks	0.97 [0.82, 1.15]	382/1303	3
		Vaginal progesterone	0.89 [0.68, 1.16]	147/458	1
		PTB < 28 weeks	0.59 [0.37, 0.93]	72/1115	2
		Vaginal progesterone	0.50 [0.25, 0.97]	35/458	1
		RDS	0.69 [0.48, 1.00]	109/1556	4
		Vaginal progesterone	0.49 [0.29, 0.85]	54/432	2
		Use of assisted ventilation	0.65 [0.36, 1.16]	41/274	1
		Vaginal progesterone	0.65 [0.36, 1.16]	41/274	1
		NEC	0.70 [0.27, 1.78]	20/1374	3
		Vaginal progesterone	0.96 [0.30, 3.11]	10/732	2
		Neonatal sepsis	0.46 [0.18, 1.20]	41/1374	3
		Vaginal progesterone	0.58 [0.15, 2.25]	27/732	2
		Neonatal death	0.55 [0.26, 1.13]	31/1571	4
		Vaginal progesterone	0.41 [0.15, 1.15]	17/732	2
		Perinatal death	0.74 [0.42, 1.29]	49/1389	3



Intervention	comparator	Outcomes by subgroups	Pooled estimate RR [95%CI]	Number of events / number of participants	Number of studies
		Vaginal progesterone	0.56 [0.27, 1.17]	30/732	2
		IVH grade III-IV	0.98 [0.17, 5.60]	4/1100	2
		Vaginal progesterone	0.32 [0.01, 7.73]	1/458	1
		PVL	1.78 [0.38, 8.24]	6/1282	3
		Vaginal progesterone	No events	0/824	1

### Conclusions

- There are indications that secondary prevention with progesterone in pregnant women with a short cervix on ultrasound reduces the occurrence of respiratory distress syndrome in the newborn.
- There are indications that progesterone reduces the risk for preterm birth before 28 and 34 weeks of pregnancy in asymptomatic pregnant women with a short cervix on ultrasound.
- There is insufficient evidence to judge the effect of secondary prevention with progesterone on the long-term outcome of neonates in pregnant women with a short cervix on ultrasound.

### Other considerations

Factor	Comment
<b>Balance between benefits and harms</b>	<b>clinical</b> Definition of a shortened cervix varied between trials (< 15mm, between 10 and 20mm, < 25mm, < 30mm). Progesterone during pregnancy reduces the risk for preterm birth before 28 and before 34 weeks of pregnancy. Evidence is, however, limited. The two studies using vaginal progesterone show a positive effect on the occurrence of respiratory distress syndrome (if studies using IM progesterone are included: $p=0.050$ ). The effect on other outcomes remains unclear, as studies are underpowered. However, the benefit of a systematic screening for short cervix by vaginal ultrasound in all pregnant women was not assessed. Women included in the trials may have had additional risk factors for preterm birth (e.g. one study only included only women after an episode of arrested preterm labour). Furthermore, screening of women without risk factors for preterm birth may result in a high number of false positive results and overtreatment and induce a lot of anxiety. There are no indications that vaginal progesterone during pregnancy has serious adverse events.



	<b>Dosage</b> To limit side effects, it is suggested to use vaginal administration at the lowest dose tested in clinical trials (200mg once daily).
<b>Quality of evidence</b>	Low level of evidence.
<b>Costs (resource allocation)</b>	No formal cost-effectiveness analysis is performed.
<b>Patients values and preferences</b>	See recommendation for women with a history of preterm birth.

NB included studies: Fonesca 2007, Grobman 2012, Hassan 2011, Rozenberg 2012

Recommendations	Strength of Recommendation	Level of Evidence
Consider vaginal progesterone in asymptomatic women with a short cervix identified on vaginal ultrasound.	Weak	Low

### 3.2.2 Cerclage

Two high quality systematic reviews (AMSTAR score 10) studying two separate asymptomatic populations of interest were selected for updating – i.e. those with short cervix or history of preterm birth. Both systematic reviews, however, were deemed to be up-to-date as no new evidence was identified.<sup>25, 89</sup>

The systematic review by Alfirevic et al. compared cervical cerclage versus no cerclage, and cervical cerclage versus progesterone in women with singleton pregnancies considered to be at 'high risk' for pregnancy loss based on women's history (e.g. previous preterm birth), short cervix (<25mm) on ultrasound scanning, or physical exam-detected cervical changes.<sup>25</sup> Details of the systematic review can be found in the evidence table in appendix.

The data on the up-to-date outcomes of interest are presented in Table 22 and Table 23.

#### 3.2.2.1 Cerclage in women at risk for preterm delivery based on women's history (e.g. previous preterm birth or cervical surgery)

Table 22 gives an overview of outcomes in asymptomatic women with a singleton pregnancy, at high risk for preterm birth based on women's history (e.g. previous preterm birth or cervical surgery).



**Table 22 – Efficacy and safety of cerclage versus no cerclage in asymptomatic women at high risk based on women's history**

Intervention	comparator	Outcomes by subgroups	Pooled estimate RR [95%CI]	Number of events / number of participants	Number of studies
Cerclage	No cerclage	<b>Asymptomatic women with history of spontaneous preterm delivery</b>			
		PTB < 37 weeks	0.86 [0.59, 1.27]	464/2045	4
		PTB < 34 weeks	0.76 [0.40, 1.46]	244/1539	3
		PTB<28 Weeks	0.82 [0.59, 1.13]	133/1539	3
		Neonatal death (before discharge)	0.67 [0.33, 1.36]	32/1964	3
		All perinatal losses	0.80 [0.58, 1.10]	139/1539	3
		Serious perinatal morbidity	No studies		
		Neonatal death (before discharge)	0.67 [0.33, 1.36]	32/1964	3
		Perinatal death and serious neonatal morbidity	No studies		
		RDS or oxygen dependency (after 28 days of life)	3.06 [0.32, 28.93]	4/194	1
		IVH of PVL	1.02[0.06, 16.09]	2/194	1
		Cesarean section	1.21 [0.96, 1.52]	258/1964	3
		Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)	1.57 [0.76, 3.24]	118/700	2
		Pyrexia	2.22 [1.22, 4.01]	49/992	2
		PPROM	1.63 [0.71, 3.70]	32/1458	2



## Conclusions

- A beneficial or harmful effect of cerclage in women with a history of preterm birth or cervical surgery on neonatal outcomes could neither be demonstrated nor refuted.
- A beneficial or harmful effect of cerclage in women with a history of preterm birth or cervical surgery on the occurrence of preterm birth could neither be demonstrated nor refuted.
- There are indications that cervical cerclage is associated with an increase of maternal pyrexia.

## Other considerations

Factor	Comment
<b>Balance between clinical benefits and harms</b>	<p>There is no proof that cerclage as secondary prevention has a beneficial effect in women at risk selected based on history (history of preterm birth, history of surgery on the cervix). On the other hand, cerclage increases the risk of maternal pyrexia and possible other side effects and the rate of caesarean sections.</p> <p>Furthermore, indirect comparison of progesterone and cerclage in these high risk women shows no clear advantage for cerclage.</p> <p>For further discussion, see also cerclage in women with a short cervix on ultrasound</p>
<b>Quality of evidence</b>	Very low level of evidence.
<b>Costs (resource allocation)</b>	No cost assessment performed.
<b>Patients values and preferences</b>	See recommendation on cerclage for women with short cervix on ultrasound.

Recommendations	Strength of Recommendation	Level of Evidence
Do not routinely offer cerclage as secondary prevention of preterm birth to women at high risk based on the woman's history of preterm birth (between 24 and 37 weeks) alone.	Strong	Very low



### 3.2.2.2 Cerclage in high risk women with a short cervix identified on ultrasound

Table 23 summarizes results for women at high risk of preterm birth further selected by a 'one-off' ultrasound scan of the cervix or serial ultrasound scanning. Also the overall pooled results, including women at risk based on history, high risk women selected by one/serial ultrasound and low risk women selected by ultrasound, are reported in the table.

Intramuscular progesterone and cerclage were compared in only one RCT. The trial lacked statistical power to deduce meaningful conclusions.

**Table 23 – Efficacy and safety of cerclage versus no cerclage in asymptomatic, high risk women with a short cervix on ultrasound**

Intervention	comparator	Outcomes by subgroups	Pooled estimate RR [95%CI]	Number of events / number of participants	Number of studies
Cerclage	No cerclage	<b>Asymptomatic women with a short cervix on ultrasound</b>			
		PTB < 37 weeks	0.80 [0.69, 0.95]	869/2898	9
		One-off US in high risk women	0.55 [0.30, 0.99]	28/56	1
		Serial US in high risk women	0.78 [0.60, 1.02]	254/510	4
		PTB < 34 weeks	0.79 [0.68, 0.93]	487/2392	8
		One-off US in high risk women	0.63 [0.27, 1.46]	17/56	1
		Serial US in high risk women	0.77 [0.55, 1.10]	155/510	4
		PTB<28 Weeks	0.80 [0.64, 1.00]	266/2392	8
		One-off US in high risk women	0.69 [0.18, 2.62]	8/56	1
		Serial US in high risk women	0.71 [0.48, 1.04]	88/510	4
		All perinatal losses	0.78 [0.61, 1.00]	228/2391	8
		One-off US in high risk women	0.77 [0.14, 4.25]	5/56	1
		Serial US in high risk women	0.66 [0.41, 1.06]	61/509	4
		Serious neonatal morbidity	0.95 [0.63, 1.43]	81/818	4
		One-off US in high risk women	0.77 [0.14, 4.25]	5/56	1
		Serial US in high risk women	0.84 [0.51, 1.37]	55/475	3
		Neonatal death (before discharge)	0.73 [0.42, 1.28]	47/2309	6
		One-off US in high risk women	2.31 [0.22,24.01]	3/56	3
		Serial US in high risk women	0.87 [0.13,5.89]	2/82	2



Intervention	comparator	Outcomes by subgroups	Pooled estimate RR [95%CI]	Number of events / number of participants	Number of studies
		Perinatal death and serious neonatal morbidity	0.82 [0.61, 1.09]	150/817	4
		One-off US in high risk women	0.58 [0.16, 2.08]	9/56	1
		Serial US in high risk women	0.75 [0.53, 1.07]	99/474	3
		RDS or oxygen dependency (after 28 days of life)	1.11 [0.66, 1.88]	50/439	5
		One-off US in high risk women	0.58 [0.06, 6.00]	3/56	1
		Serial US in high risk women	0.98 [0.53, 1.81]	36/382	3
		IVH of PVL	0.83 [0.23, 3.09]	9/439	5
		One-off US in high risk women	0.38 [0.02, 9.01]	1/56	1
		Serial US in high risk women	0.96 [0.05, 19.53]	4/382	3
		NEC	0.81 [0.16, 4.12]	5/372	3
		Serial US in high risk women	0.81 [0.16, 4.12]	5/362	3
		Retinopathy of prematurity	0.46 [0.14, 1.48]	11/553	2
		One-off US in high risk women	0.23 [0.01, 4.58]	2/56	1
		Serial US in high risk women	0.62 [0.15, 2.53]	8/300	1
		Cesarean section	1.19 [1.01, 1.40]	469/2817	8
		One-off US in high risk women	1.35 [0.52, 3.50]	13/56	1
		Serial US in high risk women	1.10 [0.82, 1.46]	135/510	4
		Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)	2.25 [0.89, 5.69]	132/953	3
		One-off US in high risk women	No studies		
		Serial US in high risk women	No studies		
		Pyrexia	2.39 [1.35, 4.23]	53/1245	3
		One-off US in high risk women	3.44 [0.15, 81.09]	1/56	1
		Serial US in high risk women	No studies		
		PPROM	0.96 [0.62, 1.48]	97/2010	6
		One-off US in high risk women	0.49 [0.14, 1.72]	10/56	1
		Serial US in high risk women	0.51 [0.18, 1.45]	39/209	3



### Conclusions

- There are indications that cerclage reduces the occurrence of preterm birth before 37 weeks in women at high risk of preterm birth with a short cervix on ultrasound.
- A beneficial or harmful effect of cerclage in women at high risk of preterm birth with a short cervix on ultrasound on neonatal outcomes could neither be demonstrated nor refuted.
- There are indications that cervical cerclage is associated with an increase of maternal pyrexia.

### Other considerations

The systematic review by Conde-Agudelo et al. compared cerclage versus no cerclage, and cerclage versus progesterone (the latter comparison, however, was actually an indirect meta-analysis with vaginal progesterone as intervention and cerclage as control) in asymptomatic singleton pregnant women with history of previous spontaneous preterm birth or a cervical length less than 25mm.<sup>89</sup> Cervical length screening occurred between 14 and 25 weeks of gestation. For cerclage versus no cerclage comparison, evidence was obtained from five studies that were either in patients with short cervix or those additionally with history of previous preterm birth – i.e. each contributing study was not in women with both short cervix and history of preterm birth. Further details for this systematic review are summarized in the evidence table in appendix. The five studies that compared cerclage with no cerclage were also included in the review of Alfirevic et al.

Results for all outcomes of interest are presented in Table 24. Indirect comparison remains inconclusive on benefits of progesterone compared with cerclage.

**Table 24 – Efficacy and safety of cerclage versus no cerclage in asymptomatic singleton women with short cervix or previous spontaneous preterm birth <37 weeks**

Intervention	Comparator	Outcomes	Pooled Estimate: RR (95%CI)	Number of events/patients (n/N)	Number of Studies
Progesterone (vaginal)	Cerclage (indirect comparison)	PTB< 37 Week	1.20 (0.84–1.72)	139/325	9
		PTB< 35 Week	0.94 (0.56–1.58)	91/325	9
		PTB< 32 Week	0.71 (0.34–1.49)	57/325	9
		PTB< 28 Week	0.80 (0.31–2.02)	38/325	9
		RDS	0.62 (0.18–2.16)	16/282	8
		IVH (Grad III or IV)	1.79 (0.15–22.0)	1/282	8
		NEC	0.76 (0.02–31.49)	1/282	8
		Neonatal sepsis	0.53 (0.08–3.35)	8/282	8
		BPD	0.28 (0.01–9.01)	7/186	3

**Other considerations**

Factor		Comment
<b>Balance between benefits and harms</b>	<b>clinical</b>	<p>Number and timing of ultrasounds performed vary between studies investigating the use of cerclage. Both a one off ultrasound at 18-20 weeks or serial measurements (e.g. two-weekly) between 14-20 weeks have been reported.</p> <p>Pooled results from all studies (high and low risk women, selected by a one off ultrasound or serial ultrasound) show a reduction of perinatal death, of preterm birth before 37 weeks, of preterm birth before 34 weeks and of preterm birth before 28 weeks but results are imprecise and the effect may be very small. There is no proof of a beneficial effect on serious neonatal morbidity, neonatal death or combined perinatal death and serious perinatal morbidity. Trials are underpowered however, certainly for subgroups of high risk patients with a short cervix on a one-off or serial ultrasound.</p> <p>Ultrasound can be used to limit the number of cerclage procedures, if cerclage is omitted in high risk women with a cervical length before 24 weeks remaining longer than 25mm.<sup>93</sup></p> <p>Taking into account the imprecision of the results and the known side effects of the procedure, the GDG recommends to consider a cerclage only in women with a history of preterm birth before 32 weeks and a short cervix on ultrasound (&lt; 25mm) measured between 14 and 24 weeks, as the potential benefit is higher in this group. Given the possible side effects of cerclage (infection, bleeding, scarred cervix...) the possible benefits must be carefully weighed against the risks for each individual woman, taking into account the woman's history and personal preferences. A cervical pessary has been proposed as an alternative, but data are still limited.<sup>94, 95</sup> Further literature review regarding the use of cervical pessary is out of the scope of this guideline.</p> <p>For women with a history of recurrent second trimester birth, a primary cerclage (at 12-14 weeks of pregnancy) may be considered.</p>
<b>Quality of evidence</b>		Very low level of evidence.
<b>Costs (resource allocation)</b>		No cost-effectiveness study was performed.
<b>Patients values and preferences</b>		Patients support a cerclage if indicated and if discussed with the future parents but they warn for false reassurance by the 'mechanical' support of the cervix. It should be clearly explained that a cerclage can be beneficial but also has limitations, i.e. a cerclage does not prevent the occurrence of preterm labour.

Recommendations	Strength of Recommendation	Level of Evidence
Consider a cerclage in women with a history of spontaneous preterm birth before 32 weeks and a short cervix on ultrasound before 24 weeks.	Weak	Very low
Consider a primary cerclage (at 12-14 weeks of pregnancy) to women with a history of recurrent second trimester birth.	Weak	Very low



### 3.2.2.3 *Rescue cerclage in women with cervical dilation early in pregnancy*

We could not identify any evidence from RCTs for progesterone and cerclage addressing the subpopulation of pregnancies with advanced mid-trimester cervical changes (i.e. cervical dilatation with membranes showing). As such, the GDG chose not to formulate a recommendation for this population.

## 3.3 Tertiary prevention

Tertiary prevention refers to interventions in women with threatened preterm labour and thus to the treatment of preterm labour.

When women present with signs of premature labour, several antenatal interventions can be considered to optimize neonatal outcomes. Often tocolytic therapy is considered, assuming that neonatal outcomes will improve by prolonging pregnancy. However, as will be discussed below, there is no proof that tocolytic therapy in itself has a beneficial effect on important outcomes.<sup>27</sup> It is demonstrated that tocolysis may be effective by prolonging pregnancy with at least 48 hours and offering the necessary time for antenatal interventions such as transfer to a tertiary perinatal centre, antenatal corticosteroids and magnesium sulphate. Antenatal steroids administered to pregnant women with threatened preterm labour have become standard practice as it is associated with a reduced risk of neonatal death, RDS, cerebro-vascular haemorrhage, NEC, intensive care admissions and systemic infections in the neonate.<sup>96</sup>

In this chapter, we discuss several questions related to tocolytic therapy and the optimisation of fetal maturity:

- Which tocolytic agents are preferred?
- Should antenatal corticosteroid therapy be administered in a single course or as repeated courses?
- Can tocolytic therapy to treat the acute phase of threatened preterm labour be arrested after 48 hours?
- Is maintenance tocolysis indicated after 48 hours acute tocolytic therapy?

### 3.3.1 *Decision to treat*

A number of important considerations need to be kept in mind when deciding whether, or not, a tocolytic therapy should be implemented:

- Only a minority of the women presenting with symptoms and signs of preterm labour will eventually give birth within the next seven days (see above).
- There is no clear proof that prolonging pregnancy in itself is safe and improves neonatal outcomes.<sup>27</sup>
- Although infrequent, tocolytic therapy can be associated with severe side effects.<sup>97</sup>

Each decision to start tocolytic treatment needs thus to be based on careful clinical assessment and expected benefits and risks and be accompanied with other interventions to optimize neonatal prognosis such as (repeated) antenatal steroids, transfer to tertiary level care and magnesium sulphate if indicated.

Furthermore, when signs of preterm labour occur very early in pregnancy, treatment decisions are professionally, ethically, and emotionally complicated and demanding. Parents confronted with difficult choices and unsure prognosis need profound counselling and support.

To offer some guidance on treatment approach and communication with future parents, representatives of all Flemish perinatal centres (maternal intensive care units (MIC) and neonatal intensive care units (NICU) recently wrote a consensus based text (without the involvement of the GDG and KCE). As mentioned in the text, the guidance is based on a review of the scientific literature on prognosis of extremely preterm birth per gestational age and existing recommendations in other countries. Retrieved data served as a starting point for the development of consensus based recommendations for treatment decisions in case of (threatened) preterm birth very early in pregnancy, at the limit of viability.

As an agreed policy is considered very helpful to support clinicians confronted with complex treatment decisions early in pregnancy, the GDG decided to adopt the consensus text. To this end, the translated text was reviewed by representatives of the Groupement des Gynécologues Obstétriciens de Langue Française de Belgique (GGOLFB) and was



adopted by the association. The consensus text can be found on the website of the VVOG ([www.vvog.be](http://www.vvog.be)) and GGOLFB ([www.ggolfb.be](http://www.ggolfb.be)).

### 3.3.2 Type of tocolytic therapy

This analysis is based on a good quality systematic review (8/11 on the AMSTAR scale<sup>a</sup>).<sup>27</sup> We did not search for more recent RCTs, if any, given that the network meta-analysis by Haas et al. was recent (mid-2012) and the statistical models for updating the network meta-analysis not available. No GRADE tables were generated because the methodology has not yet been developed for network meta-analysis and forest plots of head-to-head trials were not provided.

The authors of the review compared the effectiveness of all tocolytic therapies, the main outcome being defined as a delivery successfully delayed for 48 hours. Only RCTs were included (n=95). For the main outcome, 55 studies contributed to the network meta-analysis and 54 in the pairwise meta-analysis (one trial was excluded as it compared 2 treatments of the same class). Analysis was carried out by drug classes, i.e. no estimation of individual treatment effect was provided.

Direct and indirect comparisons were overall consistent. Betamimetics (OR<sup>b</sup>=2.41; 95%CI: 1.27; 4.55), prostaglandin inhibitors (OR=5.39; 95%CI: 2.14; 12.34), calcium channel blockers (OR=2.71; 95%CI: 1.17; 5.91), magnesium sulphate (OR=2.76; 95%CI: 1.58; 4.94) and oxytocin receptor blockers (OR=2.02; 95%CI: 1.10; 3.80) were superior to placebo in successfully delaying delivery by 48 hours<sup>c</sup>. The results from this network meta-analysis suggested that prostaglandin inhibitors had a greater beneficial effect than all the other active classes. However, uncertainty in these estimates was considerable, i.e. the probability of prostaglandin inhibitors being the “best” class being 83%. The probability of being ranked in the top 3 most efficacious classes in delaying delivery for 48h was 96% for prostaglandin inhibitors, 63% for magnesium sulphate, 57% for calcium

channel blockers, 33% for betamimetics, 24% for nitrates, 14% for oxytocin receptor blockers, 13% for others, and 0% for placebo.

As regards the other outcomes, authors found no evidence that any tocolytic treatment improved mortality or neonatal morbidity, or any clinically important outcome (maternal side effects). It is however worth mentioning that uncertainty was even higher for these outcomes than for the main outcome. For example, as regards neonatal mortality, the probability of being the “best” class was only 20% for prostaglandin inhibitors and 47% for calcium channel blockers. The most probable best class was thus not constant over all clinical outcomes considered.

Weighing the balance of benefits and harms seemed to indicate that prostaglandin inhibitors would be reasonable first-line agents, followed by calcium channel blockers. Only one small trial however compared directly prostaglandin inhibitors and calcium channel blockers. Therefore further trials are needed to assess which of these 2 classes is most effective. Of note, some studies reported a possible association between antenatal prostaglandin inhibitors and neonatal complications notably premature closure of the ductus arteriosus<sup>d</sup>.

This meta-analysis present the great merit of combining direct and indirect evidence on all tocolytic agents available, and thus to allow a comparison of their respective efficiency. However, this study also presented a number of limitations.

First, the focus of included studies was on delaying delivery by 48 hours because that enables exposure to a full course of antenatal corticosteroids to improve lung maturity. However, by focusing on gestational age at birth, the question of whether forcing babies to stay longer in a potentially hostile uterine environment is clinically beneficial is not answered by tocolytic trials at hand.<sup>99</sup> None of the individual trials was powered for assessing an

<sup>a</sup> No a priori design (no protocol registered); no list of excluded studies provided (only available from the authors); characteristics of the included studies not provided; likelihood of publication bias was not formally assessed but the authors cross-checked their results with those of Cochrane reviews of tocolytic medications.

<sup>b</sup> All such values are posterior median odds ratios

<sup>c</sup> This was not the case for the class of nitrates and the class of “other tocolytics” (alcohol, human chorionic gonadotropin, combination of tocolytic drugs)

<sup>d</sup> Although the specific cyclooxygenase (COX) inhibitors could produce the opposite effect<sup>98</sup>



improvement in neonatal morbidity. Trials included a mean of 111.9 (SD 108.8, range 20-708) participants.

Second, the characteristics of the individual studies were not described. It is likely that dosage, timing of administration and duration of treatment differed a lot among studies, contributing to the overall uncertainty of the results, although the authors reported that class treatment effects were not modified by using meta-regression to explore the effect of length of treatment delivery. The conditions of the patients are also not described although likely to modify the results and vary by studies, such as duration and frequency of uterine contractions or state of the cervix. We contacted the main author of the meta-analysis for accessing descriptive tables presenting the main features of the individual studies. Such tables were inexistent because “the trials defined preterm labour differently - there were likely 5 or 6 different definitions, and dosing regimens were different for the different drugs also” (David Haas, personal communication). Such methodological heterogeneity has contributed to the uncertainty of the results.

Lastly, not all the included studies contributed to the analysis because several studies did not include the same outcome measures as the other trials. This might have resulted to a publication bias to an unknown extent.

In conclusion, it is reasonable to propose prostaglandin inhibitors and calcium channel blockers as first-line agents, in spite of the uncertainty surrounding such ranking. As prostaglandin inhibitors (e.g. indomethacin) are only used under 32 weeks' gestation due to the risk of premature closure of the ductus arteriosus (especially when used after 32 weeks), calcium channel blockers are recommended in case of threatened preterm labour after that gestational age.

**Other considerations**

Factor		Comments
<b>Balance between benefits and harms</b>	<b>clinical</b>	<p>A network meta-analysis reported that all tocolytic agents are superior to placebo in delaying delivery with at least 48h, with prostaglandin inhibitors ranked most effective, followed by calcium channel blockers. Prolongation of pregnancy is however only an intermediate outcome for neonatal morbidity and mortality, for which there is no proof that tocolytic therapy in itself has a beneficial effect.</p> <p>The beneficial effect on an intermediate outcome must be weighed against the potential side effects for the neonate and the pregnant woman. Prostaglandin inhibitors carry the risk of in utero constriction of the ductus arteriosus, and decreased urine production with oligohydramnios and postnatal pulmonary hypertension, NEC, persistent ductus arteriosus and other neonatal morbidity.<sup>100</sup></p> <p>Beta mimetic therapy and magnesium sulphate have a very low score in the analysis with regards to probability of being ranked best for maternal side effects.</p> <p>Overall, taking into account that all tested tocolytic agents are better than placebo to prolong pregnancy for at least 48hours and there is no proof of a beneficial effect on important outcomes, calcium channel blockers and oxytocin receptor blockers may be preferred given their safety profile. Data directly comparing calcium channel blockers with oxytocin receptor blockers are too limited to draw firm conclusions. Factors other than safety profile that may influence the choice for a tocolytic agent include price and registration for use in tocolytic treatment. Atosiban is registered for use in women with signs of suspected preterm labour, while nifedipine is only used off label in pregnant women. Nifedipine however, is much cheaper than atosiban.</p> <p>Although serious adverse events are rare, the risk increases if a combination of tocolytic agents is used. As there is no evidence of additional benefit, combination therapy is never recommended.</p> <p><b>Dosage</b></p> <p>As an example, the treatment schedules from the APOSTEL III study protocol can be used: nifedipine tocolysis is initiated with 2 X 10 mg nifedipine capsules orally in the first hour, followed by 20 mg nifedipine retard per 6 hours for the next 47 hours. In the atosiban group, a bolus injection of 6.75 mg IV in 1 minute is given, followed by 18 mg/hour for 3 hours, followed by a maintenance dosage of 6 mg/hour for 45 hours.<sup>101</sup></p>
<b>Quality of evidence</b>		Due to its current limitations, GRADE was not applied to the network analysis.
<b>Costs (resource allocation)</b>		No formal cost-effectiveness study was performed. Treatment with calcium channel blockers for 48 hours is very cheap, costing only a few euros. One course of atosiban however, currently costs a few hundred euro.
<b>Patients values and preferences</b>		Information and shared decision making between health care providers and parents before starting tocolytic therapy is very important, especially when pregnancy duration is at the edge of viability. Information for the parents should include explaining what will happen (as much as possible in advance, e.g. a visit to the NICU), what the purpose is of all treatment interventions and what can be expected. Patients should be reassured that everything is done to optimize prognosis for their baby.



Recommendations	Strength of Recommendation	Level of Evidence
Consider tocolytic therapy in women with threatened preterm birth between 23+5/7 and 33+5/7 weeks of gestation to delay birth with 48h to allow administration of corticosteroid therapy and/or transfer to tertiary level. Calcium channel blockers and oxytocin antagonists are considered first choice tocolytic agents. Other tocolytic agents are not routinely recommended because of their side effects.	Weak	NA

### 3.3.3 Repeated dose(s) of corticosteroid therapy

A high quality systematic review of Crowther et al.<sup>28</sup> analysed the data from 10 RCTs comparing repeated doses of corticosteroids with no further treatment or placebo in pregnant women considered to be at risk of preterm birth who have already received a single course of steroids seven or more days previously.

Results for selected outcomes are summarized in Table 25.

Search was updated for RCTs published after the search date of the Cochrane review (see appendix). No more recent RCT was found. A systematic review published in 2011 by Peltoniemi et al. focused on placebo-controlled RCTs and included only studies that were already identified in the Cochrane review.<sup>102</sup>

One of the already included studies, the Multiple Courses of Antenatal Corticosteroids Study (MACS) published two ancillary reports and one abstract on secondary outcomes.

Murphy et al.<sup>103</sup> reported on birth weight, length and head circumference adjusted for gestational age at birth and confounding factors. In the adjusted analysis, multiple courses of antenatal steroids were associated with a decrease in birth weight (-33.50g; 95%CI -66.3 to -0.73), length (-0.34 cm; 95%CI -0.62 to 0.06) and head circumference (-0.30 cm; 95%CI -0.46 to -0.14). The unadjusted data were already included in the Cochrane review. One of the selected abstracts reported the same results.<sup>104</sup>

In another publication, Murphy et al.<sup>105</sup> analysed maternal side effects three months post-partum by a structured questionnaire including the Edinburgh Postnatal Depression Scale. There were no significant differences in the risk of maternal side effects after three months between the two groups.

Also for another trial already included in the Cochrane review, additional results were published in two abstracts.<sup>106, 107</sup> McKinlay et al. reported on long term follow-up of the ACTORDS trial and found no differences in whole body bone mineral content, bone area, spinal mineral apparent density and fracture incidence at early school-age between children exposed to repeat doses antenatal corticosteroids and those exposed to placebo. Furthermore, there was no significant difference in lung function at early school-age.


**Table 25 – Efficacy of repeated dose antenatal corticosteroids versus single dose in pregnant women with threatened preterm labour**

Intervention	Comparator	Outcomes	Pooled estimates	Number of events/patients	Number of studies	
Repeated dose(s) of corticosteroids	No treatment placebo	further or	RDS	RR 0.83 [0.75, 0.91]	1028/3206	8
			Severe lung disease	RR 0.80 [0.56, 1.14]	588/4826	6
			Composite serious outcome (variously defined)	RR 0.84 [0.75, 0.94]	957/5094	7
			Fetal and neonatal mortality	RR 0.94 [0.71, 1.23]	198/5554	9
			Small-for-gestational age at birth	RR 1.18 [0.97, 1.43]	354/3975	7
			Mean head circumference at birth (cm)	MD -0.32 [-0.49, -0.15]	5626 patients	9
			Mean length at birth (cm)	MD -0.56 [-0.89, -0.23]	4550 patients	6
			Mean birth weight (g)	MD -75.79 [ -117.63, -33.96 ]	5626 patients	9
			chorioamnionitis	RR 1.16 [ 0.92, 1.46 ]	258/4261	6
			Puerperal sepsis	RR 1.15 [0.83, 1.60]	133/3091	5

## Conclusions

- There are indications that repeated dose antenatal corticosteroids is associated with a decreased incidence of respiratory distress syndrome and serious neonatal morbidity compared to a single dose of corticosteroids if delivery is postponed to at least seven days after the first dose.
- There are indications that repeated dose antenatal corticosteroids is associated with a reduced mean head circumference and mean length at birth compared to a single dose of corticosteroids if delivery is postponed to at least seven days after the first dose.

**Other considerations**

Factor	Comments
<b>Balance between clinical benefits and harms</b>	<p>Compared to a single course, repeated dose(s) of corticosteroids reduce the risk of RDS and overall serious morbidity (as a composite outcome) without increasing maternal morbidity. However, there is concern that high doses of (antenatal) corticosteroids can have a detrimental effect on growth and neurological development of the newborn, as reflected in the lower mean head circumference, length and weight at birth. Furthermore, data on the long term effects of repeated doses of steroids are very limited. Hence, the GDG recommends to consider repeating a corticosteroid course (two doses) only once.</p> <p><b>Dosage</b></p> <p>In the majority of trials included in the meta-analysis, one course of corticosteroids consisted of two doses of 12mg betamethasone, 24 hours apart.</p>
<b>Quality of evidence</b>	Moderate level of evidence.
<b>Costs (resource allocation)</b>	No formal cost-assessment was performed.
<b>Patients values and preferences</b>	See 'choice of tocolytic therapy'.

Recommendations	Strength of Recommendation	Level of Evidence
Consider a second course of antenatal corticosteroids in women with threatened preterm birth if the first course was administered at least seven days earlier. More than two courses of corticosteroids are not recommended.	Weak	Moderate

**3.3.4 Duration of therapy**

For Key Question 5, a total of 941 bibliographic records were identified (MEDLINE=172, EMBASE=330, Cochrane Library=166, Grey Literature=10, reviewer nomination=1). Additionally, we also brought in 262 records previously flagged relevant for this question from searches undertaken for other key questions (Key Question, 3, and 6). After de-duplicating and consideration of companion articles, 727 records formed the full screening set. At the titles and abstract screen, 71 (49 reviews, and 22 primary studies) records passed to full text review (Figure 1). Of these, 10 records (6 systematic reviews and 4 primary studies) were finally included. Outside of our systematic search and screening of the literature, one systematic review

published in October 2013 pertained to maternal harms of magnesium sulphate in a wider pregnant patient population (eclampsia, neuroprotection, tocolysis) was nominated for inclusion to address Key Question 6.11 Of note, on AMSTAR this review was rated as of moderate quality, but in reviewers' judgment it was a very comprehensive evaluation of maternal harms of magnesium sulphate with no obvious validity concerns. Following quality assessment of the included systematic reviews, 4 reviews addressing unique maintenance tocolytic drugs (or classes) were selected. We assessed one of the selected reviews to be current because of its 2013 search date and did not consider it in need of updating,<sup>108</sup> so updated 3 systematic reviews:



- Conde-Agudelo et al., 2011 investigated Nifedipine maintenance therapy versus placebo/no treatment in patients with preterm labour<sup>109</sup>
- Dodd et al., 2012 compared oral betamimetics maintenance therapy with placebo/no treatment in women with arrested preterm labour<sup>110</sup>
- Papatsonis et al., 2009 evaluated oxytocin antagonist maintenance therapy versus placebo in women after threatened preterm labour<sup>111</sup>
- Han et al.'s, 2013 systematic review tested Magnesium maintenance therapy versus placebo/ no treatment for preventing preterm birth after threatened preterm labour<sup>108</sup>

### 3.3.4.1 48 hours or longer?

No systematic review was identified to answer this question. Based on expert opinion, a de novo synthesis at this time was judged to be low priority.

### 3.3.4.2 Maintenance therapy

#### 3.3.4.2.1 Efficacy and Safety of Magnesium maintenance therapy versus placebo/ no treatment for preventing preterm birth following arrested preterm labour

The SR by Han et al.<sup>108</sup> identified three RCTs comparing magnesium maintenance therapy compared with either placebo or no treatment in women with arrested preterm labour. One study used Mg(SO)<sub>4</sub>; two studies used MgCL and one used Mg oxide. In the included primary studies the gestation ranged from 20 to 36 weeks. The exact initiating and stopping time for maintenance treatment was not specified. Overall, evidence remains underpowered to proof or exclude significant benefit or harm. Magnesium therapy appears to be associated with an increased frequency of diarrhoea. Results of the meta-analyses are summarized in Table 26.

The GRADE evidence profile can be found in appendix. The overall level of evidence was considered to be very low.

**Table 26 – Efficacy and safety of magnesium maintenance tocolytic treatment versus placebo/ no treatment in women after threatened preterm labour: results**

Population	Intervention	Comparator	Outcome	Pooled Estimate: RR [ 95%CI]	Number of events/Total participants (n/N)	Number of Studies	Quality (AMSTAR)
Women after threatened preterm labour	Magnesium	Placebo/no treatment	Death before discharge (infants)	5.00 [ 0.25, 99.16 ]	2/50	1	10
			Respiratory distress syndrome	3.00 [ 0.13, 70.30 ]	1/50	1	
			PTB< 28 Weeks:	Not estimable	0/0	0	
			PTB< 32 Weeks:	Not estimable	0/0	0	
			PTB< 37 Weeks:	1.05 [ 0.80, 1.40 ]	61/99	2	
			<u>Maternal side effects</u>				
			Diarrhoea	7.67 [2.41, 24.41]	25/133	1	
			Other side effects (nausea, vomiting, tachycardia)	Various estimates (Not significant)	NA	1	

Abbreviations: CI = confidence interval; n = number of events; N = number of patients; RR = relative risk



## Conclusions

- There is no proof of a beneficial effect of magnesium maintenance therapy after arrested preterm labour on neonatal outcomes. Serious harm cannot be ruled out.
- Magnesium maintenance therapy is associated with an increased frequency of diarrhoea, compared with placebo or no treatment.

## Other considerations

Factor	Comments
<b>Balance between clinical benefits and harms</b>	<p>As there is no proof of any benefit of maintenance tocolytic therapy with magnesium, it is not recommended.</p> <p>Prolonged use of magnesium sulphate injections may be associated with serious adverse events such as bone malformations in exposed babies. For this reason, the U.S. Food and Drug Administration (FDA) recommends against its prolonged use as tocolytic agent (see section 1.1.1).<sup>112</sup></p> <p>Although severe side effects have not been described for oral use of magnesium, side effects such as diarrhoea may occur.</p>
<b>Quality of evidence</b>	Very low level of evidence.
<b>Costs (resource allocation)</b>	NA
<b>Patients values and preferences</b>	NA

Recommendations	Strength of Recommendation	Level of Evidence
After 48 hours tocolytic therapy, do not offer magnesium maintenance therapy to pregnant women with suspected preterm labour.	Strong	Very low



### 3.3.4.2.2 Efficacy and Safety of Nifedipine maintenance therapy versus placebo/ no treatment in women following arrested preterm labour

The systematic review by Conde-Agudelo et al. 2011 compared Nifedipine versus placebo/no treatment in women with preterm labour (n=3 studies). The comparators were no treatment (n=2 RCTs), and placebo (n=1 RCT).<sup>113</sup> Gestational ages ranged from 24-34 weeks in two studies but was not stated for the third study. All women received nifedipine until 36-37 weeks of gestation or delivery whichever comes first; however, timing of initiation of maintenance tocolytic was not explicitly specified (after discontinuation of acute IV tocolysis in 2 studies).

Four new RCTs met Conde-Agudelo's original review eligibility criteria; however, only one trial contributed numeric data to this update.<sup>114</sup>

The patients in the Roos 2013 trial were pregnant women (with 22% multiple gestations) with threatened preterm labour between 26 weeks and 32 weeks of gestation who had completed a course of tocolysis for 48 hours and corticosteroids but had not delivered (n= 406).<sup>114</sup>

The original SR reported subgroup analyses specifically in women enrolled at <32 weeks gestation for three outcomes (preterm labour <34 weeks, preterm labour <37 weeks, and pregnancy prolongation); rest of the analysis were overall for women with preterm birth. Because Roos et al. was

exclusively in women at < 32 weeks, we used this study data both to update the overall and subgroup analyses (Table 27).

The three trials that could not be meta-analysed were all underpowered to draw any confident conclusions. Uma et al.'s randomised study reported a significant nine day pregnancy prolongation of nifedipine maintenance therapy in keeping with corresponding meta-analysis in Conde-Agudelo's review. However, the language employed in reporting this significant finding is ambiguous whether this benefit applied to all included women or subgroup at late gestational age.<sup>115</sup> Parry et al.'s trial was underpowered to show a clear difference for the outcome of pregnancy prolongation.<sup>116</sup> Chawanpaiboon et al.'s study did not report data for any outcome of interest.<sup>117</sup>

The overall updated outcomes are reported in Table 27. Forest plots and GRADE evidence profile can be found in appendix.

Overall, there is evidence that nifedipine maintenance tocolysis prolongs pregnancy from anywhere between 1 to 11 days in women with arrested preterm labour; however, our confidence in this estimate is low. Evidence for other neonatal outcomes was inconclusive and low to very low quality. Evidence on maternal harms of therapy is absent in RCTs.

**Table 27 – Efficacy and safety of nifedipine maintenance tocolytic treatment versus placebo/ no treatment in women after threatened preterm labour: results**

Outcome of Interest	Pooled Estimate: RR or Mean Difference (95%CI)		Number of Included Studies		Number of events/Sample size (n/N) or number of patients		Last Search Date	
	Original SR	Updated Evidence	Original SR	New Primary Studies	Original SR	New Primary Studies	Original SR	New Primary Studies
Neonatal death	0.20 (0.01, 4.04)	NA	1	NA	2/80	NA	?	NA
Necrotizing enterocolitis	1.67 (0.23, 12.33)	*1.78 (0.53, 6.00)	1	1	3/154	8/406	Jun 30, 2010	Nov 7, 2013



Outcome of Interest	Pooled Estimate: RR or Mean Difference (95%CI)		Number of Included Studies		Number of events/Sample size (n/N) or number of patients		Last Search Date	
Intraventricular Haemorrhage**	0.71 (0.14, 3.54)	*0.51 (0.15, 1.66)	1	1	3/80	34/406	Jun 30, 2010	Nov 7, 2013
Neonatal sepsis	2.00 (0.19, 21.18)	0.96 (0.51, 1.78)	1	1	3/80	34/406	Jun 30, 2010	Nov 7, 2013
Ventilation support***	Not assessed	1.1 (0.67, 1.7)	NA	1	NA	69/406	NA	Nov 7, 2013
PTB< 34 Week	1.33 (0.64, 2.78)	1.04 (0.85, 1.27)	1	1	21/74	192/406	Jun 30, 2010	Nov 7, 2013
PTB<34 Weeks among women enrolled at <32 weeks' gestation	0.96 (0.43, 2.15)	1.02 (0.83, 1.24)	2	1	16/49	192/406	Jun 30, 2010	Nov 7, 2013
PTB< 37 Week	0.87 (0.69, 1.08)	0.97 (0.85, 1.12)	3	1	128/215	274/406	Jun 30, 2010	Nov 7, 2013
PTB<37 Weeks among women enrolled at <32 weeks' gestation	0.93 (0.72, 1.20)	1.00 (0.89, 1.13)	2	1	72/102	274/406	Jun 30, 2010	Nov 7, 2013
Pregnancy prolongation (days)	† 6.3 [1.2, 11.4]	NA	3	NA	‡ 215	NA	?	NA
Pregnancy prolongation (days) among women enrolled at <32 weeks' gestation	† 11.0 (-2.1, 24.2)	NA	3	NA	‡ 141	NA	?	NA

Abbreviations: CI = confidence interval; n = number of events; N = number of patients; NA= not applicable; PTB = preterm birth; RR = relative risk

\*When the event rates were <5% we used the Mantel-Haenszel method with fixed effect for the updated outcome.

\*\*The original SR does not state the degree of the Intraventricular Haemorrhage; however, it was > grade 2 in the newly identified RCT.

\*\*\*This outcome data was not reported in the original SR; however, it was in the identified new trial.

† Mean difference

‡ Total number of patients



## Conclusions

- There are indications that nifedipine maintenance therapy prolongs pregnancy anywhere between 1 to 11 days in women with arrested preterm labour.
- A beneficial or harmful effect of nifedipine maintenance therapy on neonatal outcomes could neither be demonstrated nor refuted.

## Other considerations

Factor	Comments
<b>Balance between clinical benefits and harms</b>	<p>There is no proof of a beneficial effect of nifedipine maintenance therapy on the critical neonatal outcomes as evidence lacks the necessary statistical power.</p> <p>RCTs show that nifedipine can prolong pregnancy with approximately 6 days (1 to 11 days) however, suggesting a possible benefit very early in pregnancy (23-28 weeks) assuming that a prolongation with even a few days would have a beneficial effect on neonatal outcomes in this situation. This possible benefit of maintenance nifedipine should be weighted against side effects, such as an increased risk of haemorrhage (see APOSTEL II trial).<sup>118</sup></p> <p><b>Dosage</b></p> <p>As an example, the treatment schedule from the APOSTEL II study protocol can be used: 20 mg of nifedipine slow-release tablets every 6 hours, resulting in a total daily dose of 80 mg of nifedipine. In the trial, study medication was phased out from day 10 (total daily dose of 60 mg) until day 12 (total daily dose of 20 mg) and discontinued on day 13. Maintenance nifedipine therapy was limited to 12 days following 2 days of initial tocolysis and corticosteroids.</p>
<b>Quality of evidence</b>	Low level of evidence.
<b>Costs (resource allocation)</b>	No formal cost-effectiveness evaluation was performed.
<b>Patients values and preferences</b>	See 'choice of tocolytic therapy'.

Recommendations	Strength of Recommendation	Level of Evidence
After 48 hours tocolytic therapy, do not routinely offer nifedipine maintenance therapy to pregnant women with suspected preterm labour. If no contraindication is present, nifedipine maintenance therapy can be considered in women with preterm labour before 28 weeks as prolongation of pregnancy may be beneficial in this group of women.	Weak	Low



### 3.3.4.2.3 Efficacy and Safety of oral betamimetics maintenance therapy versus placebo/ no treatment in women following arrested preterm labour

The systematic review by Dodd et al. 2011 compared oral betamimetics (terbutaline in 5 RCTs and ritodrine in 5 RCTs) versus placebo/no treatment in women following arrest of threatened preterm labour (10 studies; 1307 participants).<sup>110</sup> Three RCTs were exclusively in singleton pregnancies (Table 6). The gestational age of the women included in the trials ranged from 20-37 weeks. The exact initiation and discontinuation time for the maintenance treatment was not reported in the review (based on the included study characteristics, only 3 primary studies reported the stopping time ranging from 7 days to 38 weeks of gestation). We did not identify any new primary study and judged the review to be current.

Overall, low to very low quality of underpowered evidence with wide confidence intervals precluded meaningful conclusions about maintenance tocolysis with oral ritodrine and/or terbutaline. The GRADE evidence profile can be found in appendix.

**Table 28 – Efficacy and safety of oral betamimetics maintenance tocolytic treatment versus placebo/ no treatment in women after threatened preterm labour: results**

Population	Intervention	Comparator	Outcomes	Pooled Estimate: RR [95%CI]	Total events /Total participants (n/N)	Number of Studies	Quality (AMSTAR)
<b>Women with threatened preterm labour</b>	Oral betamimetic	Placebo/no treatment	Perinatal mortality (overall)	2.41 [0.86, 6.74]	15/681	6	9
			Necrotising enterocolitis (only Terbutaline)	0.98 [0.22, 4.28]	6/416	2	
			Intraventricular haemorrhage (Overall)	0.97 [0.27, 3.58]	8/466	3	
			Intraventricular haemorrhage (Ritodrine)	3.00 [0.13, 70.30 ]	1/50	1	
			Intraventricular haemorrhage (Terbutaline)	0.72 [0.16, 3.24]	7/416	2	
			Respiratory distress syndrome (Overall)	1.10 [0.61, 1.98 ]	39/770	6	
			Respiratory distress syndrome (Ritodrine)	1.46 [0.57, 3.73 ]	14/303	3	
			Respiratory distress syndrome (Terbutaline)	0.93 [0.43, 1.98 ]	25/467	3	
			Need for mechanical ventilation (Ritodrine only)	0.94 [0.06, 14.61]	2/120	1	



Population	Intervention	Comparator	Outcomes	Pooled Estimate: RR [95%CI]	Total events /Total participants (n/N)	Number of Studies	Quality (AMSTAR)
			PTB< 34 Weeks: (only Ritodrine)	2.81 [0.30, 26.22]	4/120	1	
			PTB< 37 Weeks (Overall)	1.11 [0.91, 1.35]	209/644	6	
			PTB< 37 Weeks (Ritodrine)	1.08 [0.75, 1.57 ]	78/405	4	
			PTB< 37 Weeks (Terbutaline)	1.12 [0.89, 1.41]	131/239	2	
			<i>Maternal Side effects</i>				
			Palpitations	5.67[1.32, 64.79]	14/140	1	
			Tachycardia (overall)	2.13 [1.52, 2.98]	99/414	4	
			Tachypnoea (overall)	3.52 [1.20, 10.33]	19/260	2	
			Hypotension (overall)	1.89 [1.13-3.19]	32/166	2	

Abbreviations: CI = confidence interval; n = number of events; N = number of patients; PTB = preterm birth; RR = relative risk

## Conclusions

- A beneficial or harmful effect of oral betamimetics maintenance therapy on neonatal outcomes could neither be demonstrated nor refuted.
- There are indications that oral betamimetics maintenance therapy is associated with an increase of tachycardia, palpitations, tachypnoea and hypotension.

**Other considerations**

Factor	Comments
<b>Balance between clinical benefits and harms</b>	<p>As summarized above, there is no proof of a beneficial effect of maintenance therapy with oral betamimetics, but the intervention can be associated with potentially serious maternal side effects.</p> <p>The European Medicine agency and the Belgian Federal Agency for Medicines and Health Products (FAMHP/FAGG/AFMPS) have issued recommendations on the restricted use of short-acting beta-agonists in obstetric indications. These medicines should no longer be used in oral or suppository forms in obstetric indications such as for suppressing premature labour or excessive labour contractions.</p> <p><a href="http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Short-acting_beta-agonists/human_referral_prac_000013.jsp&amp;mid=WC0b01ac05805c516f">http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Short-acting_beta-agonists/human_referral_prac_000013.jsp&amp;mid=WC0b01ac05805c516f</a></p> <p><a href="http://www.fagg-afmps.be/nl/news/news_beta_agonistes.jsp">http://www.fagg-afmps.be/nl/news/news_beta_agonistes.jsp</a></p>
<b>Quality of evidence</b>	Low level of evidence
<b>Costs (resource allocation)</b>	NA
<b>Patients values and preferences</b>	NA

Recommendations	Strength of Recommendation	Level of Evidence
After 48 hours tocolytic therapy, do not offer oral betamimetics maintenance therapy to pregnant women with suspected preterm labour.	Strong	Low

**3.3.4.2.4 Efficacy and Safety of oxytocin antagonist maintenance therapy versus placebo/ no treatment in women following arrested preterm labour**

The systematic review by Papatsonis et al. 2009 compared oxytocin antagonist administered by any route versus placebo in pregnant women between 20-36 of gestational week after threatened preterm labour.<sup>111</sup> The review included only one trial of 513 participants comparing atosiban (subcutaneous infusion pump) versus placebo. The exact initiation time was not reported but women received the interventions until the end of 36 week of gestation, delivery, or progression of labour requiring alternative tocolytic agent.

We did not identify any new primary study and judged the review up-to-date. Results are summarized in Table 29. Overall, low to very low quality of underpowered evidence with wide confidence intervals precluded meaningful conclusions about oxytocin antagonist maintenance tocolysis. The GRADE evidence profile can be found in appendix.



**Table 29 – Efficacy and safety of oxytocin antagonist maintenance tocolytic treatment versus placebo/ no treatment in women after threatened preterm labour: results**

Population	Intervention	Comparator	Outcomes by Subgroups	Pooled Estimate: RR [95%CI]	Total events/Total participants (n/N)	Number of Studies	Quality (AMSTAR)
Singleton pregnant women with at least one episode of preterm labour between 20 and 36 completed weeks that was suppressed or settled spontaneously without resulting in immediate preterm birth.	Atosiban	Placebo	Neonatal death	0.58 [0.14, 2.39]	8/512	1	10
			Necrotising enterocolitis	2.34 [0.46, 11.93]	7/557	1	
			Respiratory Distress Syndrome	1.06 [0.66, 1.70]	62/557	1	
			Patent ductus arteriosus	1.17 [0.47, 2.91]	18/557	1	
			PTB< 28 Week	0.75 [0.28, 2.01]	3/74	1	
			PTB< 32 Week	0.85 [0.47, 1.55]	37/285	1	
			PTB< 37 Week	0.89 [0.71, 1.12]	182/510	1	
			Maternal death	Not estimable	0/512	1	

## Conclusions

- A beneficial effect of oxytocin antagonist maintenance therapy on neonatal outcomes could neither be demonstrated nor refuted.
- There are no data from RCTs on the maternal side effects of oxytocin antagonist maintenance therapy.

**Other considerations**

Factor	Comments
<b>Balance between clinical benefits and harms</b>	Sparse available evidence cannot show proof of a beneficial effect of oxytocin inhibitor maintenance therapy. In daily practice, a repeat course of 48h oxytocin antagonist therapy is often considered, for example if symptoms reoccur. This practice is not considered maintenance therapy, evidence review on this matter is considered out of scope for this guideline.
<b>Quality of the evidence</b>	Very low level of evidence.
<b>Costs (resource allocation)</b>	Oxytocin is an expensive tocolytic agent. No formal cost-effectiveness study was performed.
<b>Patients values and preferences</b>	NA

Recommendations	Strength of Recommendation	Level of Evidence
After 48 hours tocolytic therapy, do not offer oxytocin antagonist maintenance therapy to pregnant women with suspected preterm labour.	Strong	Very low

**3.3.4.2.5 Efficacy and Safety of progesterone maintenance therapy versus placebo/ no treatment in women following arrested preterm labour**

No systematic review exclusively investigated progesterone maintenance therapy in high risk patients with threatened preterm labour. Evidence from the review of Dodd et al. however, included in the literature review for progesterone as secondary prevention, is equally relevant for this question.

Six studies were included in this analysis, of which three included women with successfully treated preterm labour, two that included women who presented with PPROM and one that randomized women with a high risk for preterm labour.

The overall results that were not updated are summarized in Table 30. Overall results (IM, oral and vaginal) were added post hoc to the separate results for oral or vaginal progesterone according to available studies.



**Table 30 – Efficacy and safety of progesterone maintenance tocolytic treatment versus placebo/ no treatment in women after threatened preterm labour or PPROM: results**

Population	Intervention	Comparator	Outcomes by Subgroups	Pooled Estimate: RR [95%CI]	Total events/Total participants	Number of Studies	Quality (AMSTAR)
Singleton pregnant women with arrested threatened PTB or women with PPROM	Progesterone	No treatment or placebo	Perinatal death	2.00 [0.16, 24.33]	2/12	1	10
			Neonatal death	0.54 [0.05, 6.24 ]	9/175	2	
			Vaginal	See Table 31			
			Neonatal sepsis	0.54 [0.17, 1.68 ]	23/214	4	
			Vaginal	0.26 [0.07, 1.00]	11/233	2	
			RDS	0.74 [0.49, 1.10 ]	93/214	4	
			Vaginal	0.48 [0.20, 1.15]	33/233	2	
			Use of assisted ventilation	0.30 [0.06, 1.37]	8/70	1	
			Vaginal	0.30 [0.06, 1.37]	8/70	1	
			NEC	3.06 [0.50, 18.69 ]	4/81	2	
			IVH grade III or IV	9.00 [0.53, 152.93 ]	2/12	1	
			PTB< 28 Weeks	0.99 [0.06, 15.60]	2/193	1	
			Vaginal	0.99 [0.06, 15.60]	2/193	1	
			PTB < 34 weeks	0.95 [0.55, 1.65 ]	29/175	2	
			Vaginal	See Table 31			
			PTB < 37 weeks	0.51 [0.20, 1.31 ]	100/223	2	
			Vaginal	See Table 31			
			Pregnancy prolongation (days)	1.88 [-8.42, 12.17 ]	232 patients	2	
			Vaginal	7.21 [ 2.39, 12.03 ]	163 patients	1	



Three meta-analyses in Dodd et al.'s systematic review (preterm birth <34 and <37 weeks, neonatal death) were updated for vaginal progesterone with addition of single new trial evidence for each analysis (Forrest plots in appendix).<sup>91, 92</sup>

The overall update remained underpowered to detect meaningful differences between vaginal progesterone therapy and routine care in the women with arrested preterm labour. For two of the three outcomes, the summary effect estimates remained very imprecise, clinically uncertain, and statistically non-significant, (Table 31). For the outcome of neonatal death, although statistical significance was reached, the number of deaths was just 18 in a total sample size of 307 singleton pregnancies across the two studies (one new, and one old in the original systematic review). As such, both the clinical significance and the stability of this estimate of effect are questionable – i.e. the estimate is fragile.

**Table 31 – Efficacy and safety of vaginal progesterone maintenance tocolytic treatment versus placebo/ no treatment in women after threatened preterm labour or PPROM: updated results**

Outcome of Interest	Pooled Estimate: RR [95%CI]		Number of Included Studies in Relevant Analyses		Sample size (n/N)		Search Date	
	Original SR	Updated Evidence	Original SR	New Primary Studies	Original SR	New Primary Studies	Original SR	New Primary Studies
Neonatal Death	0.17 (0.02, 1.40)	0.30 (0.10, 0.91)	1	1	7/163	11/144	14 Jan 2012	2012- 17 Jun 2013
PTB< 34 Week	0.92 (0.37, 2.27)	0.89 (0.49, 1.62)	1	1	17/163	22/259	14 Jan 2012	2012- 17 Jun 2013
PTB< 37 Week	0.76 (0.55, 1.06)	0.94 (0.60, 1.47)	1	1	78/163	71/259	14 Jan 2012	2012- 17 Jun 2013

## Conclusions

- A beneficial or harmful effect of progesterone maintenance therapy on neonatal outcomes could neither be demonstrated nor refuted.

**Other considerations**

Factor	Comments
<b>Balance between clinical benefits and harms</b>	<p>Evidence for the use of vaginal progesterone in this patient group is statistically underpowered and does not show a proven benefit for the neonatal outcomes.</p> <p>Meta-analysis for trials using vaginal progesterone shows a statistically significant effect for the outcome neonatal death, however this result is based on only 18 events and should thus be considered as very fragile.</p> <p>However, as discussed above, there is sufficient evidence from randomized controlled trials in women with a history of preterm birth that shows that progesterone can decrease neonatal morbidity. As vaginal progesterone has minimal side effects, the GDG considers this indirect evidence as sufficient to support potential use of vaginal progesterone as maintenance tocolytic therapy, especially if a shortened cervix is noted.</p>
<b>Quality of evidence</b>	Very low level of evidence.
<b>Costs (resource allocation)</b>	No formal cost-effectiveness evaluation was performed.
<b>Patients values and preferences</b>	See 'choice of tocolytic therapy'.

Recommendations	Strength of Recommendation	Level of Evidence
After 48 hours tocolytic therapy, consider progesterone maintenance therapy in pregnant women with suspected preterm labour.	Weak	Very low

**3.3.5 Mg(SO<sub>4</sub>) for neuroprotection**

One high quality (AMSTAR score 9) systematic review by Conde-Agudelo 2009 was selected.<sup>113</sup> The review compared magnesium sulphate neuroprotection with placebo or no magnesium in women at risk of preterm birth before 34 weeks of gestation for prevention of cerebral palsy and other neurologic abnormalities in the unborn baby (or other aims but has reported cerebral palsy). The review included 5 studies (6 trials: one trial on both tocolytic and neuroprotective effect, three on neuroprotective effect, and one for eclampsia prevention) in which a total of 4796 women and 5357 infants were included. The proportion of singletons was reported in four of the five studies and ranged from 79% to 91%. In five of the 6 trials women were administered a loading dose of 4g and in one trial 6g of intravenous

magnesium sulphate. The maintenance infusion ranged from 1-3 g/h in three trials lasting until birth or 12-24 hours. Two trials did not employ a maintenance schedule.

We found two secondary analyses of unidentified RCTs comparing magnesium sulphate versus placebo. As such, we did not use the evidence to update Conde-Agudelo 2009 for concerns about data double counting.<sup>119, 120</sup> The selected review was, therefore, judged to be current.

Results are summarized in Table 32. The GRADE evidence profile can be found in appendix.



Overall, there is high quality evidence that antenatal magnesium sulphate prevents cerebral palsy. The number needed to treat to prevent one case of cerebral palsy could be as low as 37 or as high as 143. There is also high quality evidence that neuroprotective therapy does not affect total paediatric mortality. For other outcomes such as Apgar score, need for oxygen and mechanical ventilation, no differences were noted between treatment and control. Conde-Agudelo also undertook a subgroup meta-analysis of trials conducted exclusively with neuroprotective intent and found confirming results.

**Table 32 – Efficacy and safety of magnesium sulphate neuroprotection versus no treatment in women at risk of preterm birth before 34 weeks: results**

Population	Intervention	Comparator	Outcomes by Subgroups	Pooled Estimate: RR [95%CI]	Number Patients (n/N)	of Number of Studies	Quality (AMSTAR)
Women at risk of preterm birth before 34 weeks of gestation	Magnesium sulphate	No Magnesium	<b>Neonatal outcomes</b>				
			Total paediatric mortality	1.01 (0.89–1.14)	801/5357	6	9
			Under two years of corrected age mortality	1.00 (0.84–1.19)	437/4552	5	
			Cerebral palsy:	0.69 (0.55–0.88)	256/5357	6	
			Moderate/severe cerebral palsy	0.64 (0.44–0.92)	117/4387	3	
			Mild cerebral palsy	0.74 (0.52–1.04)	128/4387	3	
			Neonatal Seizures	0.80 (0.56–1.13)	125/4387	3	
			Need for supplemental oxygen at 36 weeks	1.12 (0.95–1.32)	415/1943	2	
			Mechanical ventilation	0.99 (0.89–1.09)	2827/4387	3	
			Apgar Score<7 at 5 minutes	1.03 (0.90– 1.18)	702/4387	3	



Population	Intervention	Comparator	Outcomes by Subgroups	Pooled Estimate: RR [95%CI]	Number Patients (n/N)	of Number of Studies	Quality (AMSTAR)
<b>Maternal outcomes:</b>							
Death				0.32 (0.01–7.92)	1/3867	3	
Cardiac or respiratory arrest				Not estimable	0/3867	3	
Pulmonary oedema				2.79 (0.74–10.47)	11/2241	1	
Respiratory depression				1.31 (0.83–2.07)	72/3303	2	
Severe haemorrhage			postpartum	1.06 (0.63–1.79)	54/1626	2	

The systematic review by Conde-Agudelo 2009 that was selected to answer the question about neuroprotective effectiveness of magnesium therapy also provided evidence on maternal harms of treatment (Table 32).<sup>121</sup> Additionally, one reviewer nominated systematic review (Bain et al., 2013) was considered relevant as it (exclusively) evaluated maternal harms of magnesium in pregnancy irrespective of indication.<sup>122</sup> We graded the RCT evidence from both reviews separately because of the differences in their focus – i.e. harms when intravenous/intramuscular magnesium was administered with neuroprotective intent versus harms of magnesium therapy in general in pregnant populations. With no new evidence identified, the reviews were considered current. The results of the review of Bain et al. are summarized in the GRADE evidence profile in appendix.

Overall, between the two reviews findings of maternal harms corroborated (see appendix). There is high confidence that for maternal outcomes of death, cardiac arrest, respiratory depression, ICU admission, post-partum haemorrhage and pulmonary oedema, magnesium therapy does not increase corresponding risk. However, there is high confidence that

magnesium therapy may be discontinued because of intolerance in at least 19 out of a thousand treated women.

### Conclusions

- It is demonstrated that magnesium sulphate administered to women at risk for preterm birth before 34 weeks of pregnancy reduces the risk for cerebral palsy in the newborn.
- It is demonstrated that magnesium sulphate administered to pregnant women does not increase the risk for maternal death, cardiac arrest, respiratory depression, ICU admission, post-partum haemorrhage and pulmonary oedema.
- It is demonstrated that magnesium sulphate therapy may be discontinued because of intolerance in at least 19 out of a thousand treated women.

**Other considerations**

Factor		Comments
<b>Balance between benefits and harms</b>	<b>clinical</b>	<p>Magnesium sulphate injections must be used with caution and the use of protocols for administration is recommended. Prolonged use (&gt;48 hours) is contraindicated due to the risk of bone abnormalities and calcium, phosphorous, and magnesium derangements in mothers and infants.<sup>123</sup> These risks recently prompted the Food and Drug Administration to change its categorization of magnesium sulphate injections from Pregnancy Category “A” (adequate and well-controlled studies have failed to demonstrate a risk to the foetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters) to Pregnancy Category “D” (there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks).<sup>112</sup> Moreover, trials investigating magnesium sulphate as a tocolytic agent, have shown an association with increased mortality for the infant.<sup>124</sup></p> <p>Conde-Agudelo et al. recommend that the loading and maintenance doses, and the duration of the treatment should not normally exceed 6g, 1-2g/h, and 24 hours, respectively.<sup>121</sup> However, these authors also emphasize that further studies are required to assess the minimum effective dose of magnesium sulphate and the optimal time to administer it, as well as the short and long-term consequences of exposure for the women and their children. The shortest duration of treatment that can result in harm to the baby is not known. Hence, for safety concerns, it is advisable to keep the duration of magnesium sulphate administration short and to use the lowest total dose shown effective in clinical trials.</p> <p>Trials investigating magnesium sulphate as a neuroprotective agent started magnesium sulphate only if birth was considered imminent (more than 4 cm cervical dilatation) and continued no longer than 24 hours. For planned preterm births, guidelines suggest to start as close as possible to four hours before birth, as this was the mean time from randomization to birth in subgroup analysis.<sup>125</sup></p> <p>All the included trials administered magnesium sulphate intravenously, following various dosing schemes. Using a treatment schedule familiar to the department (e.g. for the prevention of eclampsia) may be the safest option.</p> <p>The GDG members recommend that IV magnesium sulphate should be administer only when the delivery is imminent (i.e. as close as possible to delivery) and for 24 hours maximum.</p>
<b>Quality of evidence</b>		High level of evidence
<b>Costs (resource allocation)</b>		No cost assessment was performed.
<b>Patients values and preferences</b>		See ‘choice of tocolytic therapy’.



Recommendations	Strength of Recommendation	Level of Evidence
Offer IV magnesium sulphate for neuroprotection to women presenting with imminent preterm birth and/or failed tocolytic therapy (before 32 weeks) of pregnancy. IV magnesium sulphate for neuroprotection should not be administered for more than 24 hours.	Strong	High

## 4 DISCUSSION

Preterm birth complications remain a major cause of neonatal mortality and morbidity worldwide <sup>2</sup> and preterm birth in Belgium still concerns nearly 7% of all deliveries. This demonstrates the importance of preventing the problem appropriately, particularly in women at the highest risk. For this reason, this guideline focused on the secondary and tertiary prevention of preterm delivery.<sup>21</sup>

One noticeable finding of our review is the utility of transvaginal ultrasound coupled with fFN or pHIGFBP tests to estimate the probability of preterm birth in symptomatic women. Currently, the vast majority of women presenting with uterine contractions before 37 weeks of gestation are treated whereas only a minority of them will actually deliver preterm. The proposed strategy would thus avoid inappropriate treatment in a large number of cases. Unfortunately, none of these tests is currently reimbursed in Belgium. Given the potential clinical benefits, it seems reasonable to recommend their reimbursement in this indication.

For all interventions considered in this guideline, only the highest quality evidence level (RCT) was considered. However, one constant methodological weakness of the evidence included relates to the indirectness of outcomes, i.e. the main outcome was usually gestational age at birth or preterm birth rate, and only rarely were more relevant hard outcomes such as perinatal mortality or neonatal morbidity considered. This is unfortunate as the prolongation of pregnancy intended to enhance newborn health might also entail a prolonged exposure to a suboptimal intrauterine environment. Therefore, prevention of preterm birth is not a health outcome as such, but rather a surrogate endpoint. Evidence on long-term outcomes of PTB was even sparser. Furthermore, more data on the

cost-effectiveness of preventative and therapeutic interventions could be of interest to guide further investments in optimal care for women at risk of preterm birth.

Another common limitation of the included studies was the small sample size, resulting in imprecise results. As a consequence, only the evidence on antenatal corticosteroids and on magnesium sulphate for neuroprotection could be rated as being of moderate or high quality. This is not to say that all other interventions are inappropriate, but it points to the need for further well conducted studies. In particular, randomized controlled trials with sufficient statistical power and with long-term follow-up (several years) are necessary to measure the impact of interventions on child health. Further trials are required to assess the optimal timing, mode of administration and dose of administration of progesterone, corticosteroids, or magnesium sulphate when given to women considered to be at increased risk of early delivery. It is also essential that such trials integrate the testing of mechanistic hypotheses to improve our understanding of PTB pathophysiology and subsequently strengthen our capacity to prevent it.

And, finally, this guideline only addresses the secondary and tertiary prevention of preterm birth, but it should not make us forget the importance of the primary prevention, including a sound follow-up of every pregnancy. An update of our KCE guideline on antenatal care is currently underway.



## 5 IMPLEMENTATION AND UPDATING OF THE GUIDELINE

### 5.1 Implementation

#### 5.1.1 Multidisciplinary approach

In this report we focused on the effectiveness of specific (medical) interventions, without taking into account the organization of health services. In clinical practice, a multidisciplinary approach by different health care professionals should be encouraged. This approach should not only cover the medical needs of the patient but also their psychosocial needs.

#### 5.1.2 Patient-centred care

The choice of a treatment should not only consider medical aspects but also patient preferences. Patients should be well and timely informed about all treatment options and the advantages and disadvantages they offer. Indeed, patients and patient representatives involved in the development of this report emphasized the need for patient information. This information should be clear and repeated over time. Also more emphasis should be put on potential adverse events related to each treatment.

#### 5.1.3 Barriers and facilitators for implementation of this guideline

Potential barriers and facilitators related to the use of this guideline were discussed during the stakeholder meetings and are reported below. A more detailed overview can be found in appendix. More sophisticated methods could be used, but this would go beyond the scope of this project. More information on the identification of barriers and facilitators in guidelines implementation can be found in KCE-report 212 (see KCE website).

Most important barriers for implementation of this guideline as reported by the stakeholders:

- Vaginal ultrasound with cervical length measurement is difficult to perform if assessment of women with threatened preterm labour is done by the midwife on call.
- Nifedipine is not registered for use as tocolytic treatment (off label use). Tablets of 10 mg are not available in Belgium.

- Cervical length measurement, fFN test and pHIGFBP test are not reimbursed in Belgium.
- The scope of the guideline is limited, hence for some recommendations it is unclear how interventions not included in the guideline play a role (e.g. choice between cervical cerclage or cervical pessary).
- Regarding the recommendations on secondary prevention in women with a short cervix, many practical issues remain as threshold and indications for cervical length measurement are unclear from the evidence.
- Recommendations on cerclage provide insufficient information on the exact indications, as in clinical practice several clinical factors that are not mentioned in the studies, may play a role.

#### 5.1.4 Actors of the implementation of this guideline

Clinical guidelines provide a tool for physicians to consult at different stages of the patient management pathway: screening, diagnosis, treatment and follow-up. They are developed according to highly codified principles, based on scientific information regularly updated from the international literature. KCE formulates recommendations addressed to specific audiences (clinicians, decision-makers, sickness funds, NIHD, professional organizations, hospital managers...). KCE is not involved in the decision making process itself, or in the execution of the decisions.

The content of this guideline is intended to be disseminated by scientific and professional organisations. They can make attractive and user-friendly tools tailored to caregivers groups. They will also play a key role by a dissemination that makes use of diverse channels such as websites or sessions of continuing education.



## 5.2 Monitoring the quality of care

This guideline should be considered as a starting point to develop quality improvement programs that targets all caregivers concerned.

It can be used as a tool to support health policies to improve the quality of care, e.g. through the support of actions to increase caregivers' awareness and to improve their practice, or through the development (or revision) of sets of process and outcome quality indicators.

Based on the recommendations formulated in this guideline and accounting for their respective strength, the following quality indicators can be proposed:

- Proportion of women with a history of preterm birth who received progesterone from the start of the second trimester onwards
- Proportion of women presenting with symptoms of threatened preterm labour and cervical length more than 30mm and/or negative fFN test or pHIGFBP test who did not receive treatment
- Proportion of women after an episode of arrested preterm labour who did not receive maintenance therapy with magnesium, betamimetics, or oxytocin antagonists
- Proportion of children born before 32 weeks for whom the mother received antenatal magnesium sulphate.

The Royal College of Obstetricians and Gynaecologists (RCOG) in the United Kingdom (UK) formulates the following auditable standards:<sup>126</sup>

- Number of women who received a tocolytic drug for suspected preterm birth
- Documented involvement of a consultant obstetrician in the decision to commence a tocolytic drug
- Choice and duration of tocolytic drug
- Proportion of women on local first-line tocolytic drug and on multiple drugs
- Number of women receiving a course of antenatal corticosteroids before 34 weeks of gestation
- Proportion of women and babies with adverse effects associated with tocolytic drugs

- Number of babies born without exposure to antenatal corticosteroids
- Use of a guideline on tocolysis

More extensive elaboration of possible quality indicators and assessment of their measurability is considered out of the scope of this project, but could be the subject of a future KCE project, similar to quality projects performed in the field of oncology.<sup>127-129</sup>

## 5.3 Guideline update

In view of the rapidly evolving evidence, this guideline should be updated every 5 years. If, in the meantime, important new evidence would become available, this should be taken into consideration.

The KCE processes foresee that the relevance of an update would be yearly assessed for each published guideline by the authors. Decisions are made on the basis of new scientific publications on a specific topic (e.g. Cochrane reviews, RCTs on medications or interventions). Potential interest for groups of health practitioners is also considered in this process.

This appraisal leads to a decision on whether to update or not a guideline or specific parts of it to ensure the recommendations stay in line with the latest scientific developments.



## ■ REFERENCES

1. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75-84.
2. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet*. 2012;379(9832):2151-61.
3. Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. *Lancet*. 2012;379(9814):445-52.
4. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet*. 2008;371(9608):261-9.
5. Boyle EM, Poulsen G, Field DJ, Kurinczuk JJ, Wolke D, Alfirevic Z, et al. Effects of gestational age at birth on health outcomes at 3 and 5 years of age: population based cohort study. *BMJ*. 2012;344:e896.
6. Vanhaesebrouck P, Allegaert K, Bottu J, Debauche C, Devlieger H, Docx M, et al. The EPIBEL study: outcomes to discharge from hospital for extremely preterm infants in Belgium. *Pediatrics*. 2004;114(3):663-75.
7. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet*. 2012;379(9832):2162-72.
8. Menon R. Spontaneous preterm birth, a clinical dilemma: etiologic, pathophysiologic and genetic heterogeneities and racial disparity. *Acta Obstet Gynecol Scand*. 2008;87(6):590-600.
9. Schaaf JM, Ravelli AC, Mol BW, Abu-Hanna A. Development of a prognostic model for predicting spontaneous singleton preterm birth. *Eur J Obstet Gynecol Reprod Biol*. 2012;164(2):150-5.
10. Petrini JR, Callaghan WM, Klebanoff M, Green NS, Lackritz EM, Howse JL, et al. Estimated effect of 17 alpha-hydroxyprogesterone caproate on preterm birth in the United States. *Obstet Gynecol*. 2005;105(2):267-72.



11. Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. *Br J Obstet Gynaecol.* 1985;92(9):921-8.
12. Iams JD, Berghella V. Care for women with prior preterm birth. *Am J Obstet Gynecol.* 2010;203(2):89-100.
13. Blondel B, Macfarlane A, Gissler M, Breart G, Zeitlin J. Preterm birth and multiple pregnancy in European countries participating in the PERISTAT project. *BJOG.* 2006;113(5):528-35.
14. Hackney DN, Olson-Chen C, Thornburg LL. What do we know about the natural outcomes of preterm labour? A systematic review and meta-analysis of women without tocolysis in preterm labour. *Paediatr Perinat Epidemiol.* 2013;27(5):452-60.
15. McPheeters ML, Miller WC, Hartmann KE, Savitz DA, Kaufman JS, Garrett JM, et al. The epidemiology of threatened preterm labor: a prospective cohort study. *Am J Obstet Gynecol.* 2005;192(4):1325-9; discussion 9-30.
16. Zeitlin J, Szamotulska K, Drewniak N, Mohangoo AD, Chalmers J, Sakkeus L, et al. Preterm birth time trends in Europe: a study of 19 countries. *BJOG.* 2013;120(11):1356-65.
17. Cammu H, Martens E, Martens G, Van Mol C, Jacquemyn Y. *Perinatale Activiteiten in Vlaanderen 2011.* Brussel: 2011.
18. Leroy C, Van Leeuw V, Englert Y. *Données périnatales en Wallonie-Année 2011.* Bruxelles: 2013.
19. Leroy C, Van Leeuw V, Englert Y. *Données périnatales en Région bruxelloise-Année 2011.* Brussels: 2013.
20. Alexander S, Clerx A, Deville J, Foidart J, Hanssens M, Haumont D, et al. *Perinatal referral in Belgium.* 2007.
21. Iams JD, Romero R, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. *Lancet.* 2008;371(9607):164-75.
22. Lodewyckx K, Peeters G, Spitz B, Blot S, Temmerman M, Zhang W, et al. National recommendation for prenatal care. A base for a clinical pathway aimed at following pregnancy. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2004 24/12/2004. KCE Reports 6 Available from: <https://kce.fgov.be/publication/report/national-recommandation-for-prenatal-care-a-base-for-a-clinical-pathway-aimed-at-#.U7vGKUBGuSo>
23. Berghella V, Baxter JK, Hendrix NW. Cervical assessment by ultrasound for preventing preterm delivery. Review Update of Cochrane Database Syst Rev. 2009;(3):CD007235; PMID: 19588421. *Cochrane Database Syst.Rev.* 2013;1:CD007235.
24. Dodd JM, Flenady V, Cincotta R, Crowther CA, Cochrane Database of Systematic Reviews. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. 2013(7):CD0004947.
25. Alfirevic Z, Stampalija T, Roberts D, Jorgensen AL. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Review. *Cochrane Database Syst.Rev.* 2012;4:CD008991.
26. Crowther CA, Middleton PF, Pan N, Hiller JE, Doyle LD. Magnesium sulphate for preventing preterm birth in women with threatened preterm labour: Updated systematic review. *J.Paediatr.Child Health.* 2010;46:26-7.
27. Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. Review. *British Medical Journal.* 2012;345:e6226.
28. Crowther CA, McKinlay CJ, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. *Cochrane Database Syst Rev.* 2011(6):CD003935.
29. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res.Methodol.* 2007;7:10.
30. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med.* 2011;155(8):529-36.



31. Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C. An evidence-based practice guideline for the peer review of electronic search strategies. *J Clin.Epidemiol.* 2009;62(9):944-52.
32. Canadian Agency for Drugs, Technologies in Health. Grey Matters: a practical search tool for evidence-based medicine. Internet. <http://www.cadth.ca/resources/grey-matters>. 2012.
33. Evidence Partners. DistillerSR. computer program. <http://systematic-review.net/>. 2011.
34. Grimshaw J, Hill S, Lowe D, Kaufman C, Mayhew A, Ryan R, et al. Methods for development. Internet. <http://www.cadth.ca/en/resources/rx-for-change/methods-for-development>. 2012.
35. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Internet <http://handbook.cochrane.org>. 2011.
36. Kt ClearingHouse. Centre for Evidence-based Medicine. Toronto. Stats Calculator. Internet. [ktclearinghouse.ca/cebm/practise/ca/calculators/statscalc](http://ktclearinghouse.ca/cebm/practise/ca/calculators/statscalc). 2013.
37. The Cochrane Collaboration. Diagnostic Test Accuracy Working Group Internet. <http://srdta.cochrane.org/>. 2013.
38. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol.* 2005;58(10):982-90.
39. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7(3):177-88.
40. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol.* 2013;66(2):151-7.
41. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol.* 2013;66(7):719-25.
42. Berghella V, Hayes E, Visintine J, Baxter JK. Fetal fibronectin testing for reducing the risk of preterm birth. Review 24 refs. *Cochrane Database Syst.Rev.* 2008(4):CD006843.
43. Lee GT, Burwick R, Zork N, Kjos S. Does the use of fetal fibronectin in an algorithm for preterm labor reduce triage evaluation times? *J Matern.Fetal Neonatal Med.* 2013;26(7):706-9.
44. Dutta D, Norman JE. Pilot study into the efficacy of foetal fibronectin testing in minimising hospital admissions in women presenting with symptoms of preterm labour: a randomised controlled trial of obstetric and neonatal outcomes. *Arch Gynecol Obstet.* 2011;284(3):559-65.
45. Burwick RM, Zork NM, Lee GT, Ross MG, Kjos SL. Cervical assessment of cervical length compared to fetal fibronectin in the prediction of preterm delivery in women with threatened preterm labor. *J Matern.Fetal Neonatal Med.* 2011;24(1):127-31.
46. Osorio M, Neiva R, Montes L, Silva J, Pinelo S, Pinho M, et al. The impact of fetal fibronectin assay on preterm labor management: A randomized controlled trial. *J.Matern.-Fetal Neonatal Med.* 2010;23:304-5.
47. Vis JY, Wilms FF, Oudijk MA, Bossuyt PM, van der Post JA, Grobman WA, et al. Why were the results of randomized trials on the clinical utility of fetal fibronectin negative? A systematic review of their study designs. *Am J Perinatol.* 2011;28(2):145-50.
48. Hehir MP, O'Connor HD, Kent EM, Robson MS, Keane DP, Geary MP, et al. Early and late preterm delivery rates - a comparison of differing tocolytic policies in a single urban population. *J Matern Fetal Neonatal Med.* 2012;25(11):2234-6.
49. Sanchez-Ramos L, Delke I, Zamora J, Kaunitz AM. Fetal fibronectin as a short-term predictor of preterm birth in symptomatic patients: a meta-analysis. Review 54 refs. *Obstet Gynecol.* 2009;114(3):631-40.
50. Wilms FF, van SG, Porath MM, Papatsonis DNM, Oei SG, Mol BW, et al. Prediction of threatened premature birth by determination of fetal fibronectin in vaginal fluid. *Ned.Tijdschr.Geneeskd.* 2009;153(31):1514-20.



51. Henrich W. Cervicometry and fibronectin role. *J.Matern.-Fetal Neonatal Med.* 2010;23:39.
52. Sumer C, Yalvac S, Kandemir O, Karcaaltincaba D, Haberal A. The predictive value of sonographic cervical length measurement and fetal fibronectin testing to determine true preterm labour. *Turk Jinekoloji Obstet.Dernegi Derg.* 2010;7(3):189-95.
53. Thandayathany V, Yassin MAJM, Omar MH, Ismail NAM, Tamil AM, Kampan NC. Fetal fibronectin rapid test versus phosphorylated insulin-like growth factor-1 (pHIGFBP-1) as bedside test kits for prediction of preterm delivery in the clinical setting. *BJOG Int.J.Obstet.Gynaecol.* 2012;119:5.
54. Van Baaren GJ, Vis J, Wilms F, Oudijk M, Kwee A, Porath M, et al. The accuracy of fetal fibronectin and cervical length in women with signs of preterm labor before 34 weeks: A nationwide cohort study in the Netherlands (APOSTEL1 study). *Am.J.Obstet.Gynecol.* 2013;208(1 SUPPL.1):S8.
55. Diaz J, Chedraui P, Hidalgo L, Medina M. The clinical utility of fetal fibronectin in the prediction of pre-term birth in a low socio-economic setting hospital in Ecuador. *J Matern.Fetal Neonatal Med.* 2009;22(2):89-93.
56. Rose CH, McWeeney DT, Brost BC, Davies NP, Watson WJ. Cost-effective standardization of preterm labor evaluation. *Am J Obstet Gynecol.* 2010;203(3):250-5.
57. Yoneda S, Shiozaki A, Yoneda N, Shima T, Ito M, Yamanaka M, et al. Prediction of exact delivery time in patients with preterm labor and intact membranes at admission by amniotic fluid interleukin-8 level and preterm labor index. *J Obstet Gynaecol.Res.* 2011;37(7):861-6.
58. Cooper S, Lange I, Wood S, Tang S, Miller L, Ross S. Diagnostic accuracy of rapid pHIGFBP-I assay for predicting preterm labor in symptomatic patients. *J Perinatol.* 2012;32(6):460-5.
59. Lee SM, Romero R, Park JW, Kim SM, Park CW, Korzeniewski SJ, et al. The clinical significance of a positive Amnisure test in women with preterm labor and intact membranes. *J Matern.Fetal Neonatal Med.* 2012;25(9):1690-8.
60. Riboni F, Vitulo A, Dell'avanzo M, Plebani M, Battagliarin G, Paternoster D. Biochemical markers predicting pre-term delivery in symptomatic patients: phosphorylated insulin-like growth factor binding protein-1 and fetal fibronectin. *Arch Gynecol Obstet.* 2011;284(6):1325-9.
61. Deshpande SN, van Asselt AD, Tomini F, Armstrong N, Allen A, Noake C, et al. Rapid fetal fibronectin testing to predict preterm birth in women with symptoms of premature labour: a systematic review and cost analysis. *Health Technol Assess.* 2013;17(40):1-138.
62. Tency IM, E. Martens, G. Foidart, J.M., Temmerman, M. College of Physicians for Mother and Newborn. Perinatal referral in Belgium. In. Brussels: Federal Public Service Health, Food chain safety and Environment; 2007.
63. van Baaren GJ, Vis JY, Grobman WA, Bossuyt PM, Opmeer BC, Mol BW. Cost-effectiveness analysis of cervical length measurement and fibronectin testing in women with threatened preterm labor. *Am J Obstet Gynecol.* 2013;209(5):436 e1-8.
64. Honest H, Forbes CA, Duree KH, Norman G, Duffy SB, Tsourapas A, et al. Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling. Review 736 refs. *Health Technol.Assess.* 2009;13(43):1-627.
65. Azlin MN, Kee BH, Low JA, Mohamad SN, Mansor NA, Bee SY, et al. Role of phigfbp-1 and cervical length in predicting preterm labor. *J.Matern.-Fetal Neonatal Med.* 2010;23:100.
66. Danti L, Prefumo F, Lojacono A, Corini S, Testori A, Frusca T. The combination of short cervical length and pHIGFBP-1 in the prediction of preterm delivery in symptomatic women. *J Matern.Fetal Neonatal Med.* 2011;24(10):1262-6.
67. Laudanski P, Raba G, Kuc P, Lemancewicz A, Kisielewski R, Laudanski T. Assessment of the selected biochemical markers in predicting preterm labour. *J Matern.Fetal Neonatal Med.* 2012;25(12):2696-9.
68. Audibert F, Fortin S, Delvin E, Djemli A, Brunet S, Dube J, et al. Contingent use of fetal fibronectin testing and cervical length



- measurement in women with preterm labour. *J Obstet Gynaecol.Can.* 2010;32(4):307-12.
69. Brik M, Hernandez AI, Pedraz CC, Perales A. Phosphorylated insulin-like growth factor binding protein-1 and cervical measurement in women with threatening preterm birth. *Acta Obstet Gynecol Scand.* 2010;89(2):268-74.
70. Rahkonen L, Unkila-Kallio L, Nuutila M, Sainio S, Saisto T, Rutanen EM, et al. Cervical length measurement and cervical phosphorylated insulin-like growth factor binding protein-1 testing in prediction of preterm birth in patients reporting uterine contractions. *Acta Obstet Gynecol Scand.* 2009;88(8):901-8.
71. Altinkaya O, Gungor T, Ozat M, Danisman N, Mollamahmutoglu L. Cervical phosphorylated insulin-like growth factor binding protein-1 in prediction of preterm delivery. *Arch Gynecol Obstet.* 2009;279(3):279-83.
72. Sunagawa S, Takagi K, Ono K, Miyachi K, Kikuchi A. Comparison of biochemical markers and cervical length for predicting preterm delivery. *J Obstet Gynaecol.Res.* 2008;34(5):812-9.
73. Tanir HM, Sener T, Yildiz Z. Cervical phosphorylated insulin-like growth factor binding protein-1 for the prediction of preterm delivery in symptomatic cases with intact membranes. *J Obstet Gynaecol.Res.* 2009;35(1):66-72.
74. Eroglu D, Yanik F, Oktem M, Zeyneloglu HB, Kuscü E. Prediction of preterm delivery among women with threatened preterm labor. *Gynecol Obstet Invest.* 2007;64(2):109-16.
75. Latifagic A, Balic D, Fatusic Z, Hudic I, Kapidzic M, Habibovic A. Insulin-like growth factor-binding protein-1 (IGFBP-1) in cervical secretions in women with symptoms of preterm delivery. *Med.Glas.* 2008;5(2):121-4.
76. Ting HS, Chin PS, Yeo GS, Kwek K. Comparison of bedside test kits for prediction of preterm delivery: phosphorylated insulin-like growth factor binding protein-1 (pIGFBP-1) test and fetal fibronectin test. *Ann Acad.Med Singapore.* 2007;36(6):399-402.
77. Berghella V, Baxter JK, Hendrix NW. Cervical assessment by ultrasound for preventing preterm delivery. *Cochrane Database Syst.Rev.* 2009(3).
78. Hosseini SM, Vafaei F, Vafaei H. Management of threatened preterm labor based on sonographic measurements of the cervical length. *Int.J.Gynecol.Obstet.* 2012;119:S510.
79. Moller MI, Henderson JJ, Nathan EA, Pennell CE. Cervilenz™ is an effective tool for screening cervical-length in comparison to transvaginal ultrasound. *J Matern.Fetal Neonatal Med.* 2013;26(4):378-82.
80. Paternoster D, Riboni F, Vitulo A, Plebani M, Dell'avanzo M, Battagliarin G, et al. Phosphorylated insulin-like growth factor binding protein-1 in cervical secretions and sonographic cervical length in the prediction of spontaneous preterm delivery. *Ultrasound Obstet Gynecol.* 2009;34(4):437-40.
81. Priya B, Mustafa M, Guleria K, Vaid N, Banerjee B, Ahmed R. Salivary progesterone as a biochemical marker to predict early preterm birth in asymptomatic high-risk women. *BJOG.* 2013;120(8):1003-11.
82. Tateyama N, Asakura H, Takeshita T. Correlation between an absence of cervical gland area on transvaginal sonography and cervical mucus hyaluronic acid levels in women with threatened preterm delivery. *J Perinat.Med.* 2013;41(2):151-7.
83. Kahyaoglu S, Kahyaoglu I, Kaymak O, Sagnic S, Mollamahmutoglu L, Danisman N. Can transvaginal ultrasonographic evaluation of the endocervical glandular area predict preterm labor among patients who received tocolytic therapy for threatened labor: a cross-sectional study. *J Matern.Fetal Neonatal Med.* 2013;26(9):920-5.
84. Brik M, Antonio P, Perales-Puchalt A, Diago V, Perales A. Cervical interleukin-6 as a predictive test for preterm delivery in symptomatic women: preliminary results. *Eur J Obstet Gynecol Reprod.Biol.* 2011;155(1):14-8.
85. Lee SY, Park KH, Ryu A, Oh KJ, Jeong EH, Kim SN. Prediction of impending preterm delivery based on sonographic cervical length and different cytokines in cervicovaginal fluid in preterm labor. *Am.J.Obstet.Gynecol.* 2012;206(1 SUPPL. 1):S239.



86. Defranco EA, Valent AM, Newman T, Regan J, Smith J, Muglia LJ. Adjunctive therapies to cerclage for the prevention of preterm birth: a systematic review. *Obstet Gynecol Int.* 2013;2013:528158.
87. Berghella V, Keeler SM, To MS, Althuisius SM, Rust OA. Effectiveness of cerclage according to severity of cervical length shortening: a meta-analysis. *Ultrasound Obstet Gynecol.* 2010;35(4):468-73.
88. To MS, Palaniappan V, Skentou C, Gibb D, Nicolaides KH. Elective cerclage vs. ultrasound-indicated cerclage in high-risk pregnancies. *Ultrasound Obstet Gynecol.* 2002;19(5):475-7.
89. Conde-Agudelo A, Romero R, Nicolaides K, Chaiworapongsa T, O'Brien JM, Cetingoz E, et al. Vaginal progesterone vs. cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis. *Review. Am J Obstet Gynecol.* 2013;208(1):42-.
90. Bimbashi A, Ndoni E, Dokle A. Progesterone for prevention of preterm birth. *J Perinat.Med.* 2013;41(11th World Congress of Perinatal Medicine.):June, 2013.
91. Palacio M, Cobo T, Antolin E, Ramirez M, Cabrera F, De Rosales FM, et al. Vaginal progesterone as maintenance treatment after an episode of preterm labor (PROMISE Study): A randomized, double blinded, placebo-controlled trial. *Am.J.Obstet.Gynecol.* 2013;208(1 SUPPL.1):S10-S1.
92. Saleh GS, Habibolah M, Zonobi Z, Khani Z, Sarfjoo FS, Kazemi RA, et al. Outcome of vaginal progesterone as a tocolytic agent: randomized clinical trial. *ISRN Obstet Gynecol.* 2012;2012:607906.
93. Berghella V, Mackeen AD. Cervical length screening with ultrasound-indicated cerclage compared with history-indicated cerclage for prevention of preterm birth: a meta-analysis. *Obstet Gynecol.* 2011;118(1):148-55.
94. Alfirevic Z, Owen J, Carreras ME, Sharp AN, Szychowski JM, Goya M. Vaginal progesterone, cerclage or cervical pessary for preventing preterm birth in asymptomatic singleton pregnant women with a history of preterm birth and a sonographic short cervix. *Ultrasound Obstet Gynecol.* 2013;41(2):146-51.
95. Abdel-Aleem H, Shaaban OM, Abdel-Aleem MA. Cervical pessary for preventing preterm birth. *Cochrane Database Syst.Rev.* 2013;5:CD007873.
96. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev.* 2006(3):CD004454.
97. de Heus R, Mol BW, Erwich JJ, van Geijn HP, Gyselaers WJ, Hanssens M, et al. Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. *BMJ.* 2009;338:b744.
98. Reese J, Waleh N, Poole SD, Brown N, Roman C, Clyman RI. Chronic in utero cyclooxygenase inhibition alters PGE2-regulated ductus arteriosus contractile pathways and prevents postnatal closure. *Pediatr Res.* 2009;66(2):155-61.
99. Alfirevic Z. Tocolytics: do they actually work? *BMJ.* 2012;345:e6531.
100. Norton ME. Teratogen update: fetal effects of indomethacin administration during pregnancy. *Teratology.* 1997;56(4):282-92.
101. van Vliet EO, Schuit E, Heida KY, Opmeer BC, Kok M, Gyselaers W, et al. Nifedipine versus atosiban in the treatment of threatened preterm labour (Assessment of Perinatal Outcome after Specific Tocolysis in Early Labour: APOSTEL III-Trial). *BMC Pregnancy Childbirth.* 2014;14:93.
102. Peltoniemi OM, Kari MA, Hallman M. Repeated antenatal corticosteroid treatment: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand.* 2011;90(7):719-27.
103. Murphy KE, Willan AR, Hannah ME, Ohlsson A, Kelly EN, Matthews SG, et al. Effect of antenatal corticosteroids on fetal growth and gestational age at birth. *Obstet. Gynecol.* 2012;119(5):917-23.
104. Murphy K, Willan A, Hannah M, Ohlsson A, Kelly E, Matthews S, et al. Do antenatal corticosteroids reduce fetal growth or gestational age at birth? A secondary analysis from the multiple courses of antenatal corticosteroids for preterm birth study (MACS). *Am. J. Obstet. Gynecol.* 2012;206(1):S226.
105. Murphy KE, Hannah ME, Willan AR, Ohlsson A, Kelly EN, Matthews SG, et al. Maternal side-effects after multiple courses of antenatal corticosteroids (MACS): the three-month follow-up of women in the



- randomized controlled trial of MACS for preterm birth study. *J Obstet Gynaecol Can.* 2011;33(9):909-21.
106. McKinlay CJD, Cutfield WS, Battin MR, Dalziel SR, Crowther CA, Harding JE. Repeat antenatal betamethasone does not affect bone mass at early school-age: A randomised controlled trial (actords). *J. Paediatr. Child Health.* 2013;49:49.
107. McKinlay CJD, Harding JE, Ashwood PJ, Dalziel SR, Doyle LW, Haslam RR, et al. Effect of repeat antenatal betamethasone on childhood lung function: A randomised controlled trial (actords). *J. Paediatr. Child Health.* 2013;49:92-3.
108. Han S, Crowther CA, Moore V. Magnesium maintenance therapy for preventing preterm birth after threatened preterm labour. Update of Cochrane Database Syst Rev. 2010;(7):CD000940; PMID: 20614423. *Cochrane Database Syst.Rev.* 2013;5:CD000940.
109. Conde-Agudelo A, Romero R, Kusanovic JP. Nifedipine in the management of preterm labor: a systematic review and metaanalysis (DARE structured abstract). *Am.J.Obstet.Gynecol.* 2011;204:134.
110. Dodd JM, Crowther CA, Middleton P. Oral betamimetics for maintenance therapy after threatened preterm labour. Review Update of Cochrane Database Syst Rev. 2006;(1):CD003927; PMID: 16437467. *Cochrane Database Syst.Rev.* 2012;12:CD003927.
111. Papatsonis D, Flenady V, Liley H. Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour. Review 31 refs. *Cochrane Database Syst.Rev.* 2009(1):CD005938.
112. FDA safety communications. FDA Recommends against prolonged use of magnesium sulphate to stop preterm labour due to bone changes in exposed babies. 2013. Available from: <http://www.fda.gov/Drugs/DrugSafety/ucm353333.htm>
113. Conde-Agudelo A, Romero R, Kusanovic JP. Nifedipine in the management of preterm labor: a systematic review and metaanalysis. Review. *Am J Obstet Gynecol.* 2011;204(2):134-20.
114. Roos C, Spaanderman ME, Schuit E, Bloemenkamp KW, Bolte AC, Cornette J, et al. Effect of maintenance tocolysis with nifedipine in threatened preterm labor on perinatal outcomes: a randomized controlled trial. *JAMA.* 2013;309(1):41-7.
115. Uma M, Ixora KA, Nor Azlin MI, Mahdy ZA. Maintenance nifedipine for tocolysis in preterm labour: A prospective randomised controlled trial. *BJOG Int.J.Obstet.Gynaecol.* 2012;119:35-6.
116. Parry E, Roos C, Stone P, Hayward L, Mol BW, McCowan L. The NIFTY study: A multi-centre randomised double blind placebo controlled trial of nifedipine maintenance tocolysis in Fetal Fibronectin positive women in threatened preterm labour. *Am J Obstet Gynecol.* 2012;206(1 Suppl 1):S216.
117. Chawanpaiboon S, Pimol K, Sirisomboon R. Comparison of success rate of nifedipine, progesterone, and bed rest for inhibiting uterine contraction in threatened preterm labor. 2011;37(7):787-91.
118. Roos C, Spaanderman ME, Schuit E, Bloemenkamp KW, Bolte AC, Cornette J, et al. Effect of maintenance tocolysis with nifedipine in threatened preterm labor on perinatal outcomes: a randomized controlled trial. *JAMA.* 2013;309(1):41-7.
119. Horton A. The effect of magnesium sulfate administration for neuroprotection on latency in women with preterm premature rupture of membranes. *Am J Obstet Gynecol.* 2012;206(1 Suppl 1):S209.
120. Leveno K. Antecedents to cerebral palsy in preterm infants. *Am J Obstet Gynecol.* 2009;201(6 Suppl. 1):S230.
121. Conde-Agudelo A, Romero R. Antenatal magnesium sulfate for the prevention of cerebral palsy in preterm infants less than 34 weeks' gestation: a systematic review and metaanalysis. Review 48 refs. *Am J Obstet Gynecol.* 2009;200(6):595-609.
122. Bain ES, Middleton PF, Crowther CA. Maternal adverse effects of different antenatal magnesium sulphate regimens for improving maternal and infant outcomes: a systematic review. *BMC Pregnancy.Childbirth.* 2013;13(1):195.
123. Salmeen KE, Jelin AC, Thiet MP. Perinatal neuroprotection. *F1000Prime Rep.* 2014;6:6.



124. Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour. Cochrane Database Syst.Rev. 2002(4):CD001060.
125. Magee L, Sawchuck D, Synnes A, von Dadelszen P. Magnesium Sulphate for Fetal Neuroprotection. Internet. <http://sogc.org/wp-content/uploads/2013/01/gui258CPG1106E.pdf>. 2011.
126. Royal College of Obstetricians, Gynaecologists. Tocolysis for Women in Preterm Labour. Green-top Guideline No. 1b. Internet. <http://www.rcog.org.uk/files/rcog-corp/GTG1b26072011.pdf>. 2011.
127. Stordeur S, Vrijens F, Beirens K, Vlayen J, Devriese S, Van Eycken E. Quality indicators in oncology: breast cancer. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010. KCE Reports 150C (D/2010/10.273/101) Available from: [https://kce.fgov.be/sites/default/files/page\\_documents/kce\\_150c\\_breast\\_cancer\\_1.pdf](https://kce.fgov.be/sites/default/files/page_documents/kce_150c_breast_cancer_1.pdf)
128. Vlayen J, De Gendt C, Stordeur S, Schillemans V, Camberlin C, Vrijens F, et al. Quality indicators for the management of upper gastrointestinal cancer. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2013. KCE Reports 200 (D/2013/10.273/15) Available from: [https://kce.fgov.be/sites/default/files/page\\_documents/KCE\\_200\\_Quality\\_indicators\\_for\\_the\\_management\\_of\\_upper\\_gastrointestinal\\_cancer.pdf](https://kce.fgov.be/sites/default/files/page_documents/KCE_200_Quality_indicators_for_the_management_of_upper_gastrointestinal_cancer.pdf)
129. Vlayen J, Stordeur S, Vrijens F, Van Eycken E. Quality indicators in oncology: prerequisites for the set-up of a quality system. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2011. KCE Reports 152 Available from: <https://kce.fgov.be/publication/report/quality-indicators-in-oncology-prerequisites-for-the-set%E2%80%93up-of-a-quality-system>

