KCE REPORT 228Cs

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SYNTHESIS

PREVENTION OF PRETERM BIRTH IN WOMEN AT RISK: SELECTED TOPICS

Belgian Health Care Knowledge Centre

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KCE REPORT 228Cs
GOOD CLINICAL PRACTICE

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PREVENTION OF PRETERM BIRTH IN WOMEN AT RISK: SELECTED TOPICS

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Title:	Prevention of preterm birth in women at risk: selected topics – Abstract
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	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. 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.
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FOREWORD

It remains an astonishing fact how often both doctors and patients struggle with one specific therapeutic option (often a legitimate option), namely “doing nothing”! Not intervening appears absolutely ‘*not done*’ when a pregnant woman presents with threatened preterm labour. Around the middle of the last century these women were given an alcohol infusion. This might have created a pleasant atmosphere on the ward, but the effect was ultimately negligible. However, the baby was exposed to alcohol *in utero*. Even more appalling was the decades-long use of diethylstilbestrol (DES) to treat impending miscarriage and preterm birth. The product was ineffective, and moreover, it was only in 1970 that the link was discovered to the occurrence of rare genital cancers in young women who had been exposed to this product as a foetus.

We are now half a century and many thousands of publications further down the line and we should – in theory – have a much better understanding of what works and what does not. Unfortunately the reality is far less glamorous. For most of the clinical questions there are only a hand full of really good studies, if there are any at all. Using the scant evidence that is available – supplemented by the contributions of many clinical experts (who we thank sincerely for their assistance) – we were able to provide more detailed guidelines for a large number of clinical questions.

Now we need to ensure that these recommendations are implemented effectively in practice. However, we should not hope for a spectacular decrease in the number of premature births, as many of the recommended treatments are already widely used in current practice and their efficacy is by no means absolute. The greatest benefit can probably be achieved for the women who are currently receiving treatment unnecessarily. A few simple tests can reassure a large group of women with suspected preterm labour and will save them a lot of “trouble”. Or: the difficult art of “doing nothing”!

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Deputy general director

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General director

ABSTRACT

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
CEBAM	Centre for Evidence based Medicine
CP	Cerebral palsy
fFN	Fetal fibronectin
GDG	Guideline Development Group
GGOLFB	Groupement des Gynécologues Obstétriciens de Langue Française de Belgique
GLEM	Groupes Locaux d'Evaluation Médicale
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IV	Intravenous
IVH	Intraventricular haemorrhage
KCE	Belgian health care knowledge centre
LOK	Lokale kwaliteitsgroep
LR	Likelihood ratio
MIC	Maternal intensive care
NEC	Necrotising enterocolitis
NIC	Neonatal intensive care
phIGFBP	Phosphorylated insulin-like growth factor-binding protein
PICOT	Population, Intervention, Comparator, Outcomes, Timing
PPROM	Preterm premature rupture of the membranes
PTB	Preterm birth
RCT	Randomised controlled trial
RDS	Respiratory distress syndrome
VVOC	Vlaamse Vereniging voor Ouders van Couveusekinderen

1. INTRODUCTION

1.1. General epidemiology

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 can be classified in four categories:

- extreme preterm (less than 28 weeks),
- very preterm (between 28 and 31 + 6/7 weeks),
- moderate (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 (PTB) 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).[1] The overall incidence of PTB was 6.61% (8442/127775) in Belgium in 2011.[2]

Decreasing gestational age is associated with increasing mortality, disability, intensity of neonatal care required, and hence increasing costs.[3,4] 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,[5] accounting 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, PTB can have lifelong effects on neurodevelopmental functioning such as increased risk of cerebral palsy (CP), impaired learning and visual disorders, and it is associated with and increased risk of chronic disease in adulthood.[6-9] 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.[3]

It is worth mentioning that the natural history of preterm labour itself is not very well known. A recent systematic review reported that 52.2% (median) of women with 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.[10]

2. OBJECTIVES AND SCOPE OF THIS GUIDELINE

Prevention of preterm birth 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 premature delivery based on 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).[11] This guideline concerns only secondary and tertiary prevention of spontaneous preterm birth and its sequelae.

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, progesterone, antibiotic treatment of bacterial vaginosis and asymptomatic bacteriuria etc. In symptomatic women, timely intervention (e.g. the use of antenatal steroids, in utero transfer to intensive neonatal care facilities) can significantly reduce the rate of neonatal mortality and morbidities. Many questions remain however on which preventative measures are effective, which women should receive treatment and how can overtreatment be avoided, and the usefulness, duration and type of tocolytic treatment.

The following topics are included:

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

This guideline does not address the following topics:

- Primary prevention (will be included in the update of the guideline 'National guideline for prenatal care', KCE report n°6);[12]
- Prevention of preterm birth in twin pregnancy / multiple pregnancies;
- Iatrogenic (induced or medically indicated) preterm birth;
- Management of preterm premature rupture of membranes (PPROM).

2.1. Research questions

This guideline was developed as in collaboration with representatives of health professionals involved in the care for women at risk of preterm birth (the guideline development group – GDG)

The selection of research questions was made by the members of the GDG and other representatives of professional organizations during an initial stakeholder meeting at KCE on 04/02/2013. 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.

The following 6 questions were selected:

1. What is the predictive value and clinical effectiveness of performing a fetal fibronectin (fFN) test or a phosphorylated insulin-like growth factor-binding protein (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 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 30-34 weeks?

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 repeated courses of antenatal steroids to enhance lung maturity in the newborn?

Details of the research questions in PICOT format (Population, Intervention, Comparator, Outcomes, Timing) can be found in the scientific report of the guideline.

2.2. Target users of the guideline

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

3. METHODS

3.1. Systematic review of the literature

The search for systematic reviews, meta-analyses and primary studies was carried out in Medline, Embase, and the Cochrane Library (CDSR, CENTRAL, DARE, HTA database) by two independent researchers (from 2008 onwards).

In the absence of high quality systematic reviews and meta-analyses, clinical guidelines of high quality were the starting point.

The search was completed by a search for primary studies published since the search date of the most recent systematic review/guideline. A de novo search for primary studies was performed in the absence of systematic review/guideline for a specific test.

3.2. Formulation of recommendations and external review

The GRADE methodology was followed (Table 1, Table 2 and Table 3) to determine the level of evidence and strength of recommendations.

Table 1 – Levels of evidence according to GRADE[13]

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 estimated is limited: the true effect may be substantially different from the estimate of the effect	RCTs with 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	

Table 2 – Strength of recommendations according to GRADE[14]

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

Table 3 – Interpretation of strong and conditional (weak)* recommendations

Implications	Strong recommendation	Conditional or weak recommendation
For patients	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.
For clinicians	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.
For policy makers	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*

The recommendations prepared by the GDG were tested with 4 groups of midwifes, gynaecologists and neonatologists working on a secondary or tertiary care level. They were asked to rate all recommendations for clarity and completeness and to provide comments on which factors could be a barrier for implementation of the guideline. These ratings and comments were discussed during 4 meetings in April 2014 (GLEM/LOK).

The 'Vlaamse Vereniging voor Ouders van Couveusekinderen (VVOC)' further reviewed the draft recommendations from a patient perspective.

Finally, two external assessors reviewed the scientific content of the guideline and discussed possible issues with the members of the GDG during a final meeting. The current guideline was validated by the Belgian Centre for Evidence based Medicine (CEBAM) in May 2014, making use of the AGREE II checklist.

4. CLINICAL RECOMMENDATIONS

The details of the evidence used to formulate the recommendations below are available in the scientific report and its supplements.

4.1. Secondary prevention

As women with a history of preterm birth or e.g. surgery to cervix are at increased risk for preterm birth and can benefit from preventative measures, history taking is an essential first step in the prevention of preterm birth and its sequelae.

4.1.1. Progesterone for women at risk

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
• Consider vaginal progesterone in asymptomatic women with a short cervix identified on vaginal ultrasound.	Weak	Low

From evidence to recommendations

Factor	Comments
Balance between clinical benefits and harms	**Women with a history of preterm birth** 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. There are no indications that progesterone during pregnancy has serious adverse events. **Women with a short cervix on vaginal ultrasound** 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 preterm birth 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. Moreover, 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. **Dosage** To limit side effects, it is suggested to use vaginal administration at the lowest dose tested in clinical trials (200mg once daily).
Quality of evidence	Low level of evidence.
Costs (resource allocation)	No formal cost-effectiveness analysis is performed.
Patients values and preferences	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.

4.1.2. Cerclage

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 spontaneous preterm birth (between 24 and 37 weeks) alone.	Strong	Very low
• 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	Not Applicable
• 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) in women with a history of recurrent second trimester birth.	Weak	Very low

From evidence to recommendation

Factor	Comments
Balance between clinical benefits and harms	**Women with a history of preterm birth or surgery to the cervix** There is no proof that cerclage as secondary prevention has a beneficial effect in high risk women based on history only (history of preterm birth, history of surgery to the cervix). On the other hand, cerclage increases the risk of maternal pyrexia and possible other side effects and the rate of caesarean sections. Furthermore, indirect comparison of progesterone and cerclage in these high risk women shows no clear advantage for cerclage. **Women with a short cervix on ultrasound** 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. 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. 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 25 mm.[15] 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 (< 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.[16, 17] Further literature review regarding the use of cervical pessary is out of the scope of this guideline. For women with a history of recurrent second trimester birth, a primary cerclage (at 12-14 weeks of pregnancy) may be considered.
Quality of evidence	Very low level of evidence.
Costs (resource allocation)	No cost assessment performed.
Patients values and preferences	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.

Recommendation
We could not identify any evidence from RCTs for progesterone or 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.

4.2. Tertiary prevention

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.[18]
- Although infrequent, tocolytic therapy can be associated with severe side effects.[19]

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.

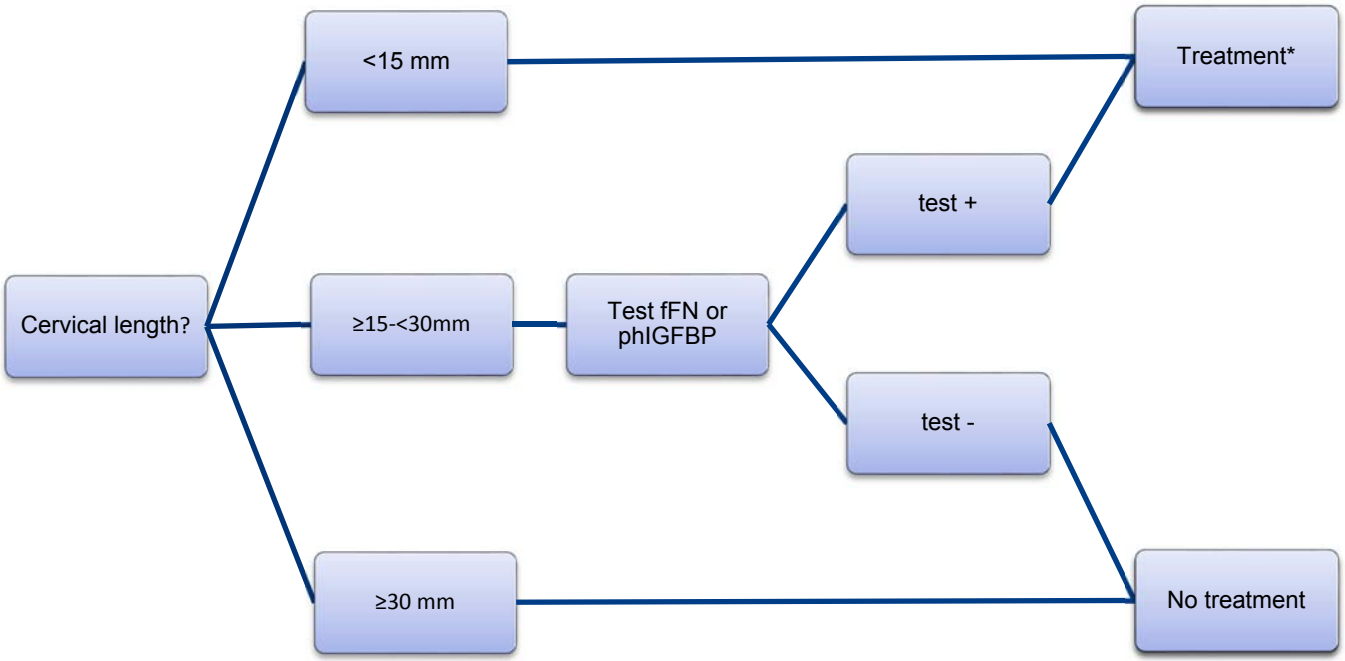
Furthermore, when signs of preterm labour occur very early in pregnancy, treatment decisions are professionally, ethically, and emotionally complicated and demanding. Parents confronted with difficult choices and unsure prognosis need profound counselling and support. To offer some guidance on approach and communication with future parents, representatives of all Flemish perinatal centres (maternal intensive care units (MIC) and neonatal intensive care units (NIC) wrote a consensus-based text. 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) and GGOLFB (www.ggolfb.be).

4.2.1. Identification of symptomatic women eligible for treatment

Recommendations	Strength of Recommendation	Level of Evidence
• Consider performing cervical length measurement in women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation to avoid overtreatment (avoid unnecesary admissions to hospital, transfer to tertiary level and administration of tocolytic therapy), using a threshold of ≥ 30mm to decline treatment. If cervical length is < 15mm, consider treatment (Figure 1).	Weak	NA
• In women presenting with symptoms of threatened preterm labour and less than 3 cm cervical dilatation, consider further assessment using a fetal fibronectin test or phIGFBP test if measured cervical length is between 16 and 29 mm. If test result is negative, no treatment is indicated as there is insufficient evidence (Figure 1).	Weak	NA

Figure 1 – Assessment of pregnant women presenting with symptoms of threatened preterm labour and less than 3cm cervical dilatation



** steroids, tocolytic therapy, transfer to tertiary level if indicated*
FNf: Fibronectine fœtale.
phIGFBP: Phosphorylated insulin-like growth factor-binding protein

From evidence to recommendation

Factor	Comments
Balance between clinical benefits and harms	**Fetal fibronectin (fFN) test** 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. 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 4.2.2) and supporting evidence for its benefit is limited, careful assessment of women with signs of PTB is warranted before starting treatment. 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 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.[20-22] For patients with a higher pre-test probability e.g. imminent labour, fFN testing is not useful. As the test is performed on a routine vaginal swab, there are no significant test-specific maternal side effects. **phIGFBP test** There are no data from randomized trials on the clinical effectiveness of phIGFBP testing. Only few observational studies compared the phIGFBP and fFN tests directly in the same population. 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. 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.

Factor	Comments
	Vaginal ultrasound: cervical length measurement 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 the number of events in the trials was very low. As for the fFN test, the most important advantage of vaginal ultrasound is that unnecessary hospital admission and treatment can be avoided. 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). The accuracy of diagnosing preterm labour can be improved by combining vaginal ultrasound with fFN or phIGFBP testing. Based on a review by DeFranco et al.[23] the following schedule can be proposed (Figure 1): • cervical length on vaginal ultrasound ≥ 30mm: no treatment • cervical length on vaginal ultrasound 16-29mm: perform fFN test or phIGFBP test o test negative: no treatment o test positive: steroids, tocolytic therapy, transfer to tertiary level if indicated • cervical length on vaginal ultrasound ≤ 15mm: steroids, tocolytic therapy, transfer to tertiary level if indicated Although vaginal ultrasound can be uncomfortable, no serious side effects are noted.
Quality of evidence	Due to current methodological limitations of the GRADE system for diagnostic tests, GRADE was not applied to the recommendations on diagnosis. **Fetal fibronectin test and phIGFBP test** Effectiveness: 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. 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. **Vaginal ultrasound** RCTs testing the clinical effectiveness of cervical length measurement by vaginal ultrasound are underpowered to show proof of clinical benefit. Observational studies show heterogeneous results and are subject to spectrum bias.
Costs (resource allocation)	**Fetal fibronectin test** 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

Factor	Comments
	tocolytic treatment is avoided. The cost of one course of atosiban equals approximately the cost of 6 fFN tests (personal communication W. Gyselaers). 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.[20] **phIGFBP test** The phIGFBP test is cheaper than the fibronectin test, its price is estimated at around 12 euros. It is currently not reimbursed in Belgium. **Vaginal ultrasound** Cervical length measurement during pregnancy is currently not reimbursed in Belgium. **Combination of tests** A cost-effectiveness analysis based on Dutch data found that vaginal ultrasound and 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.[22] No formal cost-effectiveness study based on Belgian data was performed.
Patients values and preferences	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 come back if new symptoms occur, especially as the post-test risk is not zero percent.

4.2.2. Type of tocolytic therapy

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

From evidence to recommendation

Factor	Comments
Balance between clinical benefits and harms	In a recent network meta-analysis, all tocolytic agents received a score to indicate the probability that the agent would be ranked best for 4 outcomes: delaying birth with at least 48 hours, neonatal mortality, RDS and maternal side effects. Compared to placebo, no tocolytic agent has been proven effective in reducing the risk for neonatal mortality or neonatal RDS. 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. The beneficial effect on this 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.[24] Also beta mimetic therapy and magnesium sulphate have a very low score in the analysis with regard to maternal side effects. Overall, taking into account that all tested tocolytic agents are better than placebo to prolong pregnancy for at least 48 hours and that 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 the use of nifedipine in pregnant women is off-label. Nifedipine however, is much cheaper than atosiban. 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. **Dosage** 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.[25]

Quality of evidence	Due to its current limitations, GRADE was not applied to the network meta-analysis.
Costs (resource allocation)	No formal cost-effectiveness study was performed. Treatment with calcium channel blockers for 48 hours is very cheap, costing only a few euro. One course of atosiban however, currently costs a few hundred euro.
Patients values and preferences	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.

4.2.3. Repeated antenatal corticosteroid treatment

Antenatal steroids have since long been proven to be associated with an overall reduction in neonatal death, RDS, cerebroventricular haemorrhage, NEC, respiratory support, intensive care admissions and systemic infections in the first 48 hours of life.[26] There is an ongoing debate however, if antenatal corticosteroid administration should be repeated if the interval between the first course (consisting of two doses) and suspected preterm birth is prolonged.

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

From evidence to recommendation

Factor	Comments
Balance between clinical benefits and harms	Compared to a single course, repeated course(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. **Dosage** In the majority of trials included in the meta-analysis, one course of corticosteroids consisted of two doses of 12mg betamethasone, 24 hours apart.
Quality of evidence	Moderate level of evidence
Costs (resource allocation)	No formal cost-assessment was performed.
Patients values and preferences	See 4.2.2 ‘choice of tocolytic therapy’

4.2.4. Maintenance tocolytic therapy

4.2.4.1. Maintenance tocolytic therapy with Magnesium

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

From evidence to recommendation

Factor	Comments
Balance between clinical benefits and harms	As there is no proof of any benefit of maintenance tocolytic therapy with magnesium, it is not recommended. 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 4.2.5).[27] Although severe side effects have not been described for oral use of magnesium, side effects such as diarrhoea may occur.
Quality of evidence	Very low level of evidence
Costs (resource allocation)	NA
Patients values and preferences	NA

4.2.4.2. Nifedipine

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

From evidence to recommendation

Factor	Comments
Balance between clinical benefits and harms	There is no proof of a beneficial effect of nifedipine maintenance therapy on the critical neonatal outcomes as evidence lacks the necessary statistical power. 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 by even a few days would have a beneficial effect on neonatal outcomes. This possible benefit of maintenance nifedipine should be weighed against side effects, such as an increased risk of postpartum haemorrhage (see APOSTEL II trial).[28] **Dosage** 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.
Quality of evidence	Low level of evidence
Costs (resource allocation)	No formal cost-effectiveness evaluation was performed.
Patients values and preferences	See 'choice of tocolytic therapy'

4.2.4.3. Betamimetics

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

From evidence to recommendation

Factor	Comments
Balance between clinical benefits and harms	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. The European Medicine agency and the Belgian Federal Agency for Medicines and Health Products (FAMHP/FAGG/AFMPS) have recommended to strongly restrict the use of short-acting beta-agonists in obstetric indications. These medicines should no longer be used in oral or suppository forms in obstetric indications. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Short-acting_beta-agonists/human_referral_prac_000013.jsp&mid=WC0b01ac05805c516f http://www.fagg-afmps.be/nl/news/news_beta_agonistes.jsp
Quality of evidence	Low level of evidence
Costs (resource allocation)	NA
Patients values and preferences	NA

4.2.4.4. Oxytocin antagonists

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

From evidence to recommendation

Factor	Comments
Balance between clinical benefits and harms	Sparse available evidence cannot show proof of a beneficial effect of oxytocin inhibitor maintenance therapy. In daily practice, a repeated 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.
Quality of evidence	Very low level of evidence
Costs (resource allocation)	Atosiban is an expensive tocolytic agent. No formal cost-effectiveness study was performed.
Patients values and preferences	NA

4.2.4.5. Progesterone

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

From evidence to recommendation

Factor	Comments
Balance between clinical benefits and harms	Evidence for the use of vaginal progesterone in this patient group is statistically underpowered and does not show a proven benefit for neonatal outcomes. Meta-analysis of trials using vaginal progesterone shows a statistically significant effect on neonatal death. However this result is based on only 18 events and should thus be considered as very fragile. However, as discussed above, there is sufficient evidence from randomized controlled trials in women with a history of preterm birth showing that progesterone can decrease neonatal morbidity. As vaginal progesterone has minimal side effects and is a cheap intervention, 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.
Quality of evidence	Very low level of evidence
Costs (resource allocation)	No formal cost-effectiveness evaluation was performed.
Patients values and preferences	See 4.2.2 ‘choice of tocolytic therapy’

4.2.5. Magnesium sulphate for neuroprotection

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

From evidence to recommendation

Factor	Comments
Balance between clinical benefits and harms	Magnesium sulphate injections must be used with caution and the use of protocols for administration is recommended. Prolonged use (>48 hours) is contraindicated due to the risk of bone abnormalities and calcium, phosphorous, and magnesium derangements in mothers and infants.[29] 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).[27] Moreover, trials investigating magnesium sulphate as a tocolytic agent have shown an association with increased neonatal mortality.[30] 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.[31] Hence, for safety reasons, it is advisable to keep the duration of magnesium sulphate administration short and to use the lowest total dose shown effective in clinical trials. 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.[32] 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. The GDG members recommend that magnesium sulphate should be administered only when the delivery is imminent (i.e. as close as possible to delivery) and for 24 hours maximum.
Quality of evidence	High level of evidence
Costs (resource allocation)	No cost assessment was performed.
Patients values and preferences	See 4.2.2 'choice of tocolytic therapy'

5. DISCUSSION

Preterm birth complications remain a major cause of neonatal mortality and morbidity worldwide [5] 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. [11]

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 more sparse. 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.

POLICY RECOMMENDATIONS[a]

To the attention of the scientific and professional associations in obstetrics and midwifery:

- **To enhance the dissemination of this guideline through diverse channels such as websites or continuing medical education.**

To the attention of the College of Mother and Newborn and in consultation with the National Council of Quality Promotion:

- **To promote the implementation of this guideline and to monitor its use with process and outcome indicators.**

To the attention of the Minister of Social Affairs and Public Health, the Federal Public Service for Health, the insurance committee, the Technisch Medische Raad – Conseil Technique Médical:

- **The reimbursement of the fetal fibronectin test and/or the phIGFBP test and of vaginal ultrasound can be recommended for women with symptoms of suspected preterm labour.**

To the research community:

- **To set up RCTs on the long term health benefits and risks of treatment of (suspected) preterm labour.**

[a] The KCE has sole responsibility for the recommendations.

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