

WHAT ARE THE RECOMMENDED CLINICAL ASSESSMENT AND SCREENING TESTS DURING PREGNANCY?



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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
25-OHD	25-hydroxyvitamin D
ABeFUM	Association Belge Francophone d'Ultrasonologie Médicale
AFD	Amniotic fluid depth
AFI	Amniotic fluid index
AFsF	Association francophone des sages-femmes catholiques
AFV	Amniotic fluid volume
AGREE	Appraisal of Guidelines Research and Evaluation
AMSTAR	Assessing the Methodological quality of Systematic Reviews
ANMC	Australian Nursing and Midwifery Council.
ASA	American Society of Anesthesiologists Physical Status classification
Anti-TPO	Anti-thyroperoxydase
BARA	Belgian Association for Regional Anesthesia
BHS	Belgian Hematological Socie
BMI	Body mass index
BPD	Biparietal diameter
CBR	Consensus based recommendation
CDC	Centers for Disease Control and Prevention (US)
CDT	Clinical decision threshold
CEBAM	Belgian Centre for Evidence - Based Medicine
CENTRAL	The Cochrane Central Register of Controlled Trials
CFSF	Conseil Fédéral des Sages-Femmes
CHU	Centre Hospitalier Universitaire (University Hospital Centre)
CI	Confidence interval
CMV	Cytomegalovirus
CNPQ-NRKP	Conseil national de promotion de la qualité-Nationale Raad voor KwaliteitsPromotie
CNS	Central nervous system
COI	Conflict of Interest
COPD	Chronic obstructive pulmonary disease



CRL	Crown-rump length
CSS-HGR	Conseil Supérieur de la Santé - Hoge Gezondheidsraad (Superior health council)
CTG	Cardiotocography
CVS	Chorion villus sampling
DARE	Database of Abstracts and Reviews of Effectiveness
DKF	Dienst für Kind und Familie
DM	Diabetes mellitus
DoHA	Department of Health and Ageing (Australia)
EAC	Expert Advisory Committee (Australia)
e.g.	Exempli gratia Example given
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
EMBASE	Name of an International biomedical database that covers journals and conferences
FHR	Fetal heart rate
FT4	Free thyroxin
GA	Gestational age
GBS	Group B Streptococcus
GCT	Glucose challenge test
GDG	Guideline Development Group
GDM	Gestational diabetes mellitus
GGOLFB	Groupement des Gynécologues et Obstétriciens de Langue Française de Belgique
GIP	Groupe interdisciplinaire-interuniversitaire de périnatalité ULB/UCL
GRADE	Grading of recommendations assessment, development and evaluation
GTT	Glucose tolerance test
HAPO	Hyperglycemia and Adverse Pregnancy Outcome Study
Hb	Haemoglobin
HBeAg	Hepatitis B envelope antigen
HBsAg	Hepatitis B surface antigen
HC	Head circumference



HELLP	Haemolysis, elevated liver enzymes and low platelet count
HGR-CSS	Hoge Gezondheidsraad – Conseil Supérieur de la Santé
HIV	Human Immunodeficiency Virus
IADPSG	International Association of Diabetes and Pregnancy Study Groups
ICU	Intensive care unit
IFI	Indirect immunofluorescence
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMA-AIM	InterMutualistisch Agentschap – Agence Intermutualiste
INAMI-RIZIV-NIHDI	Institut National d'Assurance Maladie-Invalidité - Rijksinstituut voor Ziekte- en Invaliditeitsverzekering - National Institute for Health and Disability Insurance
ISAgA	Immosorbent Agglutinations Assay
ISP-WIV	Institut scientifique de santé publique – Wetenschappelijk instituut volksgezondheid (Scientific institute of public health)
IUGR	Intrauterine growth restriction
KU Leuven	Katholieke Universiteit Leuven
L	Low quality evidence
LGA	Large for gestational age
LMP	Last menstrual period
LR	Likelihood ratio
LR-	Negative likelihood ratio
LR+	Positive likelihood ratio
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MD	Mean difference
MEDLINE	Medical Literature Analysis and Retrieval System Online (International biomedical database)



MeSH	Medical subject headings
MI	Micronutrient Initiative
mm	millimetre
MPD	Mean pressure difference
Mo	Months
MRI	Magnetic Resonance Imaging
NA	Not applicable
NCGC	National Clinical Guideline Centre
NHMRC	National Health and Medical Research Council (Australian)
NI	Not industry
NICE	National Institute for Health and Clinical Excellence (United Kingdom)
NICU	Neonatal intensive care
NIDHI	National Institute for Health and Disability Insurance ('Rijksinstituut voor Ziekte- en Invaliditeitsverzekering'/Institut National d'Assurance Maladie-Invalidité')
NIPT	Non-invasive prenatal testing
NNT	Number needed to treat
NR	Not reported
NS	Not significant
NSC	National Screening Committee (United Kingdom)
NST	Non-stress test
NVOG	Nederlandse Vereniging voor Obstetrie en Gynaecologie
OGTT	Oral glucose tolerance test
OHRI	Ottawa Hospital Research Institute
OIS	Optimal information size
ONE	Office de la Naissance et de l'Enfance
OR	Odds ratio
OVH	Overt hypothyroidism
PCR	Polymerase chain reaction
PP	Practice point



PROM	Premature rupture of membranes
PSFa	Protein segment finder
PTB	Preterm birth
Q1	Lower (25%) quartile
Q3	Upper (75%) quartile
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RCOG	Royal College of Obstetricians and Gynaecologists (United Kingdom)
RCT	Randomised controlled trial
RhD	Rhesus D
RIZIV – INAMI – NIHDI	Rijksinstituut voor Ziekte - en Invaliditeitsverzekering - Institut National d'Assurance Maladie-Invalidité - National Institute for Health and Disability Insurance
RoB, ROB	Risk of bias
RPR	Rapid plasma reagin
RR	Relative risk
RRR	Relative risk reduction
SAE	Serious adverse event
SCH	Sub-clinical hypothyroidism
SGA	Small for gestational age
SOGC	Society of Obstetricians and Gynaecologists (Canada)
SR	Systematic review
SS	Sample size
SSMG	Société Scientifique de Médecine Générale
STD	Sexually Transmitted Diseases
TPHA	Treponemal pallidum hemagglutination assay
TSH	Thyroid stimulating hormone
UA	Universiteit Antwerpen
UCL	Université catholique de Louvain
ULB	Université libre de Bruxelles
UGent	Universiteit Gent



UPSfB	Union Professionnelle des Sages-Femmes Belges
UVC-CHU	University hospital center (Universitair Verplegingscentrum - Centre Hospitalier Universitaire)
UVV	Unie Vlaamse Vroedvrouwen
UZ	University Hospital (Universitair ziekenhuis)
VL	Very low quality evidence
VLOV	Vlaamse Organisaties van Vroedvrouwen
Vs.	Versus
VVOG	Vlaamse Vereniging voor Obstetrie en Gynaecologie
WHO	World Health Organization
WIV-ISP	Wetenschappelijk Instituut Volksgezondheid - Institut Scientifique de Santé Publique
Wk(s)	Week(s)
yrs	Years



■ SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Background

Each year, more than 125 000 births are registered in Belgium.¹ An early, adequate and continuous prenatal care with timely identification and management of risk factors is fundamental for a good pregnancy outcome. In 2004, the KCE had published a clinical guideline for antenatal care (KCE Report 6).² The recommendations focused on low-risk pregnant women (i.e. without identified risk factors at the beginning of the pregnancy) and concerned mainly screening examinations.

1.2 The need for an updated guideline

Since 2004, the health professionals who are involved in the management of pregnant women face new scientific evidence and emerging issues (e.g. lower threshold for the diagnosis of gestational diabetes³ or new screening tests for pre-eclampsia risk). Furthermore, it appears that some laboratory tests that were not recommended in 2004 continue to be broadly prescribed in Belgium.⁴ This observation can indicate a possible overuse of screening tests with a risk of misallocation of resources but also deleterious effects on pregnant women such as overdiagnosis, overtreatment, and related anxiety. The expected impact of an updated guideline will be important in terms of quality of care, standardization of practices and resource allocation.

1.3 Remit of the guideline

1.3.1 Overall objectives

The aim of this project is to update the KCE 2004 guideline for antenatal care in low-risk women with a particular attention to emerging clinical questions. The scope of this guideline was defined in collaboration with GDG members and stakeholders (List in Appendix 1) during an initial scoping meeting held on January 13, 2014. In preparation of the meeting, experts were asked at the end of 2013 to determine the current crucial topics which would deserve a particular attention either because the topic was emerging the past few years or because the 2004 conclusion was much debated. These experts' suggestions and an overview of available recent high-quality guidelines published by international organisations (see chapter 2.4.1)



allowed to gather twenty-three proposals (List in Appendix 2) that were presented during the initial scoping meeting.

During this scoping meeting, it was decided to focus on low-risk pregnant women, i.e. women who do not have identified risk factors, known pre-existing conditions or complications requiring additional tests or adapted management. The main scope of this guideline was also delineated and focuses on the monitoring and the follow-up of pregnant women including:

- Schedule of antenatal visits
- Clinical examination
- Technical examination
- Haematological assessment
- Screening tests for infections
- Screening for maternal clinical problems
- Screening for specific pregnancy related risks

1.3.2 Risk factors that may imply additional care

In addition to this baseline clinical care, some pregnant women will require other tests or adapted management, because they have specific known risk factors that have to be followed-up before and during the pregnancy and also after the delivery. Sometimes, the health of the pregnant woman and of the baby needs to be monitored in a more sustained way. Moreover, specific advice (smoking, nutrition, alcohol, drug use) maybe required and referral to more specialized care may be indicated.

To define the risk factors to be considered, we used the original list established in the KCE 2004 guideline and completed it by risk factors listed both in the NICE 2008 guideline and the Australian 2014 guideline (Appendix 3). The completed list was submitted to the GDG members using an online Lime survey. Their comments were taken into account to propose an amended list of risk factors, which was sent for comments by e-mail to the stakeholders (March 2015). The final list of risk factors is reported on Table 1.

Table 1 – Risk factors that may require additional care (non-exhaustive list)

General information
Age < 18 years or > 40 years
Late antenatal care: 1 st antenatal consultation after 20 weeks
Lack of social support, domestic violence, psycho-social vulnerability
Use of medicines
Immunization status (lack of vaccination against hepatitis B, rubella and/or lack of history of rubella, varicella, toxoplasmosis, CMV)
Obesity (body mass index (BMI) 35 kg/m ² or more at first contact) or underweight (BMI less than 18 kg/m ² at first contact)
Lifestyle factors
Drug use
Alcohol consumption
Active and/or passive smoking
At-risk sexual behaviour (for STD)
Familial history
Familial diseases or genetic disorders
Personal history
All pre-existing pathologies or surgical interventions that can have an impact on the pregnancy, including:
<ul style="list-style-type: none">• obesity (body mass index, BMI, 35 kg/m² or more at first contact) or underweight (BMI less than 18 kg/m² at first contact)• diabetes• endocrine disorders• auto-immune disorders• cardiovascular diseases• lung diseases• renal diseases• hepatic diseases• haematological disorders



-
- malignancy
 - neurological disorders
 - psychiatric disorders
-

Gynaecological history

Uterine pathology (congenital anomaly, abnormal cervix cytology)

Uterine surgery (e.g. caesarean section, myomectomy or cone biopsy)

Genital mutilation

Experiences in previous pregnancies

Three or more documented miscarriages

Pregnancy induced hypertension, pre-eclampsia and HELLP syndrome

Gestational diabetes

Postpartum psychosis/ Depression

Rhesus isoimmunisation or other significant blood group antibodies

Preterm birth

Multiple pregnancy

Grand multiparity (parity four or more)

Severe perinatal morbidity (congenital or acquired)

This definition of risk factors leads to formulate a general recommendation.

Recommendation

To identify the need for additional care, it is recommended to collect information relative to: the current pregnancy, the lifestyle factors that may impact pregnancy, the personal and the familial history, and finally, the gynecological and obstetrical antecedents. Risk factors and pre-conditions have to be listed to inform the pregnant women and their healthcare practitioners that additional care may be required. This history taking will be completed with a clinical exam to identify risk factors (measure of blood pressure, weight, detection of a pre-existing diabetes by a fasting glycaemia measurement...).



1.3.3 Issues beyond the scope of the present guideline

During the initial scoping meeting held on January 13, 2014 a list of issues which are not considered in this guideline was defined with the stakeholders and GDG members. This list encompasses:

- Management of detected risk
- Treatment of diagnosed pathology
- General lifestyle and nutritional advice
- Management of mental health
- Immunoglobulin's administration
- Genital mutilation
- Intrapartum and post-partum care
- Cost-effectiveness analysis of specific interventions

The main objectives pursued by this guideline are to offer information on best practices for baseline clinical care of all pregnant women and comprehensive information for the follow-up of the low-risk women. This guideline includes recommendations on baseline clinical care for all healthy pregnant women but does not include information on the additional care that some women will require due to specific risk factors or pre-existing conditions. Although the guideline addresses screening for many of the complications of pregnancy, it does not include information on further investigations and appropriate management of these complications (for example, the management of pre-eclampsia, fetal anomalies and multiple pregnancies). In addition, this guideline does not provide advice neither about general lifestyle and nutrition of pregnant women (except for CMV and toxoplasmosis), nor about procedures or care that are not specifically related to pregnancy (e.g. breast examination for cancer screening). Furthermore, this guideline does not cover the long term follow-up of health status or maternal morbidity (e.g. diabetes, varicose veins, renal failure, heart failure occurring during the pregnancy and that have to be followed up after the delivery).

1.3.4 Target users of the guideline

This guideline is intended to be used by care providers involved in the care for pregnant women, especially obstetricians, midwives and general practitioners. It is also of interest for women and their partners, neonatologists, organisations of birth and childhood (e.g. ONE, Kind & Gezin), hospital managers and policy makers.

This guideline provides recommendations based on current scientific evidence. Healthcare providers are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences. Moreover some recommendations may not always be in line with the current criteria for NIHDI (RIZIV/INAMI) reimbursement of diagnostic and therapeutic interventions. The NIHDI may consider adaptation of reimbursement/funding criteria based on these recommendations.

1.4 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 healthcare professionals and researchers for use within the Belgian context. It provides advice regarding the follow-up of low-risk pregnant women.

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 healthcare professional. It is advised, however, that significant deviations from the national guideline are fully documented in the patient's file at the time the relevant decision is taken.



1.5 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 care providers 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 researchers make yearly declarations of interest and further details of these are available upon request.

2 METHODOLOGY

2.1 The Guideline Development Group

This guideline is the result of a collaboration between multidisciplinary groups of practising healthcare professionals and KCE researchers. At the start of the production of the guideline, the "College of physicians for the mother and the newborn, section maternity" submitted a list of obstetricians that were considered as potential members of the GDG. To add other healthcare providers, each organisation of midwives, general practitioners, neonatologists and organisations for birth and childhood (ONE, Kind & Gezin) were contacted. The composition of the whole GDG is documented in Appendix 1.

The roles assigned to the GDG were:

- To delimit the scope, in close collaboration with the stakeholders;
- 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 judgement about indirectness of evidence;
- To provide feedback on the draft recommendations;
- To specify the Belgian context and address additional concerns to be reported under a section on 'other considerations'.

Guideline development and literature review expertise, support, and facilitation were provided by the KCE Expert Team (P. Jonckheer, L. Verleye and S. Stordeur) and by two sub-contracting teams:

- the Ottawa Hospital Research Institute (N. Ahmadzai, M.T. Ansari, L.M. Gaudet and J.M. Tetzlaff), responsible for screening for hypothyroidism, vitamin D deficiency, risk of preterm birth, risk of pre-eclampsia and for surveillance of pregnancies that passed their due date;
- the National Clinical Guideline Centre (S. Carville, K. Dworzynski, J. Glenn, K. Jones and P. Miller), responsible for screening for cytomegalovirus, toxoplasmosis, chlamydia trachomatis, group B streptococcus infections and gestational diabetes.



2.2 General approach

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 are followed to elaborate a guideline. Firstly, clinical questions are developed and the inclusion and exclusion criteria are defined in collaboration with members of the Guideline Development Group. Secondly a literature review is conducted (including a search for recent, high quality guidelines). Thirdly, on the basis of the results of the literature review, recommendations are formulated and graded according to the GRADE approach.

2.3 Clinical research questions

2.3.1 Hierarchical approach

The KCE 2004 guideline focused on 34 main clinical questions. The discussion with the members of the GDG and representatives of professional organizations during the meeting of January 2014 and the comments received after this meeting allowed to select 10 topics for full literature search. These 10 topics were translated into research questions that are named “full search questions” in this report (Table 2).

Many of these research questions relate to the use of tests to screen for or establish the diagnosis of a certain condition or disease.

This type of research questions needs a specific approach, as there is no direct relationship between the test and the clinically important outcome since the clinical effectiveness of a test depends on the availability and efficacy of treatment.

The value of a new test will depend on its characteristics compared to the test that is considered standard and the purpose for which it is considered. The diagnostic accuracy of two tests can be compared but a new test can also replace another test with the same diagnostic accuracy because it is more safe or cheaper. Furthermore, a test can be evaluated as an extra test (add-on) in the clinical pathway in addition to the tests already used. Results

of the evidence thus always have to be interpreted in view of the clinical context.

Performing a screening test can have positive but also negative impact:

- Independent of the test results, patients may suffer from the morbidity caused by a given test and many patients will experience some anxiety when awaiting test results.
- Patients with a true positive result may benefit from an effective treatment to improve important clinical outcomes but treatment interventions may also have important side effects. The supporting evidence for the treatment efficacy may be of low quality with uncertainty around its true effect.
- False positive results lead to needless anxiety and patients who have a false positive result will be exposed to unnecessary therapeutic interventions and associated risks.
- False negative results may lead to delayed help seeking when (minor) symptoms occur, resulting in poorer clinical outcomes.
- Finally, when results are inconclusive or ‘borderline’, further follow-up and additional tests may be necessary and may be associated with additional side effects and anxiety.

All these factors need to be taken into account when considering the use of a diagnostic test or implementing a screening strategy. Evaluating the diagnostic accuracy of a test (sensitivity, specificity, predictive values in a population etc.) will provide insufficient information to judge its clinical value.

The use of a test is ideally evaluated in a randomized clinical trial that takes into account the overall risk-benefit balance for all groups of patients, the so-called test-and-treat studies. Unfortunately, very often this type of evidence is not available. The usefulness of a test can then be judged by linking data on test accuracy, prevalence, benefit-risk balance of the test and the efficacy of possible therapeutic interventions that would follow the test. Evidently, the confidence in the evidence underlying a recommendation will be weakened.

In this guideline, we used a multi-step approach for research questions on diagnostic tests. First, we searched for ‘direct’ evidence: randomized or non-randomized studies that compared a management strategy including the use of a given test with a management strategy without the use of the test.



If no direct evidence was available, we searched for evidence of possible therapeutic interventions for patients who would test positive if a test was applied. If applicable, this evidence was supplemented with diagnostic accuracy studies for the evaluated tests. Research questions were then subdivided into sub-questions as appropriate (Table 2).

2.3.2 List of clinical questions retained for the KCE 2015 guideline

In addition to the 10 full search questions, 24 clinical questions from the KCE 2004 guideline² remained and were considered to be updated using the ADAPTE procedure. All 34 research questions are listed in Table 2.

Table 2 – List of 34 clinical research questions

Full search questions

1. Should all Belgian low-risk pregnant women be screened for **cytomegalovirus infection**?
 - a. What are the benefits and harms of CMV screening in all healthy pregnant women, compared with no routine screening?
 - b. What are the benefits and harms of lifestyle advice to prevent infection with cytomegalovirus during pregnancy?

2. Should all Belgian low-risk pregnant women be screened for **toxoplasmosis infection**?
 - a. What are the benefits and harms of toxoplasmosis screening in all healthy pregnant women, compared with no routine screening?
 - b. What are the benefits and harms of lifestyle advice to prevent infection with toxoplasmosis during pregnancy?

3. Should all Belgian low-risk pregnant women be screened for **chlamydia trachomatis infection**?
 - What are the benefits and harms of chlamydia screening in all healthy pregnant women, compared with no screening or targeted tests in women with risk factors?

4. Should all Belgian low-risk pregnant women be screened for **Group B streptococcus infection (GBS) asymptomatic colonization at 35-37 weeks**?
 - What are the benefits and harms of group B streptococcus screening in all healthy pregnant women, compared to GBS prophylaxis without a particular protocol (no screening and non-specified ad hoc intrapartum antibiotic use) or to risk factors based prophylaxis?

5. Should all Belgian low-risk pregnant women be screened for **gestational diabetes**?
 - a. Which screening strategies are more accurate and effective to screen healthy pregnant women for gestational diabetes?
 - At which threshold?
 - At which gestational age (<24 weeks, 24-30 weeks, 30 weeks or more)?
 - In all women (universal) or in women at risk?
 - b. What is the diagnostic accuracy of the 50g glucose challenge test?
 - At which threshold?
 - At which gestational age (<24 weeks, 24-30 weeks, 30 weeks or more)?
 - In all women (universal) or in women at risk?



-
6. Should all Belgian low-risk pregnant women be screened for **hypothyroidism**?
- What are the benefits and harms of routine screening for hypothyroidism in asymptomatic pregnant women compared with no routine screening (or targeted screening of clinically at risk women)?
 - Compared with no or lower pharmacological doses, what are the benefits and harms of levothyroxine or selenomethionine treatment of pregnant women with subclinical hypothyroidism? Do treatment effects vary with their risk status (i.e. low versus high risk for hypothyroidism)?
-
7. Should all Belgian low-risk pregnant women be screened for **vitamin D deficiency**?
- What are the benefits and harms of routine vitamin D deficiency screening of all low-risk pregnant women compared with no routine screening (or targeted screening of clinically at risk women)?
 - Compared with no or lower dose supplementation, what are the benefits and harms of vitamin D supplementation during pregnancy? Do treatment effects vary with the patient risk status (i.e. low versus high risk for vitamin D deficiency) or baseline vitamin D levels (i.e. established baseline hypovitaminosis D versus unclear or normal baseline vitamin D levels)?
-
8. Should all Belgian low-risk pregnant women be screened for **risk of preterm birth**?
- In pregnant women judged to be **exclusively** at low risk for preterm birth based on history, physical exam, or both, what are the comparative benefits and harms of mid-to-third trimester transvaginal ultrasound for cervical length, funnelling, or both, and/or digital vaginal exam in routine patient management?
 - In pregnant women judged to be **predominantly** at low risk for preterm birth based on history, physical exam, or both, what are the comparative benefits and harms of mid-to-third trimester transvaginal ultrasound for cervical length, funnelling, or both and/or digital vaginal exam in routine patient management?
 - Compared with each other or no active intervention (i.e. expectant management), what is the comparative benefits and harms of progesterone therapy, cerclage, and/or reduced physical activity (e.g. bed rest) to prevent preterm birth and its sequelae in asymptomatic women with short cervix **but no additional risk factors for preterm birth** (i.e. exclusively low-risk populations as judged on history and physical exam before cervical assessment)?
 - Compared with each other or no active intervention (i.e. expectant management), what is the comparative benefits and harms of progesterone therapy, cerclage, and/or reduced physical activity (e.g. bed rest) to prevent preterm birth and its sequelae in asymptomatic pregnant populations with short cervix **who are predominantly at low risk** (as judged on history and physical exam before cervical assessment) for preterm birth?
-
9. Should all Belgian low-risk pregnant women be screened for **risk of pre-eclampsia**?
- What are the benefits and harms of screening for pre-eclampsia risk with additional tests compared to assessment based on history and physical exam alone, in asymptomatic pregnant women otherwise at low-risk for pre-eclampsia?
-
10. Should all Belgian **pregnant women which have past their due date** be monitored by specific technical examination?
- In low-risk (for adverse consequences of prolonged pregnancy) asymptomatic pregnant women who remain undelivered past 40 weeks of gestation, compared with each other or no intervention/routine clinical follow up, what are benefits and harms of:
 - Nonstress test cardiotocography (CTG)?
 - Ultrasound estimation of amniotic pool depth/volume/index?
 - Combination of the two tests above with or without other tests/assessments (i.e. full or modified biophysical profile)?
-



Questions for recommendations to update

11. What is the **optimal number of antenatal visits** to be scheduled considering adverse maternal or perinatal outcomes and women's preferences?
 - a. For a woman's first pregnancy without complications?
 - b. For subsequent uncomplicated pregnancies?

12. Should **weight and BMI** be regularly monitored in all Belgian low-risk pregnant women?

13. Should **blood pressure** be regularly monitored in all Belgian low-risk pregnant women?

14. Should **proteinuria** be detected in all Belgian low-risk pregnant women?

15. Should **fundal height measurement** be performed in all Belgian low-risk pregnant women?

16. Should the **fetal position** be detected by **an abdominal palpation** (Leopold manoeuvres) in all Belgian low-risk pregnant women?

17. Should a **fetal movements counting** be performed in all Belgian low-risk pregnant women?

18. Should a **fetal heart auscultation by Doppler** be performed in all Belgian low-risk pregnant women?

19. Should an **early ultrasound** be performed in all Belgian low-risk pregnant women?

20. What are the benefits and harms of **other schedules of ultrasound**? (between 18 and 22 weeks? after the 24th week? at 36th week ?)

21. Should **anaemia** be detected in all Belgian low-risk pregnant women?

22. Should **platelet and leukocyte count** be performed in all Belgian low-risk pregnant women?

23. Should **blood group and rhesus (RhD)** be determined in all Belgian low-risk pregnant women?

24. Should **irregular antibodies** be detected in all Belgian low-risk pregnant women?

25. Should **haemoglobin disorders** be detected in all Belgian low-risk pregnant women?

26. Should all Belgian low-risk pregnant women be screened for **hepatitis B**?

27. Should all Belgian low-risk pregnant women be screened for **hepatitis C**?

28. Should all Belgian low-risk pregnant women be screened for **HIV**?

29. Should all Belgian low-risk pregnant women be screened for **rubella**?

30. Should all Belgian low-risk pregnant women be screened for **sypilis**?

31. Should all Belgian low-risk pregnant women be screened for **herpes simplex**?

32. Should all Belgian low-risk pregnant women be screened for **varicella**?

33. Should all Belgian low-risk pregnant women be screened for **asymptomatic bacterial vaginosis**?

34. Should all Belgian low-risk pregnant women be screened for **asymptomatic bacteriuria**?



2.3.3 *List of KCE 2004 topics not retained for the KCE guideline 2015*

Seven topics included in the 2004 guideline were not retained in 2014:

- Three because they do not focus on a risk related to pregnancy: breast examination for breast cancer screening; breast examination for breastfeeding; pap-test for cervical cancer screening.
- Two because they were developed in a recent KCE report: screening for fetal chromosomal abnormalities such as Down syndrome (KCE report 222 on non invasive prenatal test for trisomy 21)⁵; screening for cystic fibrosis (KCE report 132 on neonatal screening for cystic fibrosis).⁶
- Two because they are not screening tests: nutritional supplementation and use of anti-D immunoglobulin as immunoprophylaxis to prevent sensitisation with anti-D.

2.4 Literature search

2.4.1 *Update of KCE 2004 recommendations*

The KCE standard guideline development process starts with a search for existing guidelines produced by other institutions. For the present guideline, this search was performed in October 2013 in various databases including the National Guideline Clearinghouse, the GIN database and eight other guidelines websites (see Appendix 6.1 for search strategies). The aim was to identify recent (i.e. published after 2004) high-quality guidelines on antenatal care. The search resulted in 95 guidelines, from which two potentially relevant guidelines were selected, covering similar inclusion criteria and topics, i.e. the NICE 2008 guideline and the Australian 2014 guideline.^{7, 8}

2.4.2 *Full search questions*

Each full search question was translated into in- and exclusion criteria using the P.I.C.O. (Participants–Interventions–Comparator–Outcomes) framework. The P.I.C.O for each question and the search strategy corresponding are available in Appendices 5 and 6. A combination of appropriate MeSH terms and free text words was used.

For each question, a search for systematic reviews was conducted in MEDLINE (including PreMedline) (<http://www.ncbi.nlm.nih.gov/pubmed>), Embase (<http://www.embase.com/>) and The Cochrane Library (Cochrane Database of Systematic Reviews, DARE, Central, NHS EED and HTA database) (<http://www.cochrane.org>). As a priority, evidence was planned to be sought from the most recent and high quality existing systematic reviews and health technology assessments (HTAs). A record that reported search end dates and database, and screened literature using eligibility criteria was qualified as a systematic review in the screening phase. Systematic review evidence was screened in reverse chronological order until one or more high quality reviews or those with reliable searches and screening were identified. In case of a recent high quality systematic review was available a search for subsequent primary studies (RCTs and observational studies) was performed in MEDLINE, Embase and the Cochrane Central Register of Controlled Trials with an overlap of updating searches by three months from the end search dates of the identified review.

When evidence synthesis of available systematic reviews/HTAs appeared to be inadequately sophisticated in minimising risk of bias associated with included primary evidence, but the searching and screening of literature were judged to be well conducted, we used the most recent systematic review to identify primary studies up to the review search dates. Additional bibliographic searches for identifying primary studies subsequent to review search dates with an overlap of three months were followed.

When no systematic review was available a full search for primary studies was performed in those databases with the aim to conduct a de novo synthesis. Bibliographies of included studies were checked for additional papers. Members of the guideline development group (GDG) were also consulted to identify additional relevant evidence that may have been missed by the search.

The search was limited to English, Dutch, and French languages in Medline and Embase. The search strategy is available in Appendices.

Inclusion / exclusion criteria for the study design are RCTs and observational studies (comparative only, with a sample of at least 100 pregnant women).

The process used for the selection of relevant studies is detailed in Appendix 7.



2.5 Quality appraisal and study selection

2.5.1 Update of KCE 2004 recommendations

The 2 selected guidelines were appraised with the AGREE II instrument by two researchers independently. Disagreements were resolved by consensus. The 2 guidelines selected were both assessed to be of sufficient quality (see Appendix 8.2); however, the Australian 2014 guideline was preferred because it is an update of the NICE 2008 guideline.

2.5.2 Full search questions

Two reviewers independently assessed the quality of the systematic reviews using the AMSTAR checklist (http://amstar.ca/Amstar_Checklist.php) or the 9-point modified AMSTAR checklist. Discrepancies were resolved through discussion or third party adjudication.

The quality appraisal of the primary studies was performed either by two independent researchers or primarily performed by one reviewer, with a senior reviewer providing verification. The following checklists were used:

- The Cochrane Collaboration's tool for assessing risk of bias for RCTs. The Cochrane risk of bias tool helps judge the validity of a randomised trial based on the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases.
- A generic assessment for selection and information bias, and confounding for observational studies.
- The QUADAS-2 checklist for diagnostic accuracy studies.

The tools used for the quality appraisal and the results of the quality appraisal are available in Appendices 8.1 and 8.3.

2.6 Data extraction

2.6.1 Update of KCE 2004 recommendations

If recent high-quality guidelines from other institutions are available on the topic to be updated, the KCE standard guideline development process proposes to adapt their recommendations to the local Belgian context according to a formal methodology developed by the ADAPTE group, an international group of guideline developers and researchers.⁹ This approach generally includes three major phases (www.adapte.org):

1. **Set-up Phase:** In which an outline of the necessary tasks to be completed prior to beginning the adaptation process (e.g., identifying necessary skills and resources) is prepared.
2. **Adaptation Phase:** In which guideline developers move from the selection of a topic to the identification of specific clinical questions; search for and retrieve guidelines; assess the consistency of the evidence considered, its quality, validity, content and applicability; decide how to best adapt the evidence found; and prepare a draft of the adapted guideline.
3. **Finalization Phase:** which guides guideline developers through getting feedback on the document from stakeholders who will be impacted by the guideline, consulting with the source developers of guidelines used in the adaptation process, establishing a process for review and updating of the adapted guideline and the process of creating a final document.

The evidence provided by the Australian 2014 guideline was extracted for the 24 clinical questions to be updated, encompassing the included studies, the conclusions and the level of evidence. The corresponding Australian clinical recommendations and the strength of each recommendation were also extracted.

When no evidence was provided by the Australian 2014 guideline, we used either the NICE 2008 guideline or other sources referred to by the Australian 2014 guideline (such as Royal College of Obstetricians and Gynaecologists from United Kingdom (RCOG)).



2.6.2 Full search questions

For each systematic review, the search date, publication year, included studies and main results were extracted. For primary studies, the following data were extracted: publication year, study population, study intervention, and outcomes. Data extraction was performed by at least one researcher and entered in evidence tables using standard KCE templates. All evidence tables are reported in Appendix 9.

For diagnostic test accuracy studies, the following data were extracted, either directly from the study report or calculated from other study data: components of the “2x2 table” (true positives, false positives, false negatives and true negatives) and test accuracy parameters: sensitivity, specificity, positive / negative predictive values. In cases where the outcomes were not reported, 2 by 2 tables were constructed from raw data using an pre-estimated prevalence (such as 5% for gestational diabetes in pregnant women) to allow calculation of accuracy measures.

2.7 Statistical analysis

As a rule, heterogeneity that may be explained by clinical or methodological differences between studies precluded any planned meta-analyses.

All meta-analyses were planned using DerSimonian’s and Laird’s random effects¹⁰ or a fixed effects approach. 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 instead of 0.05 was used to determine statistical significance because the chi-squared test is not very sensitive when there are a small number of studies and may be over sensitive when there are a high number of studies). Sparse data (e.g. zero, 1, or 2 event in either groups) was not meta-analysed but described narratively.

Relative risk were used for dichotomous outcomes. Mean difference / standardized mean difference / ratio of means were preferred measures of analysis for continuous outcomes, and rate ratios for count data. Peto ORs were used when the total event rate of one arm of the comparison was zero. This method performs well when events are very rare.¹¹ When event rates are less than <1% and when <5-10%, Peto Odds or Mantel-Hanzel method respectively were used without continuity correction as per previous guidance.¹²

A generic inverse variance (IV), fixed effect, option in RevMan5 was used if any studies reported solely the summary statistics and 95% confidence interval (95%CI) or standard error. Whenever modelling for confounders was reported the data are plotted according to the statistics reported in the study, which were usually unadjusted and adjusted odds ratios (OR) rather than risk ratios.

For a particular pre-specified outcome, we employed the following approach to include evidence from observational study designs:

- No evidence was available from RCTs
- Sparse evidence was available from RCTs – i.e. occasional events precluding any meaningful synthesis
- Outcome data were available from RCTs, but synthesis of observational evidence would likely yield higher confidence or quality of evidence.

Otherwise (i.e. only high risk of bias observational studies contributing data), observational evidence was not synthesized.

In case it was not possible to run a meta-analysis for a screening test (because high heterogeneity), GRADE analysis was carried out using the median study risk ratio with the corresponding 95% confidence interval. The median was used because the point estimates of the effects varied widely, even though the direction of effect of studies were all on one side of the forest plot favouring universal screening. Therefore the median was selected as the most representative overall value because it is less affected by skewed data.

In case it was not possible to run a diagnostic meta-analysis (no sufficient data), all data were plotted as coupled forest plots of sensitivity and specificity and as there were only ever one or two studies for each strata, all sensitivities and specificities with their corresponding 95%CI’s were presented in the modified GRADE tables.



2.8 Grading evidence

2.8.1 Update of KCE 2004 recommendations

For the 24 questions to be updated, no formal GRADE tables were produced.

It is important to stress that the authors of the Australian 2014 guideline did not use GRADE system to categorize the level of evidence or to assign a strength for each recommendation. Where sufficient evidence was available, this was graded according to the National Health and Medical Research Council (NHMRC) Levels of Evidence and Grades for Recommendations for Developers of Guidelines (2009) and formulated as recommendations ('A' Body of evidence can be trusted to guide practice; 'B' Body of evidence can be trusted to guide practice in most situations; 'C' Body of evidence provides some support for recommendation(s) but care should be taken in its application; 'D' Body of evidence is weak and recommendation must be applied with caution). For areas of clinical practice included in the systematic reviews but where evidence was limited or lacking, the authors developed consensus-based recommendations.

Where an overview of the original Australian recommendations was provided, the original levels of evidence (using the SIGN methodology) were also added.

2.8.2 Full search questions

For each recommendation, we provided 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 3 and Table 4). 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 (risk of bias), inconsistency, indirectness, imprecision and publication bias.

For RCTs, quality rating was initially considered to be of high level (Table 3). 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 points 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.

Observational studies were by default considered low level of evidence (Table 3 and Table 4). 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: The larger the magnitude of effect, the stronger becomes the evidence. As a rule of thumb, the following criteria were proposed by GRADE:
 - a. Large, i.e. $RR > 2$ or < 0.5 (based on consistent evidence from at least 2 studies, with no plausible confounders): upgrade 1 level;
 - b. Very large, i.e. $RR > 5$ or < 0.2 (based on direct evidence with no major threats to validity): upgrade 2 levels.
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 to downgrade the quality rating are summarized in Table 5. The specific situation of accuracy diagnostic study is described in Table 6.



Table 3 – 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 4 – 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 5 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations	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. Level of evidence was downgraded if studies were of poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large.
Indirectness	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.
Imprecision	<p>Evaluation of the imprecision of results was primarily based on <u>examination of the 95%CI</u>. 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 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low-risk intervention.</p> <p>Even 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 <u>optimal information size (OIS)</u>. If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.</p>
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

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

Quality element	Reasons for downgrading
Limitations	Risk of bias were assessed by considering the majority of the evidence. This method took into account the size of the studies, as well as the number of studies.
Inconsistency	Inconsistency was assessed by examining the paired sensitivity and specificity plots.
Indirectness	Indirectness were assessed by considering the majority of the evidence. This method took into account the size of the studies, as well as the number of studies.
Imprecision	Imprecision was assessed by considering the confidence interval around the sensitivity; regions of acceptability were defined – so that if the confidence interval lay wholly within a region the evidence was considered precise. But if the confidence interval crossed into two or three regions, the evidence was downgraded by one and two increments respectively. These regions were arbitrarily defined as 90-100%, 80-90% and below 80%.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

2.9 Formulation of recommendations

2.9.1 Update of KCE 2004 recommendations

For 24 clinical questions that need an update, a card was elaborated gathering the KCE 2004 recommendation, a summary of the literature quoted by the Australian 2014 guideline, the Australian recommendation and a proposition of a recommendation for the KCE 2015 guideline. The level of evidence underlying each recommendation comes from the original source, i.e. either the Australian 2014 guideline or, when no evidence was provided by the Australian 2014 guideline, the NICE 2008 guideline or other sources referred by the Australian 2014 guideline. Because both guidelines did not use the GRADE evaluation, we systematically reported their classification of the levels of evidence.

All GDG members were invited to mark if they agree or not with the propositions. Three ways were used:

- Three consultation rounds which contained roughly eight recommendations to be scored and commented using an online Lime survey (see an example in Appendix 13). The respondents could

answer if they did totally agree, rather agree, somewhat disagree, or totally disagree. In case of disagreement, a justification was required. In case of agreement, a strength of recommendation (weak or strong) could be added. Comments were always welcome.

- Three GDG meetings where the results of the Lime survey were presented and discussed (June 16, 2014; September 10, 2014; October 8, 2014). The consensus was used to take a final decision about the formulation and the strength of each recommendation.
- One consultation on the full recommendations by e-mail allowed an overview on the final set of recommendations.

Recommendations are marked as following:

- **[KCE 2004] indicates that the evidence presented in the Australian 2014 guideline did not argue to a change in the content of the KCE 2004 recommendation.**



- [KCE 2004, amended 2015] indicates that the recommendation has been amended depending on the evidence reported by the Australian 2014 guideline.
- [KCE 2015] indicates that the evidence has been reviewed but no major changes have been made to the previous recommendation.
- [new KCE 2015] indicates that the evidence has been reviewed and the recommendation has been updated or added.
- [KCE 2015, based on Australian 2014 guideline] indicates that a recommendation was imported from the Australian 2014 guideline. It was only used for patient centeredness and recommendations on informing pregnant women.

For each clinical question, a card gathered the corresponding data (KCE 2004 recommendation, summary of the literature quoted by the Australian 2014 guideline, Australian recommendation), the KCE 2015 proposition of recommendation, the comments of the GDG (in the Lime survey, during the meetings), the comments of the stakeholders (see Chapter 2.10.1) and the final recommendation in three languages (English, French and Dutch). These 24 documents are available in Appendix 14.

2.9.2 Full search questions

Based on the retrieved evidence, a first draft of recommendations was prepared by a small working group (researchers from KCE). This first draft was, together with the evidence tables, circulated to the guideline development group prior to the face-to-face meetings (September 10, 2014; October 8, 2014; December 10, 2014; January 12, 2015; February 10, 2015). Based on the discussion meetings a second draft of recommendations was prepared and once more circulated to the GDG for final approval. No formal consensus procedure was used.

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 or search for economic literature was conducted (because of resource constraints), although studies identified through the literature searches for the medical questions were sometimes taken into account. 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
Strong	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>)
Weak	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
Balance between desirable and undesirable effects	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
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	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
Costs (resource allocation)	The higher the costs of an intervention, i.e. the greater the resources consumed, the lower the likelihood that a strong recommendation is warranted

Sources: Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A et al. An Official ATS Statement: Grading the Quality of Evidence and Strength of Recommendations in ATS Guidelines and Recommendations. *Am J Respir Crit Care Med* 2006; 174:605–14.

Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B et al. Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines - Report From an American College of Chest Physicians Task Force. *Chest* 2006; 129:174-81.

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.¹³ 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.¹³ 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	Weak recommendation
For patients	<p>Most individuals in this situation would want the recommended course of action, and only a small proportion would not.</p> <p>Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.</p>	<p>The majority of individuals in this situation would want the suggested course of action, but many would not.</p>
For clinicians	<p>Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.</p>	<p>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.</p>
For policy makers	<p>The recommendation can be adopted as policy in most situations.</p>	<p>Policy-making will require substantial debate and involvement of various stakeholders.</p>

* 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.

The strength of each recommendation was taken into account within the wording (“Offer” for a strong and “Consider” for a weak positive recommendation; “Do not offer” for a strong or “do not offer routinely” for a weak negative recommendation.)

2.10 External review

2.10.1 Healthcare professionals (stakeholders)

The recommendations prepared by the guideline development group were circulated to relevant representatives of professional associations or other clinical experts not involved in the GDG (see Appendix 1), invited to act as external reviewers of the draft guideline. All expert referees made declarations of interest.

Overall, 14 stakeholders were involved in the evaluation of the clinical recommendations. All invited panellists received the scientific reports for all research questions and were asked to score each recommendation 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. This was discussed during a stakeholder meeting on March 25th, 2015. In Appendix 15, an overview is provided of how their



comments were taken into account. Again, no formal consensus method was used.

2.10.2 Patient representatives

To represent the pregnant women and their partners, we invited representatives of the two national public institutions that develop birth and childhood policies in Belgium to join the Guideline Development Group. They actively took part to the development of this guideline.

The Office of Birth and Childhood (Office de la Naissance et de l'Enfance, further referred to as ONE) is an independent organism under the Minister for Childhood of the Wallonia & Brussels Federation.

Kind en Gezin (Child and Family) is a Flemish agency that works actively in 'Public Health, Welfare and Family' policy area.

The activities of both institutions range from pre- and postnatal services and information resources. They are actively involved in the birth policy by supervising networks of prenatal clinics and centres and by organizing prenatal consultations in order to meet families' needs during pregnancy and at birth. They deliver a wealth of information for all pregnant women regarding pregnancy, delivery and birth, diet, etc. They ensure the follow-up of pregnancies owing their up-to-date websites as well as the delivery of booklets with check-up lists and a lot of advices for each pregnancy step.

2.11 Final 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 May 21st 2015. Second, the methodology was validated making use of the AGREE II checklist. This validation process was chaired by CEBAM on June 2nd 2015.

3 PATIENT CENTEREDNESS

Informing patients is paramount during pregnancy. Several issues deserve explanations and should be addressed during consultations such as the description of the different steps of pregnancy or explanations of harm and benefit for each test and care in order to promote an informed decision-making process.

In order to take into account the women's perspective in the present guideline, two approaches were used. One consists on wording the recommendation with a verb which opens the discussion with women. This is why *strong recommendations* are formulated with the verb "offer". Another approach aims to develop specific recommendations on this topic. Since it was not the aim of this guideline to draw a literature review on patient centeredness during pregnancy, the Australian 2014 guideline was used as a source of recommendations on this topic. These recommendations have no level of evidence and concern four issues:

- **Preparation for pregnancy, birth and parenthood:** Woman-centred care encompasses the needs of the baby, the woman's family, significant others and community, as identified and negotiated by the woman herself (AHMC 2006 in Australian 2014 guideline). Involving fathers/partners in antenatal care enables them to participate in decision-making and be informed about the care pathway and environmental factors that may influence the health of the baby during pregnancy (e.g. maternal passive smoking) and after the birth (e.g. infectious diseases such as pertussis).
- **Informed decision-making:** Women have the right to decline care or advice if they choose, or to withdraw consent at any time and have these choices respected (UNESCO 2005 in Australian 2014 guideline). It is important that the level of care provided does not alter because of this choice (FPA Health & Read 2006; Faunce 2008; NHMRC 2010 in Australian 2014 guideline).



- **Documented decisions:** Making a choice or consenting should be an ongoing process of discussion between a woman and the health professionals involved in her care. This implies that health professionals and women need to communicate and collaborate in a team approach (Kryzanasuskas 2005; NZ MOH 2008 in the Australian 2014 guideline). Consistency of information, especially if this is provided by different professionals, is very important (Jones et al. 1999; Price et al. 2005 in the Australian 2014 guideline). Documenting discussions and decisions is important and should include clear and consistent records of information provided, informed consent and level of woman's understanding of risk associated to her decision.
- **Sufficiently long first visit:** The initial antenatal visit provides the opportunity to discuss with the woman her expectations for the pregnancy. It is also a valuable opportunity to give verbal and other forms of information, support and advice about pregnancy and the transition to parenthood, and to explain to the woman the aims of the care offered during pregnancy.

Recommendations

"Consider that women and their partners should be assisted to prepare for pregnancy, birth and parenthood." [KCE 2015, based on Australian 2014 guideline]

"Offer to all women evidence-based information that can easily be understood and encourage them to participate in decisions about care. It is indeed important that women have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals." [KCE 2015, based on Australian 2014 guideline]

"Consider to document the discussions and decisions in a record easily available for different healthcare professionals." [KCE 2015, based on Australian 2014 guideline]

"Consider a longer first antenatal visit than the following visits because of the large volume of information which needs to be exchanged" [KCE 2015, based on Australian 2014 guideline]



4 CLINICAL RECOMMENDATIONS

4.1 Schedule of antenatal visits

4.1.1 Number of appointments – update

Antenatal visits is a mean of improving outcomes but it is important to determine the optimal schedule and propose it to the pregnant women.

A Cochrane systematic review (Dowswell et al. 2010 in Australian 2014 guideline) included studies conducted in high-, middle- and low-income countries, and found no strong evidence of differences on several outcomes (preterm births, low birth weight babies, induction of labour & caesarean) between groups receiving a reduced number of antenatal visits (8 visits in high-income countries and fewer than 5 visits in low-income countries) compared with standard care (13-14 visits). There was some evidence that in low- and middle-income countries perinatal mortality may be increased with reduced visits.

Concerning the patients' preferences, there is a risk of lower satisfaction if the number of visits is reduced, in both low- and high-resource settings (Dowswell et al. 2010 in Australian 2014 guideline). This implies to keep a reasonable schedule of visits (not less than 7). Economic analyses suggested a potential lower cost with reduced number of visits (Dowswell et al. 2010 in Australian 2014 guideline).

The Australian 2014 guideline recommended a schedule of 10 visits for a woman's first pregnancy without complications and 7 visits for subsequent uncomplicated pregnancies. This schedule was also recommended in the KCE 2004 guideline.

In conclusion, the content of the KCE 2004 recommendation was not changed and the strength of the recommendation was considered as strong. For more details on the process of recommendation development, see Appendix 14.1.

Recommendation	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">At the beginning of pregnancy, offer pregnant women without risk factors a program with either 10 appointments* if this is their first pregnancy or 7 appointments* if they have already given birth. [KCE 2004]	Strong	A**

* These appointments concern not exclusively gynaecologists but also midwives and general practitioners involved in the follow-up of pregnancies.

** Level of evidence from Australian 2014 guideline: A=One or more level I studies with a low risk of bias or several level II studies with low risk of bias



4.2 Clinical examination

4.2.1 Body mass index (BMI) - update

Routine measurement of women's weight and height and calculation of BMI at the first antenatal visit is continuously supported by evidence. The Australian 2014 guideline quoted 1 systematic review, 4 RCTs & 7 observational studies with control group that confirmed the risks associated with a low or a high pre-pregnancy BMI during pregnancy. A recommendation about the measurement of women's weight and height at the first antenatal visit and calculation of their BMI existed in the KCE 2004 guideline and is also proposed by the Australian 2014 guideline.

The amount of weight gained during pregnancy is a factor associated with pregnancy outcomes (Nohr et al. 2008; Viswanathan et al. 2008 in Australian 2014 guideline). However, two cohort studies, one with 94 696 women in US (DeVader et al. 2007 in Australian 2014 guideline) and one with 5 377 women in Canada (Crane et al. 2009 in Australian 2014 guideline), showed that many women do not gain the amount of weight recommended (17-18% gaining less and 43-52% gaining more than the recommended amount). The KCE 2004 guideline recommended to follow the weight evolution at each consultation. The Australian 2014 guideline suggested (practice point) to repeat weighing according to circumstances that are likely to influence clinical management.

According to our GDG, the arguments pro a repeated weight measurement (diagnosis of other cause of weight gain as oedema, effective educational support, cheap examination, usual in practice) outweigh the arguments contra (women feeling guilty and stressed). However, a regular measurement would be enough instead of "at each consultation" and information has to be provided to women concerning their weight gain expected, as proposed by the Australian 2014 guideline.

In conclusion, the KCE 2004 recommendations on weight measurement remained and an Australian 2014 recommendation on advice to provide was added. For more details on the process of recommendation development, see Appendix 14.2.

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> Offer to weigh each pregnant woman and calculate her BMI starting from the 1st consultation (and/or at a preconception consultation). [KCE 2004] 	Strong	B*
<ul style="list-style-type: none"> Offer to regularly monitor each pregnant woman's weight change. [KCE 2004] 	Strong	NA (PP)**
<ul style="list-style-type: none"> Advise each pregnant woman on the appropriate weight gain in relation to her BMI. [KCE 2015, based on Australian 2014 guideline] 	Strong	A***

* Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias ;
 PP=practice point ; *A=One or more level I studies with a low risk of bias or several level II studies with low risk of bias



4.2.2 Blood pressure - update

Hypertension during pregnancy is associated with higher perinatal mortality and morbidity such as preterm labour, low birth weight, placental abruption, superimposed pre-eclampsia and gestational diabetes (KCE 2004, Australian 2014 guideline). The Australian 2014 guideline recommended to measure blood pressure at the first antenatal visit and routinely afterwards to identify new onset hypertension. The KCE 2004 guideline recommended to measure it at each antenatal visit (and during the preconception consultation).

According to the Australian 2014 guideline, there is minimal recent low level evidence on how and when to measure the blood pressures during pregnancy. The GDG underlined that measurement of the blood pressure is cheap and usual for Belgian women.

In conclusion, the KCE 2004 recommendation on blood pressure remained unchanged. For more details on the process of recommendation development, see Appendix 14.3.

Recommendation	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">Offer to measure each pregnant woman's blood pressure at every visit during pregnancy, and during the preconception consultation. A diastolic blood pressure ≥ 90 mmHg is considered as a risk factor for complications such as pre-eclampsia. [KCE 2004]	Strong	NA*

* Level of evidence from Australian 2014 guideline =B only for blood pressure measurement at the first antenatal visit and consensus-based for the measurement afterwards.



4.2.3 Proteinuria - update

The Australian 2014 guideline highlighted the absence of quality evidence on the role of routine testing for proteinuria during pregnancy and formulated a consensus-based recommendation that routinely offers to test for proteinuria at the first antenatal visit, regardless of the stage of pregnancy. After the first antenatal visit, repeat testing for proteinuria is proposed for women with risk factors for, or clinical indications of, pre-eclampsia, in particular raised blood pressure. The Australian 2014 guideline also mentioned that urinary dipstick is the least accurate method to detect true proteinuria.

The GDG proposed the following schedule:

- Measurement at the first antenatal consultation for identification and treatment of kidney disease or urinary tract infection;
- No systematic measurement between the first consultation and 20 weeks;
- After 20 weeks, proteinuria measurement for pre-eclampsia screening.

Contrary to the Australian recommendation, the Belgian GDG agreed to offer proteinuria testing after 20 weeks to all women and not only “if a woman has risk factors for, or clinical indications of, pre-eclampsia”. Arguments to justify this position were that proteinuria is sometimes the first sign of pre-eclampsia and an early detection of pre-eclampsia is considered as important. Moreover, dipstick is broadly used in Belgium and this investigation is not expensive.

The GDG underlined the problem of accuracy of proteinuria testing by dipstick with high risk of false positive tests but the negative predictive value of this test is high and allows a triage. The GDG confirmed the need of an analysis of a 12-hour or 24-hour urine test in case of positive dipstick result as a gold standard.

In practice, it appears that health practitioners use dipsticks combining proteinuria, nitrite and glucose measurements. While false positive proteinuria is frequent with dipstick in case of urinary infection, the nitrite measurement can help to make a triage between likely urinary infection or not. The GDG proposed to mention this possible combination test within the recommendation.

In conclusion, the KCE 2004 recommendation was slightly amended to specify the schedule of proteinuria testing and the possible combination of proteins and nitrites measurement with dipstick. For more details on the process of recommendation development, see Appendix 14.4.

Recommendation	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> • Consider to assess proteinuria in pregnant women during the first consultation so as to identify kidney disease and urinary tract problems. After 20 weeks of pregnancy, consider to search for the presence of proteinuria at each visit in combination with taking blood pressure measurements in order to screen for pre-eclampsia. In Belgium, test strips (dipsticks) are often able to measure several elements in addition to proteins, such as nitrites. [KCE 2004, amended] 	Weak	NA*

* Level of evidence from Australian 2014 guideline = Consensus-based recommendation in absence of evidence for the first part and C for the second one but slightly different from the KCE recommendation



4.2.4 Fundal height - update

Monitoring fetal growth is important, particularly in women with high or low pre-pregnancy BMI (Robert Peter et al. 2012; HAPO 2010; Dawes & Grudzinskas 1991; Panaretto et al. 2006 in Australian 2014 guideline).

Based on two systematic reviews and one observational study, the Australian 2014 guideline mentioned that there is limited evidence on methods of intrauterine growth assessment (Bais et al. 2004; Neilson 2009; Robert Peter et al. 2012). It proposed a consensus-based recommendation offering women assessment of fetal growth by abdominal palpation and/or symphysis-fundal height measurement at each antenatal visit. In 2004, KCE had also formulated a consensus based recommendation offering a fundal height measurement at each visit from the 24th week of pregnancy.

According to the GDG, manual examination could miss some cases of intra-uterine growth restriction or large for gestational age babies but there is no evidence that ultrasound scan during each visit detects more growth problems than clinical examination. Practical reasons (access and cost of ultrasound scan) are in favour of clinical examination.

In conclusion, the KCE 2004 recommendation on fundal height measurement by abdominal palpation remained unchanged. For more details on the process of recommendation development, see Appendix 14.5.

Recommendation	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">From the 24th week of pregnancy onwards, offer to determine the height of the uterine fundus in each pregnant woman during each visit in order to detect abnormal uterine growth. [KCE 2004]	Strong	NA (CBR)*

* Level of evidence from Australian 2014 guideline: CBR=Consensus based recommendation because insufficient evidence to support recommendation



4.2.5 Fetal position - update

Identifying atypical fetal presentation (e.g. breech) is useful in preparation of the delivery.

According to the Australian 2014 guideline, no recent evidence refutes previous recommendation and it remains recommended to assess the fetal presentation by abdominal palpation at 36 weeks or later, when presentation is likely to influence the plans for birth. Before 36 weeks, this examination is not always accurate and could be uncomfortable (Australian 2014 guideline).

In 2004, KCE guideline also recommended abdominal palpation from the 36th week to determine fetal position.

The GDG underlined that abdominal palpation is an opportunity to build a patient-caregiver relationship and to enhance communication with the pregnant women. The Leopold manoeuvres are well known and broadly used in Belgium. It is a cheaper examination compared to ultrasound scan which should be used in second intention, for confirming an anomaly. In case of breech position, an attempt of “external cephalic version” can be proposed.

In conclusion, the KCE 2004 recommendation on assessment of fetal position by abdominal palpation remained unchanged. For more details on the process of recommendation development, see Appendix 14.6.

Recommendation	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> Starting from the 36th week or later, offer to each pregnant woman to determine the fetal position (using Leopold’s maneuvers). Starting from the 36th week, malposition of the fetus can influence the management at the end of pregnancy and during childbirth. When a positional anomaly is suspected, consider confirming this by ultrasound examination. [KCE 2004] 	Strong	C*

* Level of evidence from Australian 2014 guideline: C=One or two level III studies with a low risk of bias or level I or II studies with a moderate risk of bias



4.2.6 Fetal movements - update

Maternal perception of fetal movements is considered as a mean of monitoring fetal wellbeing (Australian 2014 guideline, KCE 2004 guideline). Most pregnant women become aware of fetal activity between 18 and 20 weeks of gestation (RCOG 2011 Australian 2014 guideline). Due to a lack of epidemiological studies on fetal activity patterns and maternal perception of fetal activity in normal pregnancies, it is not clear what constitutes a 'normal' pattern of fetal movement (RCOG 2011 in Australian 2014 guideline). There is considerable variation in fetal movements and estimates cover a wide range (eg from 4–100 movements per hour) (Mangesi & Hofmeyr 2007 in Australian 2014 guideline).

Decreased fetal movement indicates that even women with low-risk pregnancies may be at greater risk of adverse outcomes, including intrauterine growth restriction, fetal death and preterm birth (ANZSA 2010 in Australian 2014 guideline). However, the absence of perceived fetal movements does not necessarily indicate fetal compromise or death (Mangesi & Hofmeyr 2007). A systematic review of single studies (Heazell & Froen 2008) quoted by the Australian guideline 2014 concluded that there is no evidence that any absolute definition of reduced fetal movements is more valuable than maternal perception of reduced fetal movements in detecting intrauterine fetal death or fetal compromise. For that reason, guidelines from Australia (ANZSA 2010) and the United Kingdom (RCOG 2011) recommend that women contact their health professional or maternity unit if they are concerned about a reduction in or cessation of fetal movements after 28 weeks of gestation. The KCE 2004 guideline had the same recommendation.

A more recent RCT (Saastad et al. 2011 in Australian 2014 guideline) compared formal fetal movement counting in a group of women with no specific advice regarding fetal movements and did not show statistical difference for fetal morbidity (single difference for Apgar score<4 after 1 minute in the counting group but based on very low number of events).

In conclusion, the KCE 2004 recommendation remained (the first part regarding the lack of evidence for formal fetal movement count was removed). For more details on the process of recommendation development, see Appendix 14.7.

Recommendation	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">Advise each pregnant woman to be aware of the usual pattern of movements of her baby and to contact a health care professional if she has any concerns about decreased or absent movements. [KCE 2004]	Strong	NA (CBR)*

* Level of evidence from Australian 2014 guideline: CBR=Consensus based recommendation because insufficient evidence to support recommendation



4.3 Technical examination

4.3.1 Fetal heart auscultation - update

Detection of the fetal heart beat is a mean of confirmation that the baby is alive. However, this does not appear to have clinical or predictive value (KCE 2004, Australian 2014 guideline). According to the Australian 2014 guideline, the sensitivity of Doppler auscultation for the detection of the fetal heart reaches 80% at 12 weeks+1 and 90% after 13 weeks but before this time, it may be unsuccessful and can be associated with useless investigations (e.g. ultrasound) and maternal anxiety (Rowland et al. 2011 in Australian 2014 guideline). With the Pinard stethoscope, it is unlikely that the fetal heart will be audible before 28 weeks (Wickham 2002 in Australian 2014 guideline).

The Australian 2014 guideline proposed a consensus-based recommendation which suggested that if auscultation of the fetal heart rate is performed, a Doppler has to be used from 12 weeks and a Pinard stethoscope from 28 weeks. In 2004, the KCE also proposed a consensus-based recommendation offering to perform a doptone from 12 weeks. According to the GDG, the term “doptone” used in 2004 should be replaced by Doppler auscultation. It’s clearer and it is important to specify the mean of auscultation because there is a risk that ultrasound is used instead.

The GDG was aware that the evidence of the usefulness of Doppler auscultation is poor. However, the aim of the fetal cardiac rhythm auscultation is mainly reassurance that the baby is alive. The GDG agreed with the Australian 2014 guideline affirmation: “Although there is no evidence on the psychological benefits of auscultation for the mother, it may be enjoyable and reduce anxiety”.

In conclusion, the KCE 2004 recommendation remained but with a minor change of terminology. For more details on the process of recommendation development, see Appendix 14.8.

Recommendation	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> Starting from 12 weeks of pregnancy, consider to detect the fetal cardiac rhythm via Doppler auscultation at each visit. This exam is used to confirm that the fetus is alive. [KCE 2004, amended] 	Weak	NA (CBR)*

* Level of evidence from Australian 2014 guideline: CBR=Consensus based recommendation because insufficient evidence to support recommendation



4.3.2 *Ultrasound scan during the first trimester - update*

A good knowledge of gestational age can decrease the number of inductions (for false postdate) and improve the screening for fetal chromosomal abnormalities such as Down syndrome (KCE 2004 guideline, Australian 2014 guideline).

The Australian 2014 guideline reported a review by the NICE 2008 guideline on accuracy and effectiveness of screening methods for gestational age. Studies included a Cochrane review, four RCTs and a number of observational studies. It was found that ultrasound is more accurate in predicting gestational age than last menstrual period (LMP); crown–rump length measurement should be used in the first trimester and head circumference measurement in the second trimester. Subsequent studies of lower level of evidence did not refute these findings. The Australian 2014 guideline also quoted a recent Cochrane review (Whitworth et al. 2010) that compared selective versus routine use of ultrasound (US) in pregnancy. This review showed that ultrasound improves the early detection of multiple pregnancies.

Concerning the timing of assessment, the Australian 2014 guideline identified one prospective cohort study (n=8 313) (Verberg et al. 2008) which found that the prediction of birth date is more accurate when the ultrasound assessment is performed earlier in pregnancy (preferably between 10 and 12 weeks). After 24 weeks, it appeared that a reliable LMP provides better results.

The Australian 2014 guideline recommended to “offer pregnant women who are unsure of their conception date an ultrasound scan between 8 weeks 0 day and 13 weeks 6 days to determine gestational age, detect multiple pregnancies and accurately time fetal anomaly screening.” One practice point specified that “the timeframe for ultrasound assessment of gestational age overlaps with that for assessment of nuchal translucency thickness as part of screening for fetal chromosomal abnormalities (11 weeks to 13 weeks 6 days), which may enable some women to have both tests in a single scan. This should only occur if women have been provided with an explanation of both tests and have given their consent to them both.” There was also a practice point on the need of specific training for professionals performing this examination.

In 2004, the KCE guideline recommended to offer an early ultrasound in order to determine the gestational age and to detect multiple pregnancies.

The GDG mentioned that the aim of the first ultrasound is broader and allows also to exclude extra-uterine pregnancy for example. The GDG agreed with the Australian guideline that the assessment of gestational age and the assessment of nuchal translucency thickness should be linked if possible. The best timing for the first US, i.e. 11 weeks to 13 weeks 6 days, should be specified in the 2015 recommendation.

The question about a specific training needed for health professionals who perform US is complex in Belgium, notably because there is no officially organized specific training and certification for obstetric US at present. In the KCE report about NIPT⁵ an audit system was suggested to assure a quality in the nuchal translucency measurement, since results of Down screening in Belgium are currently below international standards. But the GDG wondered what would be the impact of a recommendation underlining the need of specific training if no official acknowledgement of this training exists. Thus, this question is considered as out of scope for clinical recommendations.

In conclusion, the KCE 2004 recommendation on ultrasound during the first trimester remained with further specification of preferred gestational age. For more details on the process of recommendation development, see Appendix 14.9.



Recommendation	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> Offer to each pregnant woman to perform an ultrasound, between 11 and 13 weeks 6 days*, notably to be able to determine the <u>gestational age</u> and to detect <u>multiple pregnancies</u>. Accurate knowledge of the gestational age improves, for example, the efficiency of screening tests for Down syndrome and could decrease the number of inductions due to an incorrect term assessment. [KCE 2004, slightly amended] 	Strong	B**

* It is recommended to provide to the pregnant woman and her partner during a previous consultation clear information on possible screening tests for Down syndrome and to allow enough time for informed consent.

** Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias

4.3.3 Ultrasound scan during the second trimester - update

Ultrasound screening for structural abnormalities could reduce perinatal mortality (if parents choose to terminate the pregnancy in case of abnormal results). The Australian 2014 guideline quoted several studies on the use of US during the second trimester to detect anomalies of the heart (Perri et al. 2005; Del Bianco et al. 2006; Westin et al. 2006; Fadda et al. 2009), renal tract (Cho et al. 2005), umbilical artery (Cristina et al. 2005), neural tube defects (Norem et al. 2005) and anomalies resulting from exposure to alcohol (Kfir et al. 2009). Sensitivity of US in detecting structural abnormalities increases after 18 weeks gestation and is considered generally higher in the second than in the first trimester (Australian 2014 guideline). Second trimester ultrasound is also effective for identifying placental location (Cargill et al. 2009), overlap of the cervical os (Robinson et al. 2012), placental length (which may assist in identifying risk of having a small-for-gestational age baby) (McGinty et al. 2012) and placenta praevia (Lal et al. 2012).

The Australian 2014 guideline recommended to offer an ultrasound screening to assess fetal development and anatomy between 18 and 20 weeks of gestation while the KCE 2004 guideline recommended to offer this US between 18 and 22 weeks. However, the Australian 2014 guideline added a practice point which specifies that “Timing of the ultrasound will be guided by the individual situation (e.g. for women who are obese, visualisation may improve with gestational age).”

The GDG mentioned that in some countries, 20 weeks is the deadline for termination. This appeared to be not so strict in Belgium. Thus, the GDG proposed to keep the previous KCE timing.

In conclusion, the KCE 2004 recommendation on ultrasound during the second trimester remained unchanged. For more details on the process of recommendation development, see Appendix 14.10.

Recommendation	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> Offer to perform an ultrasound, between the 18th and the 22nd week, on each pregnant woman to detect <u>structural abnormalities</u>. [KCE 2004] 	Strong	B*

* Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias



4.3.4 *Ultrasound scan during the third trimester - update*

The Australian 2014 guideline mentioned that there is no benefit from repeated ultrasounds during pregnancy except if there is clinical indication. It quoted the potential anxiety for the pregnant women, the lack of availability, the cost and the inconvenience of the examination. A practice point was formulated as such: “repeated ultrasound assessment may be appropriate for specific indications but should not be used for routine monitoring.”

In 2004, the KCE guideline mentioned there was no sufficient evidence to routinely offer ultrasounds after 24 weeks. However there was also one consensus-based recommendation concerning ultrasound at 36 weeks in case of doubt on fetal position and another recommendation for ultrasound at 36 weeks in case of placenta praevia with overlap of cervical os.

The GDG underlined the lack of evidence about the effectiveness of more than 2 ultrasounds during a pregnancy without risk factor or complication. However, despite the lack of direct evidence of its utility, the GDG argued to perform a universal third US because:

- The detection of breech position by palpation only is not accurate, mainly if the pregnant woman is obese.
- The third trimester US is useful not only for detection of fetal position and placenta praevia but also for identification of intrauterine growth restriction (IUGR) and macrosomia as showed in observational studies. Unrecognized IUGR is the most frequent cause of perinatal death in Western countries.
- From a patient's point of view, the third trimester US is usual, reimbursed and expected because it can often reassure the pregnant woman about the normal course of her pregnancy.

In conclusion, the three KCE 2004 recommendations on ultrasounds during the third trimester were gathered in one single weak recommendation in favour of this examination. For more details on the process of recommendation development, see Appendix 14.10.

Recommendation	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">• During the 3rd trimester, consider performing an ultrasound so as to determine the fetal position, to assess fetal growth and to re-assess placental position if indicated by the second trimester ultrasound. [KCE 2004, amended]	Weak	NA



4.4 Haematological assessment

4.4.1 Anaemia - update

During pregnancy, iron deficiency is the most common cause of anaemia (KCE 2004, Australian 2014). The effect of severe iron-deficiency anaemia (haemoglobin concentration <7 g/dl) is known (cardiac failure and less tolerance of blood loss associated with birth) but the impact of less severe anaemia on fetal outcomes (such as birth weight) is unclear (KCE 2004).

No recent evidence was identified by the Australian 2014 guideline concerning screening for anaemia during pregnancy. Based on consensus, the guideline recommended to offer routine testing for haemoglobin concentration early in pregnancy and at 28 weeks gestation. It is also proposed to repeat screening for anaemia at 36 weeks in certain circumstances (symptoms, risk factors for anaemia or area of high prevalence). The KCE 2004 guideline recommended a screening at the start of pregnancy and a second examination at the beginning of the third trimester for the delivery and postpartum care.

As haemoglobin concentration is not sensitive enough to diagnose iron-deficiency anaemia (KCE 2004, Australian 2014), the Australian 2014 guideline recommended additional tests and suggested to measure ferritin at the first antenatal visit in areas where prevalence of iron-deficiency anaemia is high. The GDG mentioned that in Belgium, MCV, MCH and MCHC are automatically measured with haemoglobin (for the same cost).

In case of abnormal results, a measurement of serum ferritin can be requested by the physician afterwards in the same blood sample despite it implies extra cost. Moreover, if a woman has known risk factors for anaemia, ferritin measurement is done systematically.

In the KCE 2004 guideline, a platelet and leukocyte counts were suggested by certain experts in order to detect haematological disorders such as thrombocytopenia. In Belgium, these counts are automatically done with haemoglobin concentration (and for the same cost) and it appears that some anaesthetists require this test before epidural analgesia despite it is not explained nor recommended in recent Belgian guidelines for analgesia.

No evidence was quoted on this topic neither by the Australian 2014 guideline nor by the NICE 2008 guideline.

The GDG proposed to erase the part of the sentence on expert opinion and replace it by an additional information about the usual practice.

In conclusion, the KCE 2004 recommendation on anaemia screening remained and the sentence on thrombocytopenia was slightly amended. For more details on the process of recommendation development, see Appendices 14.11 and 14.12.

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> Offer to test each pregnant woman for anaemia in early pregnancy. In addition to the haemoglobin level, it is also useful to measure the MCV, MCH and MCHC levels. A second examination at the beginning of the 3rd trimester may be indicated ahead of childbirth. [KCE 2004] 	Strong	NA (CBR)*
<ul style="list-style-type: none"> There is no evidence that platelet and leukocyte counts are useful during pregnancy. However, in Belgium, this test is often routinely performed in the laboratory at the time of anaemia detection. [KCE 2004, amended] 	NA	NA

* Level of evidence from Australian 2014 guideline: CBR= Consensus based recommendation because insufficient evidence to support recommendation



4.4.2 Blood group, rhesus and atypical red cell antibodies - update

The Australian 2014 guideline underlined the importance of identifying blood group and rhesus D status in order to prevent haemolytic disease of the newborn. However, the 2008 NICE recommendation was quoted as such and no new evidence was searched by the Australian guideline authors. The NICE recommendation offered testing for blood group, rhesus D status and atypical red cell antibodies in early pregnancy. The KCE 2004 guideline recommendation was consistent with this content.

In conclusion, the KCE 2004 recommendation on blood group, rhesus and atypical red cell antibodies determination remained unchanged. For more details on the process of recommendation development, see Appendix 14.13.

Recommendation	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">Offer to determine in early pregnancy each pregnant woman's blood group and rhesus (Rh) factor if they are unknown and to screen for atypical red cell antibodies. [KCE 2004]	Strong	B*

* Level of evidence from NICE 2008 guideline: B= recommendation directly based on level II evidence or extrapolated recommendation from level I evidence

4.4.3 Haemoglobin disorders - update

The most frequent haemoglobin disorders are sickle cell disease and beta-thalassemia. Sickle cell disease causes anaemia and increases the susceptibility to infections and infarction in different organs (including brain). Beta-thalassemia causes severe anaemia from childhood which, if not treated, can be fatal within 10 years (KCE 2004). Prevalence of these diseases differs depending on ethnic origin.

The aim of preconception / prenatal detection of sickle cell disease and thalassemia is to identify women with these disorders in order to enable them to make an informed decision before or at the beginning of the pregnancy on the basis of genetic counselling. No treatment exists, the only possible option is early termination of pregnancy.

The Australian 2014 guideline quoted a paucity of literature on this topic and focused mainly on the kind of tests (screening using MCV, MCH or haemoglobin electrophoresis). It formulated a consensus-based recommendation which routinely offers screening for haemoglobin disorders by full blood count as early as possible in pregnancy. It also considered offering ferritin testing and haemoglobin electrophoresis as part of initial screening to women from high-risk population groups (practice point). The KCE 2004 guideline recommended to offer a selective screening based on familial origin.



In agreement with the Australian guideline, given the lack of evidence regarding the use of electrophoresis in all women, the GDG decided to keep the 2004 recommendation unchanged: ferritin and electrophoresis should only be added to the initial screening based on MCH and MCV (see paragraph 4.4.1) in women at high risk. A disadvantage is that specific history taking, including obtaining place of birth of parents, grandparents and great-grandparents, is time-consuming and can be very challenging. The definition of high risk women is based on the Australian 2014 guideline and on the Belgian Hematological Society (BHS) guideline (http://www.redcellnet.be/guidelines/depistage_prenatal_FR.pdf).

The following women are considered at high risk:

- Women who have a family history of anaemia, thalassaemia or other abnormal haemoglobin variant; and/or
- Women who originate from areas other than North Europe (Southern Europe, Middle East, Asia, Africa, Pacific Islands, New Zealand (Maori), South America and some northern Western Australian);
- Women with clinical symptoms suggesting a haemoglobin disorder (such as recurrent acute pain syndromes or increased susceptibility to infections);
- Women with abnormal low results of MCV or MCH.

In conclusion, the KCE 2004 recommendation on haemoglobin disorders remained unchanged. For more details on the process of recommendation development, see Appendix 14.14.

Recommendation	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> • Do not routinely offer to each pregnant woman screening for haemoglobin disorders based on haemoglobin electrophoresis. Offer selective screening based on risk factors. [KCE 2004] 	Weak	NA (CBR)*

* Level of evidence from Australian 2014 guideline: CBR=Consensus based recommendation because insufficient evidence to support recommendation



4.5 Screening tests for infections

4.5.1 CMV – full search

4.5.1.1 Background

Cytomegalovirus (CMV) infections are globally widespread. According to a study carried out in Brussels¹⁴, from 1996 until 2007, the seroprevalence for CMV in pregnant women was 60.8% which is similar to other countries (such as 53.1% in Paris).¹⁵

Between 0.15% and 2% of pregnant women go through a primo-infection during pregnancy.¹⁶ In 20 to 40%, the fetus will also get infected, making CMV the most frequent cause of congenital infection in developed countries. Women who had CMV infection before their pregnancy are not protected at 100% and can suffer from reactivation. In these cases, the risk for transplacental transmission is rare, between 0.2–2.2%.¹⁷

Symptoms in the fetus and neonate vary from asymptomatic to severe morbidity, mainly neurological. At birth, 10 to 15% of infected children have symptoms, such as low birth weight, microcephaly, splenomegaly, hepatomegaly, jaundice, thrombocytopenia, severe eye problems and deafness. The risk of any sequelae (such as hearing loss, psychomotor retardation, visual impairment and expressive language delays) in infants with symptomatic congenital CMV at birth is 90%.^{17, 18} If asymptomatic at birth, approximately 5 to 15% of children will nevertheless develop neurosensory problems, mostly hearing problems but also chorioretinitis and developmental impairment.

A screening program for congenital CMV infections would thus have to identify women who go through a primary or secondary CMV infection during pregnancy but also have to diagnose transversal transmission and predict which fetuses will be affected and have (severe) sequelae of the intra-uterine infection. The diagnosis of primary CMV infection in pregnant women is based on serological tests with detection of specific type G (IgG) and type M (IgM) immunoglobulins but several steps are needed to identify the timing of primary infection (before or after pregnancy) in cases with positive IgM. In case maternal infection is confirmed, amniocentesis and imaging (ultrasound, MRI) are performed to investigate if the infection was vertically transmitted and whether or not the fetus is (severely) affected. For each

step, all possible benefits and risks, including false positive tests and side effects of tests and treatments, need to be taken into consideration. A pathway of these steps is available in Appendix 4.

Some interventions such as antiviral therapies (e.g; valacyclovir) and intravenous hyperimmune globulin have been suggested to reduce fetal infection and fetal morbidity, but their efficacy and safety remain insufficiently proven. Current approach is mainly based on the identification of severely affected fetuses and proposing termination of pregnancy.

In this context, as young children who shed high numbers of viruses in saliva and urine are a frequent source of infection, several non-pharmacological measures are proposed in order to prevent CMV infection during pregnancy (e.g. maternal education on hand hygiene after contact with small children).

To investigate if screening for maternal CMV infection during pregnancy may be useful, we reviewed the evidence to answer the following questions:

- What are the benefits and harms of **CMV screening** in all healthy pregnant women, compared with no routine screening (direct evidence)?
- What are the benefits and harms of **lifestyle advice** to prevent infection with cytomegalovirus during pregnancy (indirect evidence)?

For detailed research questions in the PICO format, we refer to Appendix 5.

A single search strategy was performed for both questions (see Appendix 6). A total of 1 428 records were identified, and after de-duplicating, 1 023 records formed the first screening set. A total of 92 records were screened on full text. A description of the study selection (including Prisma flowchart) is available in Appendix 7.

4.5.1.2 Benefits-harms of universal screening for CMV infection in pregnant women - results

Among the 92 records screened on full text, no systematic reviews, randomized controlled trials or observational studies were identified that investigated the effects of screening vs. no screening for CMV infection.



Conclusions

- No evidence was identified concerning the benefit-harm of **universal CMV screening** during pregnancy.

The GDG and stakeholders underlined that CMV infection during pregnancy is a frequent problem in Belgium (that can lead to severe neurological complications and mental disability).

To take a decision about the management of a pregnant woman, we need clear results (positive or negative) after the first screening step (IgG and IgM measurements in the maternal serum). However, in a large proportion of cases, results remain in a 'grey zone' and need further serological tests for clarification. Furthermore, congenital infection is possible even if a pregnant woman is immune, so there is a risk of false reassurance.

If maternal seroconversion is confirmed, further amniocentesis is required to confirm fetal transmission, and this procedure induces risks, possibly leading to complications and termination of pregnancy.

There is a risk of a cascade of additional procedures that have high psychological, ethical and economic consequences. Moreover as there is no established preventive action to avoid intra-uterine transmission or therapeutic intervention for intra-uterine infections, one option in case of suspicion of severe fetal infection is termination of pregnancy. But infected fetus is not affected fetus (infected fetus can have no lesion or only minor trouble) and the decision has to be taken in a context of uncertainties. Anxiety and distress of CMV screening and decisions-making are not negligible.

Nevertheless, a lot of issues were raised during the meeting with the stakeholders indicating that in routine practice, a lot of health care practitioners are convinced that such a screening is essential at least during the first trimester of the pregnancy. Some of them proposed to repeat this procedure each month. A change in screening practices will be really difficult to implement. Moreover patients would possibly prefer to know and prevent neonatal morbidity. A French study¹⁵ was quoted during the last stakeholders meeting on March 2015 because it showed that if clear information on CMV infection during pregnancy is given, patients frequently agree to undergo screening.

In the KCE 2004 guideline, a one off screening before or at the beginning of pregnancy was suggested if it can encourage (non-immune) women to take preventive measures or if it can reassure (at least partially) those who are immunized. However, caregivers should be aware of the undesirable situation that these prenatal tests may be performed routinely and they should make sure that sufficient information is provided about the possible consequences before testing.

4.5.1.3 Benefits-harms of lifestyle advice regarding CMV infection during pregnancy - results

Among the 92 records screened on full text, no systematic review investigated the effectiveness of advice on cytomegalovirus (including educational programmes) compared to general advice (not including specific systematic details on cytomegalovirus). One cluster randomised controlled trial was identified.¹⁹

The RCT included 166 women who had a child at one of the 124 childcare centres involved. This study comprised an indirect population as 15.7% of participants were not pregnant at any time during enrolment, and there is no information provided about what stage of pregnancy the remaining 84.3% of women were in during their enrolment. This study investigated lifestyle advice in combination with adherence measures (home visits) compared to no advice (nor any adherence measures). Lifestyle advice for the intervention group included information about the potential complications of CMV, detailed written and oral instructions for behaviour recommendations and an educational video demonstrating techniques to avoid acquisition of CMV. Protective behaviour included frequent hand washing (i.e. after exposure to a child's bodily fluids, handling dirty laundry, touching the child's toys or bathing the child) and wearing protective gloves. Behaviour to avoid included intimate contact with a child (i.e. kissing on the mouth), sleeping together, and sharing towels, food and drink. In comparison the control group received only basic information about CMV (no details provided by authors on what this was). The only studied outcome was not an important outcome and concerned the maternal seroconversion rate. For the quality appraisal, evidence tables, GRADE profiles and the single forest plot, we refer to Appendices 8, 9, 10 and 11.



Maternal seroconversion

- This study showed no difference in seroconversion rates between women who received an intervention combining lifestyle advice and adherence measures compared to the control group who received no lifestyle advice or adherence measures (7.8% seroconverted in both groups; 9/115 in intervention group and 4/51 in control group).
- The authors did not report any information regarding whether women in the intervention group felt any increased anxiety or stress in relation to the information they received. Neither did they report on the women's views on the feasibility of incorporating the behaviour recommendations into their daily routine.
- This evidence is of very low quality. This is due to limitations in allocation concealment and incomplete outcome reporting, an indirect population, and very high imprecision around the effect estimate which means we have considerable lack of confidence in the results.

Conclusions

- Based on the limited available, very low quality evidence no clear conclusion can be drawn on whether or not giving pregnant women **CMV-specific life-style advice** is effective in lowering the rate of maternal cytomegalovirus infections. There was no evidence identified that focused on the pregnancy-, fetal, neonatal- or maternal-specific adverse outcomes listed in the review protocol.

The GDG underlined that information on CMV and lifestyle advice are easy to explain and can be useful for other viral infections. The training material is not expensive. As neonatal CMV infection can have severe consequences, the GDG suggested to inform pregnant women on the possible route of infection and how simple measures may reduce risk.

4.5.1.4 Recommendation for CMV infection

Based on the retrieved evidence and the discussion with GDG and stakeholders, we developed two recommendations concerning the CMV infection during pregnancy. The considerations that lead to the recommendations are summarized below.



Other considerations

Factor	Comment
<p>Balance between clinical benefits and harms</p>	<p>There are no comparative studies in the scientific literature that compare using a screening program for CMV infections during pregnancy versus no screening. The final recommendations are thus based on indirect considerations.</p> <p>Proposed screening programs aim to prevent mother-to-child transmission and/or to reduce the consequences for the neonate. The detection of a maternal primo-infection through serological tests is usually followed by amniocentesis and imaging later during pregnancy to identify the cases with transplacental infection and to evaluate which babies would be severely affected. If severe anomalies are detected, the possibility of termination of pregnancy can be offered but so far, no less invasive preventative or therapeutic measures have been established.</p> <p>The possibility of terminating pregnancy when (high risk of) severe morbidity is diagnosed, must be weighed against the harm that is caused by performing screening for CMV infections in normal pregnancies. A large proportion of serology results are unclear and need confirmation and/or further investigations and follow-up, causing unwanted anxiety and stress. Amniocentesis is associated with infrequent but possibly serious side effects such as amniotic leak and even miscarriage. Diagnostic accuracy of ultrasound and MRI to predict neonatal morbidity is limited and diagnosis of severe lesions may occur often only late in pregnancy, at a time termination of pregnancy may be complicated and difficult to accept.</p> <p>According to the GDG, the overall benefit-risk balance does not justify the implementation of generalized screening for CMV infections in low-risk pregnancies.</p> <p>Nevertheless, CMV screening is often performed in Belgium in view of occupational health regulations and because health professionals prefer to offer the possibility of interrupting pregnancy in case of serious fetal impact of the infection. In case serological tests for CMV infections are performed, pregnant women and their partners should be informed in detail about all the possible consequences and asked for their consent.</p> <p>As the debate continues in Belgium, considering the implementation of a universal screening protocol is only possible when valuable epidemiological data become available on the results of screening, diagnostic accuracy of serological tests, value of amniocentesis and imaging in order to evaluate the benefits and harms appropriately, both on the short and long-term. From a society's point of view, these data are also mandatory to balance the need for congenital CMV screening against measures to reduce other important causes of perinatal handicap, such as prematurity.</p> <p>There are no proven measures for primary prevention of CMV infection during pregnancy. The very limited evidence available did not show a significant reduction in seroconversion rate with lifestyle advice, but the study has serious methodological flaws. As neonatal CMV infection can have severe consequences, the GDG suggests to inform pregnant women on the possible route of infection and how simple measures may reduce risk. These preventive measures are considered very important as long as therapeutic options are very limited. After discussion with the stakeholders, the balance benefit-risk of these lifestyle advice was assessed sufficiently high to formulate a strong recommendation.</p>



Quality of evidence	Very low level of evidence
Costs (resource allocation)	No formal cost assessment was performed.
Patients values and preferences	The uncertainty around the benefits of screening and subsequent treatment and the possible associated risks preclude an effective and acceptable screening strategy. However, pregnant women would possibly prefer to be informed about (1) their immune status, (2) how to avoid seroconversion, (3) the occurrence of a seroconversion during pregnancy, and finally, (4) how high the probability is that such seroconversion has impacted the fetus. For that reason, a single serology test with informed consent (preferably prior to pregnancy), appropriate counselling on the consequences of antenatal screening and advice on preventive measures are considered acceptable to most women by the GDG.

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> There is insufficient evidence to support routine screening in all pregnant women for cytomegalovirus infection. A single serological test preferably prior to pregnancy may be useful as it may encourage (non-immune) women, to take preventive measures and it can reassure (at least partially) those who are immune. [KCE 2015] In case serological tests for CMV infections are offered, pregnant women and their partners should be informed in detail about all the possible consequences and asked for their consent. [KCE 2015] 	Weak	Very low
<ul style="list-style-type: none"> Despite a lack of clearly proven benefit, discuss primary prevention measures with pregnant women to reduce the risk of cytomegalovirus infection, such as [new KCE 2015]: <ul style="list-style-type: none"> Regularly wash your hands, especially after contact with saliva or urine of small children (e.g. changing diapers) or wear protective gloves when changing diapers or handling children’s dirty laundry. Clean toys, countertops, and other surfaces that come into contact with young children’s bodily fluid. 	Strong	Very low
<ul style="list-style-type: none"> More data on the diagnostic accuracy of serological tests, value of amniocentesis and imaging, clinical evolution of infected infants and harmful effects for healthy pregnancies need to be collected in the Belgian context in order to evaluate the benefits and harms, both on the short term and on the long term, of CMV screening appropriately. [new KCE 2015] 	NA	NA



4.5.2 *Toxoplasmosis – full search*

4.5.2.1 *Background*

Toxoplasma gondii is a parasitic infection mainly acquired by ingestion of viable tissue cysts in undercooked meat, or of oocysts excreted by cats and contaminating soil or water. The infection is usually asymptomatic in adults but, during pregnancy, women who have not previously been exposed can transmit the infection to the fetus with a risk of congenital toxoplasmosis (inflammatory lesions in the brain or eye). In a meta-analysis by Li et al. (2014)²⁰, a pooled vertical transmission rate of 20% was reported with incidences of transmission increasing from the first to the third trimester.

In Belgium, seroconversion rate estimate for toxoplasmosis during pregnancy at the end of nineties was very low (0.09% in a study performed in Brussels, 1991-2001).²¹

Current screening programs are based on the identification of maternal (primo-) infection by means of IgG and IgM measurements in the maternal serum. In case maternal infection is confirmed, amniocentesis and imaging (ultrasound) are performed to investigate if the infection was vertically transmitted and whether or not the fetus is (severely) affected. A pathway of these steps is available in Appendix 4.

Some medications have been used to treat toxoplasmosis with the aim of reducing mother-to-child transmission and the severity of fetal infection but it is not sure that the possible benefits outweigh the potential harms to the baby. Pooled rates of vertical transmission in treated pregnant women were reported to be lower than in untreated women, but there was too much variability around these results to be certain about these findings (as described in the meta-analysis by Li et al., 2014).²⁰

For each step, all possible benefits and risks, including false positive tests and side effects of tests and treatments, need to be taken into consideration. For pregnant women who are seronegative, measures can be proposed to prevent toxoplasmosis infection during pregnancy.

To investigate if screening for maternal toxoplasmosis infection during pregnancy may be useful, we reviewed the evidence to answer the following questions:

- What are the benefits and harms of toxoplasmosis screening in all healthy pregnant women, compared with no routine screening (direct evidence)?
- What are the benefits and harms of lifestyle advice to prevent infection with toxoplasmosis during pregnancy (indirect evidence)?

For detailed research questions in the PICO format, we refer to Appendix 5.

A single search strategy was performed for both questions (see Appendix 6). A total of 2 516 records were identified, and after de-duplicating, 960 records formed the first screening set. A total of 123 records were screened on full text. A description of the study selection (including Prisma flowchart) is available on Appendix 7.

4.5.2.2 *Benefits-harms of screening for toxoplasmosis infection in pregnant women - results*

Among the 123 records screened on full text, no systematic review was identified that investigated the effects of screening vs. no screening for toxoplasmosis infection. No randomized controlled trials were identified and six observational studies were included.²²⁻²⁷

For the details of the quality appraisal and evidence tables, please see Appendices 8 and 9.

Due to study differences in populations, time periods, populations and outcomes, results could not be pooled. There were four pre-post comparisons (before and after implementation of a national screening program) and two concurrent comparisons (comparing prenatal with neonatal screening). Outcomes from four of the six studies are summarised in GRADE tables with narrative reports of the two remaining studies (Appendix 10).

Evidence from four studies was analyzed:

- mandatory monthly screening (1992-1995) versus recommended (i.e. non-compulsory without recommended re-testing intervals) screening (1987-1991) in France;²⁶
- after (1984 - 1990) versus prior (presumably not screened but described as 'followed without treatment') (1966) implementation of screening plus treatment (Sabin-Feldman dye test repeated twice, and after 1986 three



times during pregnancy, with treatment consisting of spiramycin during the first 16 weeks and pyrimethamine thereafter).²⁴ Another before and after study at similar time points investigated prenatal screening (consisting of monthly serological assays in seronegative women) and treatment (spiramycin and sulfadiazin-pyrimethamine) (1976 – 1987) vs. untreated during pregnancy (presumably not screened but this was not explicitly stated in the publication) (1966 – 1975);²⁵

- countries with prenatal screening (ranging from three times to monthly retesting) plus treatment (spiramycin in France and Italy and pyrimethamine and sulfonamide after 15 weeks in Austria) policies (1996 – 2000) vs. countries with neonatal screening programmes (in Sweden and Denmark (1992-1996) with IgG_R^a and IgM, and in Poland and Denmark (1997-2000) with IgM and IgA) (1992 – 2000).²³

Evidence from two further studies could only be reported narratively:

- a pre-post implementation of systematic screening (Sabin-Feldman test or indirect Fluorescent Antibody test in the first instance and IgM and IgA when primary infection is suspected) plus treatment (spiramycin before 16th week of gestation and pyrimethamine in combination with sulfadiazin thereafter);²²
- a comparison of concurrent outcomes from prenatal screening (IgG and IgM testing and monthly retesting) plus treatment (with spiramycin before the 16th week of gestation and pyrimethamine in combination with sulfadiazine thereafter) vs. neonatal screening (a cord blood sample taken in the delivery room or a venous blood sample obtained on the first day of life; ELISA, IgG, IgM and direct agglutination assessed).²⁷

Evidence was not identified for the following critical outcomes: maternal adverse events of treatment and psychological impact of testing. Miscarriages and stillbirths were considered as part of one composite outcome in one study, but not individually reported as a separate outcome in the other studies.

Studied outcomes are presented in 2 main categories: sequelae of toxoplasmosis after at least 1 year and toxoplasmosis infection in newborns.

Sequelae of toxoplasmosis at ages 4, 3 or 1 year follow-up (critical outcome)

- **Serious neurological sequelae or death at a median of 4 year follow-up** (a composite outcome of clinician reports of any of the following: microcephaly, insertion of intraventricular shunt, an abnormal or suspicious neurodevelopmental examination that resulted in referral to a specialist, seizures during infancy or at an older age that required anticonvulsant treatment, severe bilateral visual impairment (visual acuity of Snellen 6/60 or less in both eyes assessed after 3 years), cerebral palsy, or death from any cause before 2 years of age including termination of pregnancy). Very low quality evidence from one observational study²⁸ comprising 293 newborns infected with toxoplasmosis suggested that there was a **lower rate** of serious neurological sequelae or death at a median 4 year follow-up for children born in countries with a **prenatal screening** and treatment schedule compared to children born in countries where **neonatal screening** and treatment programmes are implemented. This finding was adjusted for gestational age at seroconversion (OR 0.24; 95% Bayesian credible limits 0.07 – 0.71).
- **Clinical signs in children at 3 year follow-up** (symptoms not described). Very low quality evidence from one observational study²⁶ comprising 2 048 mother-child pairs (of which 513 newborns were infected) suggested that mandatory monthly screening was **more effective** than **recommended screening** (i.e. non-compulsory without recommended re-testing intervals) in lowering the rate of clinical signs in children at 3 year follow-up, when accounting for gestational age at seroconversion (OR 0.59; 95%CI 0.40 – 0.89; p=0.12). However, as the higher value of the confidence interval crosses the clinical decision threshold (RR 0.75), we cannot be sure that the difference is clinically important.

^a The acronym IgG_R was defined in the study as follows: it involves the detection of IgG seroconversion by comparing the neonatal sample with prenatal booking sample from the mother (presumably as a ratio).



- **Sequelae of congenital toxoplasmosis at 1 year follow-up** (consisting of chorioretinitis, central nervous system calcification, central nervous system toxicity, hydrocephalus). Very low quality evidence from one observational study²⁷ (which could only be reported narratively - see Appendix 10) comprising 163 newborns infected with toxoplasmosis suggested that there was a lower rate of sequelae of toxoplasmosis in neonates that had been screened and treated than neonates from women who were not treated during pregnancy (OR 4.5; p=0.04). However, after adjusting for trimester of infection the rates were similar in neonates with or without prenatal treatment (OR 0.4; p=0.5) – (for neonatal screening programmes the gestational age was adjusted using statistical modelling – see the evidence table in Appendix 9). Confidence intervals for odds ratios were not reported.
- **Symptomatic congenital toxoplasmosis at 1 year follow-up** (symptoms not described). Very low quality evidence from one observational study²⁵ comprising 200 newborns of seroconverted mothers suggested that implementation of a complete screening programme with systematic treatment was no more effective in lowering the rate of symptomatic congenital infection at 1 year follow-up than an incomplete screening programme without systematic treatment (RR 1.02; 95%CI 0.21 – 4.93; p=0.98). No differences for baseline characteristics or gestational age at seroconversion were considered in this result.

For GRADE profiles and forest plots, we refer to Appendices 10 and 11.

Toxoplasmosis infections in newborns (important outcome)

- Very low quality evidence from one observational study²⁶ comprising 2 048 mother-child pairs suggested that mandatory monthly screening was **more effective** than recommended screening (i.e. non-compulsory without recommended re-testing intervals) in lowering the rate of congenital infection with toxoplasmosis (RR 0.81; 95%CI 0.68 – 0.96; p=0.02). However, this result was not accounting for gestational age at seroconversion or any other possible confounding factors and there was some uncertainty about the clinical significance of this finding (an absolute risk difference of 0.6%).

- Very low quality evidence from one observational before-after study²⁴ comprising 1 697 women before and 109 935 women after implementation of a screening programme suggested **fewer** congenital infections associated with the screening programme compared to previous rates (RR 0.69; 95%CI 0.40 – 1.18; p = 0.17). This result did not adjust for any factors that may be related to the results.
- Very low quality evidence from one observational before-after study²² (which could only be reported narratively - see Appendix 10) suggested improvements in the rates of congenital infections when screening was implemented. However, results are not reported in detail and it is therefore difficult to draw conclusions from this finding.
- Very low quality evidence from one study²⁷ (which could only be reported narratively - see Appendix 10) with 5 288 prenatally screened neonates and 9 730 neonates who were not screened showed lower transmission rates in unscreened than screened neonates. However, baseline characteristics were not accounted for in this result which lowers our confidence in these results.

For GRADE profiles and forest plots, we refer to Appendices 10 and 11.

Conclusions

- Based on the limited available, very low quality evidence no clear conclusion can be drawn on whether or not systematic screening programmes for toxoplasmosis during pregnancy are effective in lowering the rate of **symptomatic congenital infections at age 4, 3 or 1 year follow-up**.
- Based on the limited available, very low quality evidence no clear conclusion can be drawn on whether or not systematic screening programmes for toxoplasmosis during pregnancy are effective in lowering the rate of **congenital toxoplasmosis infections in newborns**.



The GDG acknowledged that the available evidence from observational studies has several flaws and results of the different studies are conflicting. However, as for CMV, a lot of health care practitioners are convinced that the toxoplasmosis screening is essential and they perform it not only during the first trimester of the pregnancy but repeatedly. They argue that treatment appears to be more efficient if it is started earlier.

Possible disadvantages of a general screening program, with repeated serological tests, include the limited diagnostic accuracy of serological tests with the need for confirmation with amniocentesis and the difficulty to predict which of the infected foetus will suffer from sequelae (some infected foetus will have no lesion or only minor trouble). The most severe lesions, such as hydrocephalus can be detected by routine ultrasound. The effectiveness of proposed treatments during pregnancy also remains uncertain.

The absolute gain of a screening program including repeated blood sampling would thus be limited and may not weigh up to the disadvantages. Moreover, the GDG considered the costs associated with repeated blood sampling not defensible, as the added benefit is at most limited. In the KCE 2004 guideline, one screening before or at the beginning of pregnancy was suggested if it can encourage (non-immune) women to take preventive measures or if it can reassure those who are immunized.

4.5.2.3 *Benefits-harms of lifestyle advice regarding toxoplasmosis infections during pregnancy - results*

Among the 123 records screened on full text, one systematic review from the Cochrane collaboration (Di Mario et al. 2013)²⁹ as well as two observational studies (pre-post design)^{21, 30, 31} were identified that investigated the benefits and harms of advice on toxoplasmosis (including educational programmes) compared to general advice (not including specific systematic details on toxoplasmosis).

The systematic review was based on two randomised controlled trials. All studies reported on educational programmes rather than general routine advice.

Evidence was not identified for all of the critical outcomes: Miscarriages and stillbirths, neurological lesions, chorioretinitis, permanent neurological damage and adverse events of nutritional and lifestyle advice (such as quality of life, anxiety nutritional restriction). The reported outcomes, i.e.

seroconversion, knowledge about toxoplasmosis and risk behaviour, are therefore surrogates rather than critical outcomes.

For the details of the quality appraisal, evidence tables, Grade profile and forest plots, please see Appendices 8, 9, 10 and 11.

Seroconversion rate

- Very low quality evidence from one observational before-after study^{21, 30} comprising a total of 27 827 pregnant women showed **lower** seroconversion rates when women were educated about toxoplasmosis with written advice compared to women before any particular advice was implemented. In the before phase (i.e. first period: N=2 986) of the study no specific recommendations on how to prevent toxoplasmosis during pregnancy were made (1979 – 1982: N=8 300). In a second period (1983-1990: N=16 541) a written list of recommendations was provided by the physician during the first prenatal consultation (not to eat raw or undercooked meat, hand washing after touching meat and avoidance of contact with cat faeces or possibly contaminated items for instance during gardening). The third period (1991 – 2001) consisted of a more rigorous campaign including both a leaflet with a detailed description of the disease as well as the recommendations that featured in the second phase. Additionally in the third period around mid-gestation midwives reiterated these recommendations. The relative effects of educational programme compared to no specific advice were larger for the third (RR 0.07; 95%CI 0.03 – 0.15) than for the second period (RR 0.37; 95%CI 0.20 – 0.69).

Knowledge and risk behaviour

- Very low quality evidence from one observational before-after study³¹ comprising a total of 8 267 (with relevant data for this outcome for N=7 021) pregnant women showed that knowledge of toxoplasmosis increased when more information was provided, from 24.3% to 45.3% from before (no particular toxoplasmosis information) to phase three (in phase 2 training of health care professionals, fact sheets on the prevention of congenital toxoplasmosis for pregnant women and other activities with additional material provided in phase 3) of the study. Correct behaviour was only reported in 1 496/2 710 (55.2%) of women in the third phase of the programme. However, only 352 women (24%) had read the material and correct behaviour was reported to be higher



in women who had not read the material (62.8%) than those who had (54.1%).

- Very low quality evidence from two randomised controlled trials were summarised in a Cochrane review.²⁹ In one of the trials³² included in this review the training material consisted of a three-page leaflet along with a display poster and resource material for teachers (with a ten minute presentation during the first prenatal class). The second trial (Wallon et al., 2006 as reported in Gollub et al. 2008³³) used a twenty-page brochure containing four pages of information on toxoplasmosis as well as an audiotape containing a conversation between a physician and her patient on issues relevant to pregnancy including questions on toxoplasmosis. There were reported improvements in behaviour in one study and improvements in knowledge but not behaviour in the other trial.

Conclusions

- Based on the limited available, very low quality evidence there is a suggestion that a leaflet (or leaflet plus classes) about toxoplasmosis is effective in lowering the **rate of seroconversion** during pregnancy, but we cannot be confident about or draw any clear conclusions from this finding because no confounders were considered in this analysis.
- Based on the limited available, very low quality evidence there is a suggestion that training programmes may be effectively increasing **knowledge about toxoplasmosis risk factors** but whether this also improves **risk related behaviour** is unclear.

The GDG added that information on nutritional and lifestyle advice are relatively well-known by the Belgian women and are useful not only for toxoplasmosis infection. They are easy to explain and the training material is not expensive. As neonatal toxoplasmosis infection can have severe consequences, the GDG suggested to inform pregnant women on the possible route of infection and how simple measures may reduce risk. As previous infection guarantees protection, identification of the non-immune women by a single serological test can be argued if it encourages them to follow the advice such as it was suggested in the KCE 2004 recommendation.

4.5.2.4 Recommendation for toxoplasmosis infection

Based on the retrieved evidence and the discussion with GDG and stakeholders, we developed two recommendations concerning the toxoplasmosis infection during pregnancy. The considerations that lead to the recommendations are summarized below.



Other considerations

Factor	Comment
Balance between clinical benefits and harms	<p>The available evidence from observational studies has several flaws and results of the different studies are conflicting. Furthermore, the utility of universal screening is reduced given the fact that the most severe lesions, such as hydrocephalus can be detected by routine ultrasound and that the effectiveness of proposed treatments during pregnancy remains uncertain. Moreover, a general screening program has possible disadvantages (such as repeated serological tests, need for confirmation with amniocentesis, difficulty to predict which of the infected fetus will suffer from sequelae).</p> <p>Information on how toxoplasmosis infection can be prevented appears to be well-known by pregnant women in Belgium and seroconversion rate is very low (0.09% in a study performed in Brussels, 1991-2001).²¹ The absolute gain of a screening program including repeated blood sampling would thus be limited and may not counterbalance the disadvantages. A single screening before or at the beginning of pregnancy was suggested if it can encourage (non-immune) women to take preventive measures or if it can reassure those who are immunized.</p> <p>Concerning the preventive measure, the evidence available are very limited about the possible decrease in seroconversion rate with lifestyle advice. However, the balance benefit-risk of these lifestyle advice (well-known by clinicians and patients, useful for other infections, easy to explain, not expensive) was assessed sufficiently high to formulate a strong recommendation.</p>
Quality of evidence	Limited and very low quality
Costs (resource allocation)	The GDG considers the costs associated with repeated blood sampling not defensible, as the added benefit is at most limited.
Patients values and preferences	The GDG considers a single serological test followed by advice on preventive measures for non-immune women well accepted by pregnant women in Belgium.

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> There is insufficient evidence to support a routine screening in all pregnant women for toxoplasmosis infection, repeated at different periods of pregnancy. A single serological test prior to or at the beginning of pregnancy can be useful as it may encourage (non-immune) women to take preventive measures or as it may reassure those who are immune. [KCE 2015] 	Weak	Very low
<ul style="list-style-type: none"> Despite a lack of clearly proven benefit, discuss with the non-immune pregnant women prevention measures to reduce the risk of toxoplasmosis infection, such as [new KCE 2015]: 	Strong	Very low

- washing hands before handling food
- thoroughly washing all fruit and vegetables, including ready-prepared salads, before eating
- thoroughly cooking raw meats and ready-prepared chilled meals
- wearing gloves and thoroughly washing hands after handling soil and gardening
- avoiding cat faeces.

4.5.3 Chlamydia – full search

4.5.3.1 Background

Chlamydia trachomatis is sexually transmitted. The infection is asymptomatic in 75% of women and at least 50% of men. Prenatal chlamydia infection may be associated with premature rupture of membranes (PROM), premature delivery and stillbirth.³⁴ Chlamydia infection can also cause pelvic inflammatory disease (PID). PID is a major cause of infertility, ectopic pregnancy and miscarriage. Maternal chlamydia infection can have potential adverse effects on new-born infants. They may acquire chlamydia through contact with infected maternal genital secretions during birth.³⁵ For a minority of neonates born with chlamydia the illness may manifest in the form of conjunctivitis or pneumonia.³⁴ While important, these neonatal conditions are rarely severe and can be easily recognised and treated.^{34, 35} Treatment of chlamydia in pregnancy is complicated by the limited range of acceptable antibiotics available to pregnant women due to the possible impact of the drugs on the developing fetus. Furthermore the optimal timing of screening is also contentious as earlier testing may mean better chances of treating to cure, however there is also potential need for re-testing closer to birth to ensure absence of infection.

Chlamydia trachomatis urogenital infection in women can be diagnosed by testing urine (first-catch urine sample) or by collecting swab specimens (or brush of cells or secretion) from the endocervix or vagina.

To investigate if screening for maternal chlamydia infection during pregnancy may be useful, we reviewed the evidence to answer the following question:

- What are the benefits and harms of chlamydia screening in all healthy pregnant women, compared with no screening or targeted tests in women with risk factors?

For detailed research question in the PICO format, we refer to Appendix 5.

A search strategy was performed and found 2 298 records (see Appendix 6). After de-duplicating, 1 502 records formed the first screening set. A total of 64 records were screened on full text. A description of the study selection (including Prisma flowchart) is available on Appendix 7.

4.5.3.2 Benefits-harms of universal screening for chlamydia infection in pregnant women - results

Among the 64 records screened on full text, no systematic reviews or randomized controlled trials that investigated the effects of universal screening vs. no screening or risk based testing for chlamydia trachomatis were retrieved in the search. Two observational studies have been found, one focused on universal screening compared to no screening using a before-and-after design,³⁶ and the other used a prospective study design to investigate universal screening compared to screening at medical staff discretion in a sample of women ≤17 years of age.³⁷ For full details of the included studies, please see the quality appraisal and evidence tables in Appendices 8 and 9.

The following prioritized outcomes were not reported: conjunctivitis and pelvic inflammatory disease (PID). Therefore this review is focused on the outcome of preterm birth which was only reported by one of the two included studies.³⁶ Both studies also reported on aspects of febrile morbidity (high temperature/fever and antibiotic use), however these outcomes were considered indirect outcomes as they were not listed on the review protocol



and are included only for interest due to the lack of evidence identified. For GRADE profiles and Forest plots, we refer to Appendices 10 and 11.

The following two main comparisons were reported:

- Universal screening compared to no screening for chlamydia trachomatis infection
- Universal screening compared to screening at medical staff discretion for chlamydia trachomatis infection.

Universal screening vs. no screening

Preterm birth (important outcome)

- Very low quality evidence from one before-and-after observational study³⁶ comprising of 288 pregnant women suggested that universal screening for chlamydia was associated with **higher rates** of preterm birth compared to no chlamydia screening (RR 1.34, 95%CI 0.57–3.18). However, the wide confidence interval around the point estimate suggests universal screening is associated with both clinical benefit and clinical harm so we cannot be confident in the effect.

Febrile morbidity

- Very low quality evidence from the before-and-after study³⁶ comprising of 288 pregnant women suggested a **benefit** of universal screening with respect to maternal fever (RR 0.71, 95%CI 0.4–1.26). Although this had a wide confidence interval crossing the line of no effect into clinical harm. There was no difference between screening vs. no screening for maternal antibiotic treatment (RR 0.99, 95%CI 0.66–1.5).

Universal screening vs. screening at discretion of medical staff

Febrile morbidity

- Very low quality evidence from a prospective observational study³⁷ comprising of 160 pregnant women ≤ 17 years of age comparing universal screening with screening at the discretion of medical staff (no information provided on the basis on which they make their decisions) showed no statistical difference in respect to **maternal fever** and antibiotic use (RR 0.73, 95%CI 0.32–1.67).

- With respect to **neonatal fever** and antibiotic treatment the very low quality evidence from the same study³⁷ suggested a clinical **benefit** for universal screening (RR 0.4, 95%CI 0.19–0.83) which although it featured a wide confidence interval was consistent with not causing clinical harm.

Conclusions

- Based on the available, very low quality, indirect evidence showing increased cases of preterm birth (important outcome) and decreased cases of maternal febrile morbidity with universal screening for chlamydia infection, **it may not be concluded that universal screening is more effective than no screening.**
- Based on the available, very low quality, indirect evidence **it may be concluded that universal screening is not more effective than screening at medical staff discretion** with respect to maternal febrile morbidity in young pregnant women, but may be effective with respect to neonatal febrile morbidity.

The GDG acknowledged there is no proof of a beneficial effect of screening for chlamydia trachomatis in all pregnant women. Moreover, treatment options are limited by the restricted range of acceptable antibiotics available to pregnant women and the frequent use of antibiotic treatment may lead to resistance.

However, the stakeholders and GDG underlined that it can be considered to test for chlamydia in pregnant women who are at increased risk. Major identified risks are age younger than 25 years old or history of sexually transmitted disease.

4.5.3.3 Recommendation for chlamydia infection

Based on the retrieved evidence and the discussion with GDG and stakeholders, we developed one recommendation concerning the screening for chlamydia infection during pregnancy. The considerations that lead to the recommendations are summarized below.



Other considerations

Factor	Comment
Balance between clinical benefits and harms	There is a lack of evidence on the beneficial effect of screening for chlamydia trachomatis in all pregnant women. Moreover, treatment options are limited by the restricted range of acceptable antibiotics available to pregnant women and the frequent use of antibiotic treatment may lead to resistance. However, due to the potentially severe outcome of chlamydia infection during pregnancy, it can be considered to test for chlamydia in pregnant women who are at increased risk, such as pregnant women younger than 25 years old or women with a history of sexually transmitted disease.
Quality of evidence	Limited and very low quality evidence
Costs (resource allocation)	The GDG considers the costs associated with universal screening not defensible, as there is no proof of a beneficial effect.
Patients values and preferences	NA

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> Do not routinely offer to each pregnant woman a Chlamydia trachomatis test [new KCE 2015]. 	Weak	Very low

4.5.4 Group B streptococcus – full search

4.5.4.1 Background

Streptococcus agalactiae, also known as group B streptococcus (GBS), is a common bacterium that colonizes the gastrointestinal tract and genital tract. It rarely causes symptoms or problems in healthy adults but can cause infections and serious illness in newborns.

GBS can be passed from mother to child before or during delivery, causing early-onset GBS disease that appears within hours to days of birth. Symptoms in newborns include fever, difficulty with feeding and breathing, irritability or lethargy, and a blue tint to their skin. GBS can cause serious infections such as pneumonia, sepsis, and meningitis. Asymptomatic vaginal carriage of Group B haemolytic streptococci is one of the most

common causes of neonatal infectious morbidity and mortality in the US since 1970 (Ohlsson, Cochrane 2014).³⁸

Group B strep screening identifies the presence of the bacteria in the vaginal/rectal area of a pregnant woman. A culture of a vaginal-rectal swab for GBS colonization at 35-37 weeks is the conventional screening test. In case of positive results, antibiotic can be provided during labour. Instead of universal screening, intrapartum antibiotic prophylaxis can be given, based on risk factors or ad hoc.

To investigate if screening for maternal GBS colonization during pregnancy may be useful, we reviewed the evidence to answer the following questions:

- What are the benefits and harms of group B streptococcus screening in all healthy pregnant women, compared to GBS prophylaxis without a particular protocol (no screening and non-specified ad hoc intrapartum antibiotic use) or to risk factors based prophylaxis?



35. For detailed research question in the PICO format, we refer to Appendix 5.

A single search strategy was performed for both questions (see Appendix 6). A total of 3 958 records were identified, and after de-duplicating, 1 481 records formed the first screening set. A total of 103 records were screened on full text. A description of the study selection (including Prisma flowchart) is available on Appendix 7.

4.5.4.2 *Benefits-harms of universal screening for group B streptococcus - results*

Among the 103 records screened on full text, one systematic review was identified (Taminato et al. 2011)³⁹ that investigated the effects of universal screening at 35 – 37 weeks gestation vs. no screening or risk based prophylaxis for Group B streptococcus. There were a number of studies missing from this systematic review and some errors in the data that were entered into the analysis. It also included studies with universal screening protocols at 26-28 weeks. Therefore rather than updating this review, we carried out a new review and excluded the systematic review by Taminato et al. (2011).

No randomized controlled trials were retrieved in the search and 19 observational studies⁴⁰⁻⁵⁷ were found. Two of these studies were associated with other publications from which data were extracted:

- The study by Puopolo et al. (2005)⁵² refers to an earlier publication by Chen et al. (2001)⁵⁸ with data of comparison groups.
- Schrag et al. (2013) report on the largest multistate USA study and a number of other publications⁵⁹⁻⁶² are linked to this study as well as a website of the Active Bacterial Core Surveillance (Center for Disease Control and Prevention, 2013; <http://www.cdc.gov/abcs/reports-findings/survreports/gbs13.html>).⁶³ In the latest report on the website the population size is described as representing a total of 32 714 664 persons and 442 164 live births. This set of studies included several analyses that could not be combined within the same analysis as the other studies. The results⁵⁵ are provided as a narrative summary (neonatal sepsis rates at different time periods were reported as cases/1000 rather than raw).

Prior to 1992 most studies did not use a particular prophylactic protocol. Following on from this in the majority of studies the prophylactic strategies often directly refer to three particular guidelines published in the USA:

- The earlier (1992) risk based approach refers to guidance provided by the American Academy of Pediatrics⁶⁴ and the American College of Obstetricians and Gynecologists (ACOG)⁶⁵ which advocated an approach that does not require antenatal screening for GBS colonization, but relies on monitoring for specific obstetric risk factors such as preterm labor, preterm premature membrane rupture, intrapartum fever or prolonged membrane rupture. Intrapartum antibiotic prophylaxis (IAP) is then offered to pregnant women presenting with these risk factors.
- The Consensus guidelines for the prevention of perinatal GBS disease were issued by the Centers for Disease Control and Prevention,⁶⁶ the American Academy of Pediatrics,⁶⁷ and the American College of Obstetricians and Gynecologists in 1996.⁶⁸ This was a hybrid protocol recommending either universal screening or risk based prophylaxis. IAP would then be offered to GBS positive women and women with known risk factors.
- Revised USA national guidelines recommending universal late (35 – 37 weeks gestation) screening were published in 2002.^{62, 69}

For details of the particular protocols used in each study please refer to evidence table in Appendix 9.

The following prioritized outcomes were not reported in the selected studies: adverse events such as candida infection, and allergic reaction to antibiotics. Stillbirth or group B streptococcal related mortality were reported very infrequently.

Therefore the focus was mainly on two outcomes: neonatal Group B Streptococcal (GBS) sepsis which was reported by all studies and mortality due to early onset GBS sepsis. The definition of the outcome “sepsis” varied with some studies including newborns with a strong suspicion of GBS infection to other studies which only reported those with positive GBS cultures.

For the details of the quality appraisal, evidence tables, GRADE profiles and Forest plots, please see Appendices 8, 9, 10 and 11.



The following three comparisons were reported:

- Universal screening compared to no screening for GBS
- Universal screening compared to risk factor based prophylaxis of GBS
- Universal late Group B streptococcal screening vs. universal early Group B streptococcal screening

Universal Group B streptococcal screening vs. no screening

Early onset Group B streptococcal sepsis (critical outcome)

- Very low quality evidence from eleven observational studies^{44, 46, 49-54, 56, 70, 71} comprising 320 772 neonates showed that **lower rates** of early onset Group B streptococcal disease were associated with universal screening compared to no screening (median RR 0.32; 95%CI 0.24-0.43). Even though there was wide variability in point estimates across studies the direction of effect was consistent.

Mortality due to early onset GBS sepsis (critical outcome)

- Very low quality evidence from two observational studies^{54, 56} comprising 40 236 newborns suggests lower mortality rates associated with universal screening. However, the event rate is low even in the control group (0.2 per 1000) and therefore the results are uncertain (Peto OR 0.18; 95%CI 0.03 -1.10).

Universal Group B streptococcal screening vs. risk based prophylaxis

Early onset Group B streptococcal disease

- Very low quality evidence from nine observational studies^{40-42, 45, 50-52, 56, 72} comprising 352 123 newborns showed that universal screening was **effective** in lowering rates of early onset Group B streptococcal disease compared to risk-based prophylaxis (median RR 0.19; 95%CI 0.06 – 0.55). Even though there was wide variability in point estimates across studies the direction of effect was consistent.
- One study⁵⁷ which could only be reported narratively provided results consistent with the rest of the observational studies, i.e. **lower** rates of 'infections' associated with universal screening (a drop from 1.45% to 0.86%, $p < 0.05$). This outcome is less precise since it included clinical

or biological signs of Group B streptococcal infection. Therefore this result could be considered less robust compared to the other studies.

- In an ongoing multistate study from the US⁵⁵ it is described that the incidence of invasive early-onset GBS disease **decreased** by more than 80% from 1.8 cases/1 000 live births in the early 1990s to 0.26 cases/1 000 live births in 2010. During this time risk-based prophylaxis was implemented in 1992 and universal screening in 2002. By 1996-1997 when the Consensus guidelines (either risk-based or screening prophylaxis) the incidence of Early onset Group B streptococcal disease was under 1.0 per 1 000 and by 2002 the incidence had fallen to below 0.5 per 1 000 and has fallen further since to 0.26 cases per 1 000 in 2010. In another analysis from the same data the univariate as well as an adjusted risk ratio (for a number of confounding factors such as preterm delivery, previous infant with Group B streptococcal disease) were reported. Early onset Group B streptococcal disease was less likely to occur in neonates from universal screening programmes rather than those from the risk-based prophylaxis group (univariate RR 0.48, 95%CI 0.38 – 0.61; adjusted RR 0.46, 95%CI 0.36 – 0.59).

Mortality due to early onset GBS sepsis (important outcome)

- Very low quality evidence from one observational study⁵⁶ comprising 16 455 newborns suggests lower mortality rates associated with universal screening. However, the event rate is low even in the control group (0.2 per 1 000) and therefore the results are uncertain (Peto OR 0.2; 95%CI 0.00 -11.63).



Universal late Group B streptococcal screening vs. universal early Group B streptococcal screening

Early onset Group B streptococcal disease

- Very low quality evidence from one observational study⁴⁸ (n= 1 682) in which pregnant women with risk factors were excluded suggested that a higher rate of positive GBS culture screens was associated with universal screening compared to no/early screening. However, the outcome is not comparable to outcomes in other studies because it is unclear how many newborns were symptomatic. Furthermore the power of the study is too small due to the small sample size.
- Very low quality evidence from one observational study⁴³ comprising 3 755 neonates suggests lower rates of positive blood and group B culture results were associated with earlier screening (25-28 weeks gestation) than later screening (35-37 weeks gestation). However, the outcome is not comparable to outcomes in other studies because it is unclear how many newborns were symptomatic. Furthermore the power of the study is too small due to the small sample size.

Conclusions

- Based on the available, very low quality, evidence for fewer cases of early onset Group B streptococcal disease and lower mortality rates due to Group B streptococcal disease it may be concluded that **universal screening is more effective than no screening.**
- Based on the available, very low quality, evidence for fewer cases of early onset Group B streptococcal disease and lower mortality rates due to Group B streptococcal disease it may be concluded that **universal screening is more effective than risk-based prophylaxis.**
- Based on the limited available, very low quality evidence, from a study trying to match groups and one comparing different timings of screening strategies no clear conclusions can be drawn.

In 2004, the KCE quoted three situations (previous child with invasive disease due to GBS; detection of GBS bacteriuria during pregnancy in progress; childbirth before 37 weeks), where the treatment can be established without sampling. In 2015, the GDG still agrees to start treatment without sampling in these situations.

4.5.4.3 Recommendation for GBS infection

Based on the retrieved evidence and the discussion with GDG and stakeholders, we developed one recommendation concerning the screening for GBS infection during pregnancy. The considerations that lead to the recommendations are summarized below.



Other considerations

Factor	Comment
Balance between clinical benefits and harms	<p>Evidence suggests that universal screening is associated with reduced rates of early-onset neonatal sepsis and GBS related early mortality. Large observational studies are available, but the majority of the evidence comes from retrospective studies where groups are unadjusted for any baseline differences. Data on possible adverse events such as resistance to penicillin were not reported.</p> <p>In spite of these limitations, the overall balance is judged to be in favour of universal screening by the GDG as the events that are prevented are very severe and adverse events are rare and acceptable. Furthermore, a narrow spectrum antibiotic agent is used and GBS has still not developed resistance to penicillin in spite of its long-term use. This treatment is usually provided in case of a previous child had invasive GBS infection or if the woman has a GBS bacteriuria during pregnancy in progress. A childbirth before 37 weeks implies also a systematic treatment.</p>
Quality of evidence	Very low level of evidence
Costs (resource allocation)	GBS screening is already widely implemented in Belgium as it was already recommended by KCE and the Superior Health Council in 2004. Therefore, no important additional resources are presumed.
Patients values and preferences	In the experience of the members of the GDG, GBS screening is acceptable to the vast majority of pregnant women.

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> Offer a vaginal and rectal sampling for all women between the 35th and 37th weeks of pregnancy in view of a culture for the detection of Group B Streptococcus, except: <ul style="list-style-type: none"> - if a previous child has contracted invasive disease due to GBS; - if the GBS bacteriuria has been detected during pregnancy in progress; - if childbirth occurs before 37 weeks. In these three situations, the treatment can be established without sampling [KCE 2015]. 	Strong	Very low



4.5.5 Hepatitis B - update

Routine antenatal screening for hepatitis B is considered by the Australian 2014 guideline as “essential for preventing babies from becoming carriers of hepatitis B; and enables appropriate follow-up and management of the woman, identification of the immune status of other household members, and protection of those who are susceptible”(ATAGI 2009 in Australian 2014 guideline). Administration of vaccine and hepatitis B immunoglobulin to the baby at birth can prevent around 95% of the mother-to-child transmission (Australian 2014 guideline).

Universal screening for hepatitis B is supported by results of several observational studies (Summers et al., 1987; Jensen et al. 2003; Cowan et al.2009). One systematic review (Lin & Vickery 2009 in the Australian guideline) presented no new evidence. Universal screening was recommended at the first antenatal visit by the Australian 2014 guideline and at the beginning of pregnancy or before by the KCE 2004 guideline.

In Belgium, there is a routine vaccination of infants and of pre-teens (11-12 years old) against hepatitis B since 1999. This implies that in a few years, more and more young pregnant women will have received the vaccination. In this context, the GDG proposed to test for the hepatitis B surface antigen (HBsAg) in women with unknown immune status.

In conclusion, the KCE 2004 recommendation for a universal screening for hepatitis B remained focusing on women with an unknown immune status. For more details on the process of recommendation development, see Appendix 14.15.

Recommendation	Strength of Recommendation	Level of Evidence
For pregnant women with an unknown immune status, offer a detection of HBsAg (surface antigen of the hepatitis B virus) as effective postnatal intervention reduce the risk of mother-to-child transmission. [KCE 2004, slightly amended]	Strong	A*

* Level of evidence from Australian 2014 guideline: A=One or more level I studies with a low risk of bias or several level II studies with low risk of bias

4.5.6 Hepatitis C - update

The risk of mother-to-child transmission for hepatitis C was estimated at 3-5%. However the clinical evolution of an infection in a newborn is not clear, some children becoming sero-negative a few months after childbirth (KCE 2004) but other developing chronic hepatitis C with risk of hepatic fibrosis, cirrhosis and hepatocellular carcinoma (Australian 2014 guideline).

The Australian 2014 guideline recommended to not routinely offer hepatitis C screening. It underlined the limited evidence on screening of pregnant women for hepatitis C and mentioned the lack of effective treatment options

(or interventions to prevent transmission) and potential psychological harm of false positive screening results as reasons not to screen routinely (Pembrey et al. 2003; 2005 in Australian 2014 guideline).

Concerning a selective screening based on risk factors, some population-based cohort studies suggested that this approach may not identify all women with hepatitis C (Hutchinson et al. 2004; Lui et al. 2009 in Australian 2014 guideline), particularly if risk factors are not present or women conceal them (Prasad et al. 2007 in Australian 2014 guideline). However, a practice point in the Australian 2014 guideline mentioned that hepatitis C screening may be offered to women with some identifiable risk factors (intravenous



drug use or needle sharing, tattooing or body piercing, incarceration, receipt of blood products or invasive procedures overseas or before 1990 in Australia, country of origin has a high prevalence of hepatitis C). Another practice point recommended for hepatitis C screening before an invasive procedure (e.g. chorionic villus sampling, amniocentesis).

In 2004, the KCE guideline concluded there was not sufficient evidence to recommend routine hepatitis C screening.

In 2015, the GDG acknowledged that the balance benefit-harm is not in favour of routine hepatitis C screening:

- Effective interventions to prevent transmission remain currently unavailable and screening does not change anything in the pregnancy outcomes. New treatments will possibly become available but are not yet in use during pregnancy.
- Taking pregnancy as an opportunity to test the overall health of women is out of scope for this guideline. Screening for hepatitis C during pregnancy can be justified from a public health point of view (protection of sexual partners, healthcare professionals, etc.) but has no proven medical benefit for the pregnant woman or her baby.
- If a universal screening is applicable, it would be preferable to ask general practitioners to perform screening in their entire population because men also should have access.

- Antibody measurement is not expensive at an individual level but if we consider 125 000 pregnancies/year and if we add the follow-up of screening, this is not cheap.
- Screening focusing only on people with high risk is not sufficient because history taking may not be accurate. Certainly if sexual behaviour is added within the list of risk factors.

However the GDG underlined that prevalence of hepatitis C is not the same in all areas in Belgium and suggested that in some hospitals where prevalence is high, hepatitis C maybe deserves specific management (notably in terms of protection of healthcare practitioners). Moreover, such screening may be offered to women with some identifiable risk factors (e.g. women with a history of intravenous drug use, tattoos or body piercing, needle sharing, incarceration).

In conclusion, the KCE 2015 acknowledgement of insufficient evidence was changed in a recommendation against systematic hepatitis C screening but with the possibility to offer screening to women with some identifiable risk factors. For more details on the process of recommendation development, see Appendix 14.16.

Recommendation	Strength of Recommendation	Level of Evidence
Do not routinely offer to each pregnant woman hepatitis C testing. [KCE 2004, amended]	Weak	C*

* Level of evidence from Australian 2014 guideline: C=One or two level III studies with a low risk of bias or level I or II studies with a moderate risk of bias



4.5.7 HIV - update

Human immunodeficiency virus (HIV) infection undiagnosed during pregnancy can have serious impact on women's and children's health. The mother-to-child transmission of HIV infection can be significantly reduced by an antiretroviral therapy and other measures (Australian 2014 guideline, KCE 2004 guideline).

Universal screening for HIV in pregnancy is recommended at the beginning of pregnancy by the Australian 2014 guideline and the KCE 2004 guideline. This recommendation is supported by the effectiveness of interventions to prevent mother-to-child transmission but also by the availability of accurate diagnostic tests and the risk of missing a substantial proportion of women with HIV with a screening based on risk factors only.

Concerning adverse events of treatment, the Australian 2014 guideline quoted some prospective cohort studies and meta-analyses which have found no significant association between antiretroviral treatments and intrauterine growth restriction (n=8 192) (Briand et al. 2009 in Australian 2014 guideline), congenital abnormalities (n=8 576) (Townsend et al. 2009 in Australian 2014 guideline), or preterm birth (n=20 426) (Kourtis et al. 2007 in Australian 2014 guideline). The acceptability of the interventions is underlined by the Australian 2014 guideline. However, the personal and social impact of an HIV infection might not be minimised and deserves information and support before and after testing (DoHA 2006 in Australian 2014 guideline).

The GDG agreed with the Australian 2014 recommendation. In the KCE 2004 guideline, the test was proposed before or during pregnancy but the GDG considered that, if the test is performed before pregnancy, there is a risk that a pregnant woman is infected more recently. To avoid missing recent infections, the GDG proposed the test should be performed at the beginning of pregnancy.

In conclusion, the KCE 2004 recommendation was slightly changed to recommend HIV testing at the beginning of pregnancy but not before. For more details on the process of recommendation development, see Appendix 14.17.

Recommendation	Strength of Recommendation	Level of Evidence
Offer to each pregnant woman HIV testing at the beginning of the pregnancy after having explained to her why it is useful. [KCE 2004, slightly amended]	Strong	B*

* Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias



4.5.8 Rubella - update

Rubella during pregnancy can result in spontaneous miscarriage, stillbirth, fetal growth restriction or congenital rubella syndrome (Australian 2014 guideline). There is no treatment to reduce the risk of mother-to-child transmission but a determination of the immune status during the first consultation may be useful because a postpartum vaccination can offer protection during subsequent pregnancies. In addition, unprotected women can take preventive measures (such as avoiding contact with infected people) during the first 4 months of pregnancy (KCE 2004 guideline).

The Australian 2014 guideline mentioned the availability of accurate diagnostic tests and the lack of association between inadvertent vaccination in pregnancy and congenital rubella syndrome.

Universal screening for rubella in pregnancy is recommended at the beginning of pregnancy by the Australian 2014 guideline and the KCE 2004 guideline.

The GDG acknowledged the importance of universal rubella screening and had no additional comments.

In conclusion, the KCE 2004 recommendation remained unchanged except further specification to test for IgG antibodies only. For more details on the process of recommendation development, see Appendix 14.18.

Recommendation	Strength of Recommendation	Level of Evidence
For pregnant women with an unknown immune status, offer prior or at the beginning of pregnancy to test for IgG against rubella, in order to identify women who are not immune to rubella, advise them to avoid sick people with skin rash and to vaccinate them during the postpartum period. [KCE 2004, slightly amended]	Strong	B*

* Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias



4.5.9 Syphilis - update

Syphilis is a sexually transmitted infection caused by the spirochete bacterium *Treponema pallidum*. This infection might remain asymptomatic and latent for many years. During pregnancy, mother-to-child transmission of syphilis is associated with fetal death, neonatal mortality, preterm birth and congenital syphilis (KCE 2004). Mother-to-child transmission of syphilis can be prevented by antibiotic therapy.

The Australian 2014 guideline mentioned that universal syphilis screening programs increase the detection of pregnant women who have syphilis compared with selective screening of women at high-risk. Convincing observational evidence showed also that universal screening decreases the proportion of babies with clinical symptoms of syphilis infection. Moreover, universal screening for syphilis has been shown to be cost-effective (Garland & Kelly 1989; Abyad 1995; Cameron et al. 1997; Connor et al. 2000; Walker 2001 in Australian 2014 guideline) even in areas of low prevalence.

Universal screening for syphilis in pregnancy is recommended at the first antenatal visit in the Australian 2014 guideline and before or at the beginning of pregnancy in the KCE 2004 guideline.

The GDG acknowledged that the prevalence of syphilis is low in Belgium but a universal screening is supported by the fact that an effective treatment is available, screening is cheap and a selective approach based on risk factors is inaccurate.

Concerning the type of tests, the diagnosis of *Treponema pallidum* infections is based on nontreponemal (e.g. Rapid plasma regain (RPR) test) and treponemal serologic tests (e.g. *T. pallidum* hemagglutination assay (TPHA)).

The traditional syphilis testing algorithm consists of first a non-treponemal test such as the RPR test to screen patients followed by a treponemal test to confirm reactive serological tests.⁷³

In recent years, many high-volume laboratories have begun to offer a reverse syphilis testing algorithm to screen populations with low prevalence of the disease with treponemal tests which can be automated in EIA or similar formats. In this reverse algorithm a treponema-specific test is used for screening, followed by a non treponemal test to diagnose active disease and to monitor response to treatment. The rationale is to reduce high labour costs (owing the automation of the immunoassay), and with a low prevalence of the disease, few cases of syphilis would require confirmation using a labour intensive non-treponemal test.

However, the interpretation of discordant results is an important concern for the practitioners. The most difficult question to answer is how to interpret a positive treponemal, but negative non-treponemal result. Answering this question has implications for decisions regarding treatment, contact investigations, and reporting.⁷³

Both the Association of Public Health Laboratories and the United States Centers for Disease Control and Prevention (CDC) continue to recommend the traditional algorithm but acknowledge the use of treponemal immunoassays as screening assays and provide recommendations for laboratories that choose this reverse algorithm approach.

Given this debate, the GDG and stakeholders proposed that the choice of test remains open.

In conclusion, the KCE 2004 recommendation on syphilis screening remained unchanged but specifications of the type of test were omitted. For more details on the process of recommendation development, see Appendix 14.19.

Recommendation	Strength of Recommendation	Level of Evidence
As treatment is favourable for the prognosis of both the mother and child, offer each pregnant woman to test for syphilis, in the beginning of pregnancy (or before). [KCE 2004]	Strong	B*

* Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias



4.5.10 Herpes Simplex - update

In 2004, the KCE guideline underlined that there was not sufficient evidence to recommend systematic screening for herpes simplex (HSV). The Australian 2014 guideline did not formulate any recommendation on this topic but referred to the Royal College of Obstetricians and Gynaecologists from United Kingdom (RCOG) 2007 recommendations which mentioned that “identifying women susceptible to acquiring genital herpes in pregnancy by means of type-specific screening for HSV antibodies in pregnancy is not currently indicated.”^b

The RCOG quoted one study which has compared universal serum screening for HSV and targeted screening (for women estimated to be at high risk of infection with current care (no screening) for a hypothetical cohort of women in early pregnancy, using a decision analysis model (Cleary et al. 2005). Both screening strategies decreased neonatal transmission and caesarean section deliveries for recurrent herpes but with very high medical resource costs. According to the very low incidence of neonatal herpes, the RCOG found it is unlikely that such a screening programme would be cost-effective at the present time.

The GDG agreed with the RCOG conclusion. There is a risk of vertical transmission by herpes simplex during delivery but the low prevalence of infection and the fact that screening during pregnancy does not change the outcome of the pregnancy do not support systematic screening. The GDG proposed to focus on history taking and to check before the delivery by a clinical examination if the woman is infected.

In conclusion, the KCE 2015 acknowledgement of insufficient evidence was changed in a recommendation against systematic herpes simplex screening. For more details on the process of recommendation development, see Appendix 14.20.

Recommendation	Strength of Recommendation	Level of Evidence
Do not routinely offer each pregnant woman a serological test for herpes simplex. [KCE 2004, amended]	Weak	IV*

* Level of evidence from RCOG 2007: IV= evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.

^b <http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT30GenitalHerpes2007.pdf>



4.5.11 Varicella - update

In 2004, the KCE guideline underlined that there was not sufficient evidence to recommend systematic screening for varicella. The Australian 2014 guideline did not formulate any recommendation on this topic but referred to the RCOG 2007⁷⁴ recommendations which mentioned that antenatal varicella screening by history and serological testing in those with a negative history, followed by postpartum vaccination, could be cost effective but this is currently not part of a UK screening programme.

Non-immunized women of childbearing age can be vaccinated if followed by one month of contraception and non-immunized pregnant women can be vaccinated after delivery.^{75, 76}

The GDG mentioned that in Belgium, a large proportion of women are infected by varicella during childhood. A study from Leuridan et al. conducted in Antwerpen between 2006 and 2008 showed the presence of antibodies against varicella in 98% of participating pregnant women.⁷⁷

History taking has been shown to be reliable in terms of positive predictive value but not in negative predictive value. According to the Belgian Superior Health Council, about 90% of people over 17 years age who think they have never had varicella, still have positive antibodies.⁷⁶

Given the relative high current cost of two vaccine doses, there is interest in having a serological test prior to vaccination. History taking can be used to select women who can be offered screening. It is the case in the Netherland⁷⁸: if women do not know if they have had varicella and if they had a recent contact with an infected person, a test is performed.

As for rubella, screening for varicella is interesting for non-protected women, to provide them some advice (such as avoiding contact with infected people) and to propose vaccination after delivery.

In conclusion, the 2015 KCE acknowledgement of insufficient evidence was changed in a positive recommendation for varicella screening in women who have not had chickenpox according to their medical history. For more details on the process of recommendation development, see Appendix 14.21.

Recommendation	Strength of Recommendation	Level of Evidence
For pregnant women who have not had chickenpox according to their medical history, consider to perform a detection of IgG against chicken pox. Non-immune pregnant women should stay away from anyone who has chickenpox or a skin rash. [KCE 2004, amended]	Weak	NA



4.5.12 Asymptomatic bacterial vaginosis - update

Bacterial vaginosis during pregnancy has been associated with preterm birth, even if the infection occurred early and spontaneously resolved later (KCE 2004, Australian 2014). A systematic analysis of ten randomized clinical trials showed that oral or vaginal antibiotic are effective in the treatment of bacterial vaginosis but do not change the risk of preterm birth (KCE 2004).

The Australian 2014 guideline recommended not to routinely screen for asymptomatic bacterial vaginosis in pregnancy and quoted a systematic review supporting this statement (Nygren et al. 2008 in Australian 2014 guideline) because:

- “no studies directly addressed the adverse effects of screening pregnant women who are asymptomatic for bacterial vaginosis;
- there is no clear benefit for the general population from screening and treating asymptomatic bacterial vaginosis during pregnancy; and
- although a subgroup of high-risk women may benefit from screening and treatment for bacterial vaginosis in pregnancy, a sizeable group would receive either no benefit or may experience harm.”

In 2004, the KCE guideline concluded there was not sufficient evidence to support systematic screening for asymptomatic bacterial vaginosis.

The GDG acknowledged that the balance benefit-harm is not in favour of this test for women without history of previous preterm birth. Moreover, in case of positive result, there is a risk that treatment is offered systematically despite uncertainties about efficacy and despite potential harmful effect.

In conclusion, the 2015 KCE acknowledgement of insufficient evidence was changed in a negative recommendation against screening for asymptomatic bacterial vaginosis. For more details on the process of recommendation development, see Appendix 14.22.

Recommendation	Strength of Recommendation	Level of Evidence
Do not routinely offer pregnant women to test for asymptomatic bacterial vaginosis. In fact, evidence suggests that the detection and treatment of asymptomatic bacterial vaginosis for pregnant women at low risk does not have any effect on the risk of premature birth. [KCE 2004, amended]	Weak	B*

* Level of evidence from Australian 2014 guideline: B=One or two level II studies with a low risk of bias or systematic review/several level III studies with a low risk of bias



4.5.13 Asymptomatic bacteriuria - update

Asymptomatic bacteriuria during pregnancy increases the risk of preterm birth, especially if the infection has progressed to pyelonephritis (Australian 2014 guideline).

The Australian 2014 guideline recommended to routinely offer screening for asymptomatic bacteriuria given the effectiveness of available treatments and the reduced risk of pyelonephritis.

According to the Australian 2014 guideline, universal screening is supported by a Cochrane review (Smaill & Vasquez 2007) and an analysis of cost-effectiveness of screening (Rouse et al 1995). The Cochrane review found that antibiotic treatment compared with placebo or no treatment is effective in clearing asymptomatic bacteriuria and reduces the incidence of pyelonephritis by 75% (Smaill & Vasquez 2007 in Australian 2014 guideline).

There is no consensus in the literature about the optimal timing and screening frequency for asymptomatic bacteriuria. However, in a prospective study (n=3 254), a single urine specimen obtained between 12 and 16 weeks gestation identified 80% of women who ultimately had asymptomatic bacteriuria (Stenqvist et al. 1989 in Australian 2014 guideline).

Although most guidelines recommended a single urine culture at the first antenatal visit, two prospective studies have concluded that urine should be cultured in each trimester of pregnancy to improve the detection rate of asymptomatic bacteriuria (McIsaac et al. 2005; Tugrul et al. 2005 in Australian 2014 guideline). However, there has been no prospective evaluation of repeated testing during pregnancy (Schnarr & Smaill 2008 in Australian 2014 guideline).

The KCE 2004 guideline recommended the systematic screening for asymptomatic bacteriuria and mentioned this could be done during the first visit but without having found evidence supporting this timing.

The GDG agreed with the recommendation of universal screening for asymptomatic bacteriuria. According to the Australian 2014 guideline, the aim of the test is to avoid pyelonephritis (and indirectly preterm birth). The GDG proposed to add this aim to the Belgian recommendation. Concerning the timing, the Australian 2014 guideline proposed to perform the test during the first antenatal visit but it appears this is scheduled between 12-16 weeks. It is not the timing of the first antenatal visit in Belgium. The GDG proposed to replace "at the first antenatal visit" by "at the beginning of the second trimester."

In conclusion, the KCE 2004 recommendation for universal screening for asymptomatic bacteriuria remained but with two minor changes about the aim and the timing of the screening. For more details on the process of recommendation development, see Appendix 14.23.

Recommendation	Strength of Recommendation	Level of Evidence
Offer each pregnant woman testing for asymptomatic bacteriuria (on a mid-stream urine sample for a white blood cell count and culture) as treatment is effective and reduces the risk of pyelonephritis. Consensus among experts recommends performing this culture at the start of the second trimester. [KCE 2004, amended]	Strong	A*

* Level of evidence from Australian 2014 guideline: A=One or more level I studies with a low risk of bias or several level II studies with low risk of bias



4.6 Screening for maternal clinical problems

4.6.1 Gestational diabetes - full search

4.6.1.1 Background

Gestational diabetes mellitus (GDM) is a risk factor for later development of Type 2 Diabetes for pregnant women and is associated with perinatal outcomes such as macrosomia.⁷⁹ During decades, a two-steps screening method was widely accepted. It consists of a first step with the 50g glucose challenge test (GCT) administered between 24 and 28 weeks and, for those who have an abnormal GCT, a second step with 100g oral glucose tolerance test (OGTT). Multiple diagnostic criteria for the 3-hour OGTT currently exist.^{80,81} The National Diabetes Data Group (NDDG) from US specifies using fasting, 1-hour, 2-hour, and 3-hour plasma glucose levels of 105mg/dL, 190mg/dL, 165mg/dL, and 145mg/dL, respectively. The Carpenter-Coustan criteria are more inclusive with thresholds of 95mg/dL, 180mg/dL, 155mg/dL, and 140mg/dL, with minimal two abnormal values leading to the diagnosis of gestational diabetes.

In 2008, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study examined the risks of adverse outcomes associated with various degrees of maternal glucose intolerance less severe than that in overt diabetes mellitus.⁸² The results of this study led the International Association of Diabetes Pregnancy Study Groups (IADPSG) to review the screening strategy for diagnosing GDM: 2-step screening can be abandoned in favour of a single 75 g oral glucose tolerance test at 24-28 weeks. The criteria are 92mg/dL, 180mg/dL, and 153mg/dL, using fasting, 1-hour and 2-hour plasma glucose levels respectively. One abnormal value is sufficient to diagnose gestational diabetes.

However there is an absence of a universally accepted gold standard for diagnosis and there is continuing debate about which are the most appropriate diagnostic criteria to apply. Moreover, there is little consensus on the best diagnostic methods (who should be screened, if screening should be universal or selective, or how screening should be performed) and thresholds at which therapeutic management is necessary.⁸³⁻⁸⁵

In Belgium, several strategies co-exist (see Appendix 4). In agreement with most international guidelines, both strategies recommend to test for unknown pre-existing diabetes by measuring fasting glucose level, random glucose values or glycosylated haemoglobin before or at the beginning of pregnancy. This becomes more and more important as the prevalence of obesity and type II diabetes is rising, also in women of childbearing age.

A prospective multi-centric cohort study, the BEDIP study (Belgian Diabetes in Pregnancy study), has started in 2014 with the aim to compare the difference in GDM prevalence between the 2-step (50 glucose challenge test followed by a 75g OGTT) and 1-step IADPSG (directly 75g OGTT) screening strategy. The first results are not expected before 2017.

In this chapter, we reviewed the evidence to answer the following questions:

- Which screening strategies are more accurate and effective to screen healthy pregnant women for gestational diabetes?
- What is the diagnostic accuracy of the 50g glucose challenge test?

For detailed research questions in the PICO format, we refer to Appendix 5.

A single search strategy was performed for both questions (see Appendix 6). A total of 4 871 records were identified, and after de-duplicating, 2 445 records formed the first screening set. A total of 111 records for the first question and 41 records for the second question were screened on full text. A description of the study selection (including Prisma flowchart) is available on Appendix 7.

4.6.1.2 Benefits-harms of different screening strategies for gestational diabetes

Among the 111 full texts that investigated the effects of different screening strategies for gestational diabetes, one Cochrane Review, two RCTs and six observational studies were found which seemed to match inclusion criteria. However, on closer inspection the Cochrane review⁸⁶ included one RCT⁵⁶ which was excluded from our report on the basis of incomplete outcome reporting – outcomes of interest are only reported for the subset of participants who were diagnosed with gestational diabetes, therefore the outcome is not a complete representation of the clinical effectiveness of the screening strategies. The other three cohort studies included in the Cochrane Review were investigating different methods of glucose loading



(e.g. chocolate bar or drink) and this was not a comparison of interest in the current review protocol. Therefore this Cochrane Review was not included or expanded upon as part of the current review.

- From the two randomized controlled trials found with the search strategy^{87, 88}, one comparing routine with selected screening which was only available in abstract format so details are limited.⁸⁸ The other comparing different combinations of one-step (75g OGTT) or two steps (50g GCT followed by 75g or 100g OGTT) screening tests.⁸⁷ This RCT was focused on a cost analysis so reporting for outcomes of clinical interest is very limited.
- Among the six observational studies included:⁸⁹⁻⁹⁴
 - Three papers investigated universal screening compared to some form of selected screening^{43, 90, 94}; however, one of these papers⁹⁰ reported the outcomes of clinical interest for this review only by describing them narratively in the text. Therefore the findings from this paper could not be analyzed and compared alongside the rest of the evidence.
 - Three papers investigated early screening strategies (<24 weeks) compared to late screening strategies.⁹¹⁻⁹³ Only one of these papers was a true early vs. late screening comparison⁹², as the other two involved a comparison of an early group screened because they had risk-factors compared with a group who were screened later because they did not have risk factors. Therefore the two groups were not comparable at baseline and the effect may be confounded and not a representation of the screening strategies themselves. One paper (also represented in the universal vs. selected screening comparison) investigated different thresholds for the 75g OGTT when used for selected screening.⁹⁴

The included RCTs and observational studies, while capturing all of the different aspects around screening strategies listed in the review protocol (at which threshold, at which gestational age, and in all women or not), used a variety of different combinations of random blood glucose and/or glucose challenge test and/or oral glucose tolerance test, and reported a diverse range of outcomes, so none of the outcomes could be pooled. For full details of the included studies please see evidence tables in Appendix 9.

The following prioritized outcomes were reported: macrosomia, large for gestational age, birth weight $\geq 4000\text{g}$, malformations, neonatal hypoglycemia and respiratory distress, stillbirth/neonatal death –including fetal mortality and perinatal mortality, and long-term diabetes 2 – including diabetes on follow-up. Some included papers also reported on the maternal outcome of pre-eclampsia. While this outcome was not prioritized as important in the review protocol, for papers already included in the review that reported this outcome, findings have been added for interest only.

For the quality appraisal, evidence tables, Grade profiles and Forest plots, we refer to the Appendices 8, 9, 10 and 11.

Universal screening vs. selected screening

Macrosomia (important outcome)

- Very low quality evidence from one RCT⁸⁸ comprising of 2 401 pregnant women suggested that there was no clinically important difference in neonatal macrosomia between women who received universal screening for gestational diabetes or selected screening if indicated during pregnancy using the 50g GCT followed by the 100g OGTT (RR 1.03, 95%CI 0.83–1.29).
- Very low quality evidence from a before-and-after observational study⁸⁹ comprising of 261 pregnant women suggested that universal screening at 26-30 weeks was harmful with respect to neonatal macrosomia compared with selected screening based on risk at 24-28 weeks using the 75g OGTT (RR 3.79 95% 0.82–17.51). However, the wide confidence interval around the point estimate suggests universal screening is associated with both no clinical harm and clinical harm so we cannot be confident in the effect.

Large for gestational age (important outcome)

- Very low quality evidence from a before-and-after observational study⁸⁹ comprising of 261 pregnant women suggested that there was no clinically important difference between women who experienced universal screening at 26-30 weeks compared with women who had selected screening based on risk at 24-28 weeks, with respect to having a baby who was considered large for their gestational age (RR 1.22 95%CI 0.47–3.14). The wide confidence interval around the point

estimate suggests universal screening is associated with both clinical benefit and clinical harm so we cannot be confident in the effect. This study used the 75g OGTT with a 2 hour threshold of ≥ 8.0 mmol/L for both universal and selected screening groups.

- Very low quality evidence from a retrospective observational study⁹⁴ comprising of 125 510 pregnant women found no clinically important difference in large for gestational age babies between women who received universal screening for gestational diabetes or selected screening based on risk factors (RR 1.02 95%CI 0.95–1.1). This study used the 75g OGTT with a 2 hour threshold of ≥ 180 mg/dl (10.0mmol/L) for both universal and selected screening groups.

Respiratory distress (important outcome)

- Very low quality evidence from a before-and-after observational study⁸⁹ comprising of 261 pregnant women suggested that universal screening for gestational diabetes in pregnancy at 26-30 weeks using the 75g OGTT was beneficial when compared to selected screening with the same test at 24-28 weeks, for neonatal respiratory distress (RR 0.34, 95%CI 0.11–1.05). However, the wide confidence interval around the point estimate suggests universal screening is associated with both clinical benefit and no clinical benefit so we cannot be confident in the effect.

Neonatal hypoglycaemia

- Very low quality evidence from a before-and-after observational study⁸⁹ comprising of 261 pregnant women suggested that universal screening at 26-30 weeks was harmful with respect to neonatal hypoglycaemia compared with selected screening based on risk at 24-28 weeks using the 75g OGTT (RR 1.42 95% 0.71–2.83). However, the wide confidence interval around the point estimate suggests universal screening is associated with both clinical benefit and clinical harm so we cannot be confident in the effect.

Conclusions

- Based on very low quality evidence, it cannot be concluded whether **universal screening is more or less effective compared with selected screening with respect to neonatal morbidity**, including macrosomia and large for gestational age. On the basis of neonatal hypoglycaemia it may be concluded that universal screening may be less effective compared with selected screening, but not with respect of respiratory distress.

Early screening vs. late screening

Birth weight ≥ 4000 g (important outcome)

- Very low quality evidence from one prospective observational study⁹² comprising of 600 pregnant women suggested that early screening (between 9-20 weeks) for gestational diabetes using the 50g GCT then the 100g OGTT was associated with higher rates of babies born whose birth weight exceeded 4000g compared to those screened later (27-31 weeks) using the same series of tests (RR 1.39, 95%CI 0.83–2.32). However, the wide confidence interval around the point estimate suggests early screening is associated with both no clinical harm and clinical harm so we cannot be confident in the effect.

Macrosomia (important outcome)

- Very low quality evidence from one retrospective observational study⁹¹ comprising of 865 pregnant women suggested that there was no clinically important difference between women who had early screening due to gestational diabetes in a previous pregnancy (<24 weeks) using the glucose tolerance test with an unspecified glucose load compared to those without the presence of the risk factor who were screened later (26-30 weeks) using the same test with respect to having a macrosomic neonate (RR 0.83, 95%CI 0.57–1.21). However, the wide confidence interval around the point estimate suggests early risk-factor screening is associated with both clinical benefit and no clinical benefit so we cannot be confident in the effect.
- Very low quality evidence from one prospective observational study⁹³ comprising of 458 pregnant women suggested that early screening due to risk-factors (10-14 weeks) using the 50g GCT followed by the 100g



OGTT was associated with **higher rates of macrosomia** compared to those without the presence of the risk factor who were screened later (24-28 weeks) using the same combination of tests (RR 2.09, 95%CI 1.19–3.67).

Malformations (important outcome)

- Very low quality evidence from one retrospective observational study⁹¹ comprising of 865 pregnant women suggested that there was no clinically important difference between women who had early screening due to gestational diabetes in a previous pregnancy (<24 weeks) using the glucose tolerance test with an unspecified glucose load compared to those without the presence of the risk factor who were screened later (26-30 weeks) using the same test with respect to rates of major malformations (RR 0.91, 95%CI 0.35–2.37). However, the wide confidence interval around the point estimate suggests early risk-factor screening is associated with both clinical benefit and clinical harm so we cannot be confident in the effect.
- Very low quality evidence from one prospective observational study⁹³ comprising of 458 pregnant women suggested that early screening due to risk-factors (10-14 weeks) using the 50g GCT followed by the 100g OGTT was associated with higher rates of infant malformations compared to those without the presence of the risk factor who were screened later (24-28 weeks) using the same combination of tests (RR 4.79, 95%CI 0.56–40.65). However, the extremely wide confidence interval around the point estimate suggests early risk-factor screening is associated with both clinical benefit and clinical harm so we cannot be confident in the effect.

Fetal mortality (important outcome)

- Very low quality evidence from one prospective observational study⁹³ comprising of 458 pregnant women suggested that early screening due to risk-factors (10-14 weeks) using the 50g GCT followed by the 100g OGTT was associated with higher rates of fetal mortality compared to those without the presence of the risk factor who were screened later (24-28 weeks) using the same combination of tests (Peto OR 7.08, 95%CI 0.14–357.14). However, the extremely wide confidence interval around the point estimate suggests early risk-factor screening is

associated with both clinical benefit and clinical harm so we cannot be confident in the effect.

Perinatal mortality (important outcome)

- Very low quality evidence from one retrospective observational study⁹¹ comprising of 865 pregnant women suggested that early screening due to gestational diabetes in a previous pregnancy (<24 weeks) using the glucose tolerance test with an unspecified glucose load was associated with **higher rates** of perinatal mortality compared to those without the presence of the risk factor who were screened later (26-30 weeks) using the same test (RR 3.81, 95%CI 0.96–15.07). However, the wide confidence interval around the point estimate suggests early risk-factor screening is associated with both no clinical harm and clinical harm so we cannot be confident in the effect.

Respiratory distress syndrome (important outcome)

- Very low quality evidence from one prospective observational study⁹³ comprising of 458 pregnant women suggested that early screening due to risk-factors (10-14 weeks) using the 50g GCT followed by the 100g OGTT was associated with fewer rates of respiratory distress syndrome compared to those without the presence of the risk factor who were screened later (24-28 weeks) using the same combination of tests (RR 0.19, 95%CI 0.02–1.68). However, the wide confidence interval around the point estimate suggests early risk-factor screening is associated with both clinical benefit and clinical harm so we cannot be confident in the effect.

Diabetes on follow up (important outcome)

- Very low quality evidence from one retrospective observational study⁹¹ comprising of 633 pregnant women found that early screening due to gestational diabetes in a previous pregnancy (<24 weeks) using the glucose tolerance test with an unspecified glucose load was associated with **higher rates** of diabetes on follow-up compared to those without the presence of the risk factor who were screened later (26-30 weeks) using the same test (RR 38.64, 95%CI 9.24–161.60).



Pre-eclampsia

- Very low quality evidence from one retrospective observational study⁹¹ comprising of 865 pregnant women suggested that early screening due to gestational diabetes in a previous pregnancy (<24 weeks) using the glucose tolerance test with an unspecified glucose load was associated with higher rates of pre-eclampsia compared to those without the presence of the risk factor who were screened later (26-30 weeks) using the same test (RR 1.5, 95%CI 0.81–2.79). However, the wide confidence interval around the point estimate suggests early risk-factor screening is associated with both no clinical harm and clinical harm so we cannot be confident in the effect.

Conclusions

- Based on very low quality evidence **it cannot be concluded whether early risk-factor screening is more or less effective compared with late non-risk-factor screening with respect to neonatal morbidity, including birth weight $\geq 4000\text{g}$, macrosomia, malformations and respiratory distress syndrome. On the basis of increased cases of fetal/neonatal mortality and diabetes on follow up it may be concluded that early risk-factor screening is less effective than late non-risk factor screening.**

Comparisons of different thresholds for the 75g OGTT for screening for gestational diabetes

Large for gestational age (important outcome)

- Very low quality evidence from one retrospective observational study⁹⁴ comprising of 113 322 pregnant women suggested that there was no clinically important difference between screening using the 75g OGTT with a threshold of 160 mg/dl (8.9mmol/L) compared to 180 mg/dl (10.0mmol/L) (RR 1.06 95%CI 0.96–1.17) with respect to large for gestational age neonates.
- Very low quality evidence from one retrospective observational study⁹⁴ comprising of 58 673 pregnant women suggested that there was no

clinically important difference between screening using the 75g OGTT with a threshold of 160 mg/dl (8.9mmol/L) compared to 220 mg/dl (12.2mmol/L) (RR 1.16 95%CI 1.04–1.3) with respect to large for gestational age neonates. However as the lower value of the confidence interval crosses the clinical decision threshold (RR 1.25), we cannot be sure that the difference is clinically important.

- Very low quality evidence from one retrospective observational study⁹⁴ comprising of 154 727 pregnant women suggested that there was no clinically important difference between screening using the 75g OGTT with a threshold of 180 mg/dl (10.0mmol/L) compared with 220 mg/dl (12.2mmol/L) (RR 1.1 95%CI 1.04–1.16) with respect to large for gestational age neonates. However as the higher value of the confidence interval is below the clinical decision threshold (RR 1.25), we cannot be sure that the difference is clinically important.

Conclusions

- Based on the available, very low quality, evidence it may be concluded that **no particular threshold of 160, 180 or 220 mg/dl for the 75g OGTT is more effective than the other with respect to large for gestational age neonates.**

Comparisons of different combinations of glucose challenge and glucose tolerance tests when screening for gestational diabetes

Neonatal hypoglycaemia (important outcome)

- Low quality evidence from one RCT⁸⁷ comprising of 1000 pregnant women suggested that using the one-step method of 75g OGTT to screen for gestational diabetes was associated with higher rates of hypoglycaemia compared to using the two-step method of 50g GCT followed by the 75g OGTT (RR 1.57, 95%CI 0.92–2.68). However, the wide confidence interval around the point estimate suggests universal screening is associated with both no clinical harm and clinical harm so we cannot be confident in the effect.



- Low quality evidence from one RCT⁸⁷ comprising of 1 000 pregnant women suggested that using the **one-step method of 75g OGTT** to screen for gestational diabetes was associated with higher rates of hypoglycaemia compared to using the two-step method of 50g GCT followed by the 100g OGTT (RR 1.83, 95%CI 1.05–3.21). However, as the lower value of the confidence interval crosses the clinical decision threshold (RR 1.25), we cannot be sure that the difference is clinically important.
- Very low quality evidence from one RCT⁸⁷ comprising of 1000 pregnant women suggested that using the two-step method of 50g GCT followed by the 75g OGTT to screen for gestational diabetes was associated with no clinically important difference in rates of hypoglycaemia compared to using the two-step method of 50g GCT followed by the 100g OGTT (RR 1.17, 95%CI 0.63–2.16). However, as the lower value of the confidence interval crosses the clinical decision threshold (RR 1.25), we cannot be sure that the difference is clinically important.

Pre-eclampsia

- Low quality evidence from one RCT⁸⁷ comprising of 1000 pregnant women suggested that using the one-step method of 75g OGTT to screen for gestational diabetes was associated with higher rates of pre-eclampsia compared to using the two-step method of 50g GCT followed by the 75g OGTT (RR 1.5, 95%CI 0.84–2.69). However, the wide confidence interval around the point estimate suggests universal screening is associated with both no clinical harm and clinical harm so we cannot be confident in the effect.
- Low quality evidence from one RCT⁸⁷ comprising of 1000 pregnant women suggested that using the one-step method of 75g OGTT to screen for gestational diabetes was associated with higher rates of pre-eclampsia compared to using the two-step method of 50g GCT followed by the 100g OGTT (RR 1.88, 95%CI 0.88–2.88). However, the wide confidence interval around the point estimate suggests universal screening is associated with both no clinical harm and clinical harm so we cannot be confident in the effect.
- Very low quality evidence from one RCT⁸⁷ comprising of 1000 pregnant women suggested that using the two-step method of 50g GCT followed

by the 75g OGTT to screen for gestational diabetes was associated with no clinically important difference in rates of pre-eclampsia compared to using the two-step method of 50g GCT followed by the 100g OGTT (RR 1.06, 95%CI 0.55–2.03). However, the wide confidence interval around the point estimate suggests universal screening is associated with both clinical benefit and clinical harm so we cannot be confident in the effect.

Conclusions

- Based on the available, low to very low quality, evidence showing increased cases of hypoglycaemia, it may be concluded that **the one-step method of 75g OGTT may be less effective than either two-step GCT/OGTT method, and that neither of the two-step methods is more or less effective than the other.**

The GDG acknowledged that although no high-quality studies have compared a policy of screening for GDM with no screening, the use of diabetes screening strategy during pregnancy is no longer questioned as moderate level of evidence shows a reduced risk of pre-eclampsia, shoulder dystocia and macrosomia if gestational diabetes is treated.⁹⁵ Moreover, it is important to remember the need for screening for unknown pre-existing diabetes at first prenatal contact using the tests to diagnose diabetes outside pregnancy (for instance by measurement of a fasting glycaemia). Due to the increasing prevalence of type 2 diabetes and obesity worldwide and therefore also in women of childbearing age, this is now recommended by most associations including ADA, Endocrine Society, WHO and also by the Flemish and French speaking Belgian Associations. The GDG underlined also that an integrated approach should be encouraged and that the management of overweight and obesity should ideally be started before pregnancy. A preconception assessment might be provided with counselling (including information on the maternal and fetal risks of obesity in pregnancy and promotion of weight-reduction program). Concerning the IADPSG criteria, a study was published after the literature search performed for this guideline (Duran A et al. 2014).⁹⁶ This Spanish study compared two cohorts (before and after implementing the IADPSG strategy) and showed that using the one-step approach with the IADPSG



criteria was associated with reduced rates of adverse pregnancy outcomes and was also cost-effective compared to the previous use of the two-step screening strategy with the Carpenter and Coustan criteria. However, the methodological quality of this study (non-contemporary cohorts, effect on fetal outcomes non adjusted for confounders such as smoking, low number of events, no information on adverse maternal outcomes such as hypoglycemia but also anxiety) implies that uncertainties remain and do not allow any change in the conclusions.

4.6.1.3 Diagnostic accuracy of the 50g glucose challenge test as a screening strategy for gestational diabetes

Among the 41 full texts that investigated the diagnostic accuracy of the 50g glucose challenge test, five cohort studies were found looking at the diagnostic accuracy of the 50g GCT compared with a reference standard of 100g OGTT. Two prospective studies used a 140mg/dl threshold in women not at high risk for gestational diabetes^{97, 98}; one retrospective cohort in a high-risk Mexican population investigated thresholds of 130, 135 and 140mg/dl⁹⁹; one cross-sectional cohort in a high-risk population in Thailand investigated thresholds of 140mg/dl¹⁰⁰; and one prospective cohort study in a high-risk population also in Thailand investigated the diagnostic accuracy of threshold ranges rather than specific cut-offs (130-139mg/dl and 140-149mg/dl).¹⁰¹

Results are presented in two subgroup of population: non-risk and high risk population. For details on quality appraisal, evidence tables, GRADE profiles and Forest plots, please see Appendices 8, 9, 10 and 11.

Non-risk population

50g glucose challenge test & glycaemia after 1H with threshold 140mg/dl

- Very low quality evidence from two prospective cohorts^{97, 98} comprising of 861 pregnant women *not at high risk* for gestational diabetes reported low and variable sensitivities of 77% (95%CI 46-95%) and 58% (95%CI 37-77%); and higher, more consistent specificities of 87% (95%CI 82-30%) and 91% (95%CI 88-93%).

High-risk population

50g glucose challenge test & glycaemia after 1H with threshold 130mg/dl

- Low quality evidence from one retrospective cohort⁹⁹ comprising of 445 *high risk* pregnant women reported a sensitivity of 91% (95%CI 71-99%) and a specificity of 81% (95%CI 77-84%).

50g glucose challenge test & glycaemia after 1H with threshold 135mg/dl

- Low quality evidence from one retrospective cohort⁹⁹ comprising of 445 *high risk* pregnant women reported a sensitivity of 87% (95%CI 66-97%) and a specificity of 86% (95%CI 82-89%).

50g glucose challenge test & glycaemia after 1H with threshold range of 130-139mg/dl

- Very low quality evidence from one prospective cohort¹⁰¹ comprising of 304 *high risk* pregnant women reported a sensitivity of 93% (95%CI 68-100%) and a specificity of 63% (95%CI 57-69%) when using cut-offs ranging anywhere between 130-139mg/dl.

50g glucose challenge test & glycaemia after 1H with threshold 140mg/dl

- Very low quality evidence from one retrospective cohort study⁹⁹ and one cross-sectional cohort study¹⁰⁰ comprising of 804 pregnant women at *high risk* for gestational diabetes reported consistent and moderately high sensitivities of 87% (95%CI 66-97%) and 90% (95%CI 79-96%); and lower and variable specificities of 87% (95%CI 83-90%) and 61% (95%CI 55-66%).

50g glucose challenge test & glycaemia after 1H with threshold range of 140-149mg/dl

- Very low quality evidence from one prospective cohort¹⁰¹ comprising of 304 *high risk* pregnant women reported a sensitivity of 93% (95%CI 68-100%) and a specificity of 78% (95%CI 73-83%) when using cut-offs ranging anywhere between 140-149mg/dl.

**Conclusion**

- For pregnant women *not at high risk* of gestational diabetes, **the 140mg/dl threshold of the 50g GCT does not seem to be sensitive, although performs better for specificity.** This seems to suggest a rule in rather than rule out test. For pregnant women who are *at high-risk* of gestational diabetes, there does not seem to be a great difference between the 130, 135 and 140mg/dl thresholds in terms of gaining higher sensitivity or specificity. When using a range of thresholds sensitivity may improve but specificity falls.

The GDG underlined that higher sensitivity may be preferable at initial investigation, in order to reduce the range of diagnostic possibilities and to rule out the disease being screened for. This is especially the case where a failure to diagnose may cause important complications. Whereas specificity may be preferable at the later stage to confirm diagnosis or when false-positives could result in physical, emotional or financial harm.⁹⁷ As well as these clinical considerations, complexity of performing the test, practicality, resource costs, and reproducibility should all be taken into consideration.

4.6.1.4 Recommendation for gestational diabetes

Based on the retrieved evidence and the discussion with GDG and stakeholders, we developed two recommendations concerning the screening for gestational diabetes. The considerations that lead to the recommendations are summarized below.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	<p>Although no high-quality studies have compared a policy of screening for GDM with no screening, the use of a diabetes screening strategy during pregnancy is no longer questioned as moderate level of evidence shows a reduced risk of pre-eclampsia, shoulder dystocia and macrosomia if gestational diabetes is treated.⁹⁵</p> <p>It remains unclear if screening should be applied to all women or only to women who are at increased risk. Defenders of the universal screening strategy argue that randomized controlled trials have shown that also treatment of mild gestational diabetes has beneficial effect on important outcomes.^{102, 103} Cases of mild gestational diabetes may be missed when only women at risk are screened.</p> <p>For the same reason, the use of the new diagnostic criteria proposed by the IADPSG has been promoted. The IADPSG criteria are based on the findings in the HAPO study that show a continuum of increasing risk for adverse outcomes (elevated birth weight, cord C-peptide) with increasing maternal glucose, also at levels below the diagnostic thresholds of gestational diabetes. As the RCTs in women with mild gestational diabetes mentioned earlier^{102, 103} have shown a positive effect of treatment, it may be reasonable to lower diagnostic thresholds according to the IADPSG criteria and consequently diagnose and treat a larger group of pregnant women.</p> <p>However, many issues remain unresolved. First, the main outcomes considered by the HAPO study are mainly intermediate outcomes, data on important clinical outcomes such as perinatal death and birth trauma are less convincing.⁸² Second, the study population included in the studies on mild GDM do not exactly match the population that would be additionally diagnosed with gestational diabetes by using the IADPSG criteria. Third, a</p>



high BMI is a risk factor for GDM and for adverse pregnancy outcomes and can be in itself an indication for diet measures and follow-up. Fourth, it remains unclear if the group of women who are additionally diagnosed with GDM are at increased risk to develop diabetes mellitus type II and if screening and subsequent preventive measures would help. In a Scottish follow-up study, especially women with a fasting glucose of more than 126 mg/dl (7.0mmol/l) and high weight were at risk for developing type II diabetes in later life.¹⁰⁴ Finally, the validity of the HAPO findings in real-world is questionable as laboratory tests routinely used lack sufficient precision and reproducibility (in the HAPO study, an enzymatic method with high accuracy was used in a central laboratory). Overall, there remains too much uncertainty about the clinical effectiveness of adopting the screening strategy recommended by IADPSG to recommend general implementation in Belgium, also in view of the additional resources that would be needed (see below). If the strategy is adopted, it should be in the framework of further research and data collection to clarify its effect on important maternal and neonatal outcomes, both in the short and long term.

Quality of evidence

Low to very low level of evidence

Costs (resource allocation)

The use of the IADPSG screening strategy is associated with an increase of resources needed compared to the two-step approach often used in Belgium (50g challenge test followed by OGTT if abnormal). All women have to present after a period of fasting, and need more blood samplings, which may be an organisational challenge to obstetric clinics. Furthermore, as more women will be diagnosed with GDM, more women will need frequent follow-up and treatment during pregnancy. Also after childbirth, this large group of women will require further follow-up in view of the possible development of diabetes type II, which may put a lot of workload on general practitioners.

Patients values and preferences

A false positive result for gestational diabetes can lead to a significant decline in pregnant women's perceptions of their own health and negatively affect their experience of pregnancy^{105, 106} A diagnosis of GDM also raises patient anxiety and compromises the perception of a woman's own health and the health of her baby. Some women may experience the challenge test or OGTT as uncomfortable. The fasting state required for the OGTT may be difficult to pregnant women. Therefore, it is important to define diagnostic criteria as precise as possible so that only women who clearly benefit from treatment and follow-up are labelled as having gestational diabetes. As it is uncertain if women who are at low risk for GDM benefit from screening, they should be well informed about the possible advantages and disadvantages of screening and have the possibility to opt out.



Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> Offer a screening test for gestational diabetes mellitus to at-risk women between 24 and 28 weeks. [KCE 2015] 	Strong	NA*
<ul style="list-style-type: none"> Consider to perform a screening test for gestational diabetes mellitus in pregnant women otherwise not at risk for gestational diabetes. [KCE 2015] 	Weak	Very low
<ul style="list-style-type: none"> There is currently insufficient evidence to generally recommend the replacement of the two-step screening strategy for gestational diabetes by another kind of screening or by other thresholds. The IADPSG criteria should preferably be used within the framework of research and clinical data collection. [KCE 2015] 	NA	NA

* The aim of the full search of literature was not to assess the efficacy of diabetes screening but to determine which screening strategies are more accurate. In the 2004 KCE guideline, screening of gestational diabetes between 24 and 28 weeks was supported by evidence of high level (level A)

4.6.2 Hypothyroidism – full search

4.6.2.1 Background

Clinical and subclinical hypothyroidism have been linked with adverse maternal, neonatal and infant outcomes. An increased thyrotropin level has been associated with an increased incidence of miscarriage, gestational diabetes, pre-eclampsia, premature delivery and neuropsychological development of the offspring.¹⁰⁷ Results have been inconsistent however, and many studies were small. Nevertheless, screening for subclinical hypothyroidism has been suggested, as timely treatment could possibly reverse the risk for adverse outcomes.

A large cross-sectional study was conducted in Belgium in the period from September 2010 to June 2011 and included 1 311 women in their first and third trimesters.¹⁰⁸ The data originated in the same cross-sectional study that also evaluated the prevalence of vitamin D deficiency in Belgian women.¹⁰⁹

Women in first and third trimesters were approximately equally distributed. The frequencies of thyroid stimulating hormone (TSH) values above normal trimester specific values in the first and third trimester were 8.3% (95%CI, 6.16 - 10.44) and 6.1% (95%CI, 4.28 - 7.92), respectively. Overall, prevalence of subclinical and overt hypothyroidism was 6.8% (95%CI, 5.44 to 8.16) and 0.4% (95%CI, 0.06 to 0.74), respectively. Gestational age was significantly and negatively associated with TSH; because reference values differ by trimester, this does not imply an association with hypothyroidism.

To investigate if screening for maternal subclinical hypothyroidism during pregnancy may be useful, we reviewed the evidence to answer the following questions:

- What are the benefits and harms of routine screening for hypothyroidism in asymptomatic pregnant women compared with no routine screening (or targeted screening of clinically at risk women) (direct evidence)?
- Compared with no or lower pharmacological doses, what are the benefits and harms of levothyroxine or selenomethionine treatment of pregnant women with subclinical hypothyroidism? Do treatment effects vary with their risk status (i.e. low versus high risk for hypothyroidism) (indirect evidence)?

For detailed research questions in the PICO format, we refer to Appendix 5.

A search strategy was performed separately for the two questions (see Appendix 6). A total of 1 236 records were identified concerning the screening for hypothyroidism, and after de-duplicating, 1 147 records formed the first screening set. A total of 16 records were screened on full text. Concerning the hypothyroidism therapy, a total of 517 records were identified, and after de-duplicating, 480 records formed the first screening set. A total of 98 records were screened on full text. A description of the study selection (including Prisma flowchart) is available on Appendix 7.



4.6.2.2 Benefits-harms of routine screening for hypothyroidism in asymptomatic pregnant women - results

Among the 16 records screened on full text, no systematic review was identified. Two large RCTs met the eligibility criteria^{110, 111} and no comparative observational evidence was found.

- Lazarus et al. (2012)¹¹⁰ compared universal screening with no screening in 21 846 women. A blood sample was taken at the first antenatal hospital visit, before 15 weeks and 6 days of pregnancy. Serum samples from the screening group were immediately assayed for levels of free T4 and thyrotropin. Following delivery, frozen samples were tested for thyroid function in the no-screening group. For design efficiency, analysis was restricted to patients across both arms that tested positive for hypothyroidism. Follow-up duration was 3 years and the main objective was to evaluate differences in childhood cognition.
- In 4 562 pregnancies, Negro et al. (2010)¹¹¹ investigated universal versus targeted screening for hypothyroidism and hyperthyroidism (only 0.4% of the participants were hyperthyroid) but **specifically in TPO-antibody positive** pregnant women. Hypothyroidism was defined as TSH > 2.5 mIU/L in mothers who tested positive for thyroid peroxidase antibody (TPO-Ab positives). Antibody negative women with raised TSH were considered euthyroid (i.e. false negatives). TPO-Ab positive euthyroid mothers (i.e. TSH ≤ 2.5 mIU/L) underwent repeat TSH testing in second and third trimester but were not treated on the basis of antibody status alone. While all women underwent risk stratification (blinded to assigned strategy) as well as TPO-antibody, TSH and FT4 testing, the trial was designed in such a way that the following randomised hypothyroidism screening strategies could be inferentially compared:
 - **Universal** TPO-antibody testing of all women, followed by TSH screening of all antibody positive mothers. TPO-Ab positive hypothyroid mothers were treated with levothyroxine.
 - Clinical risk stratification followed by TPO-antibody screening of **high risk cases** and further followed by TSH screening of antibody positive mothers. TPO-Ab positive hypothyroid mothers were treated with levothyroxine.
 High risk was defined as presence of at least one of the following

risk factors: family history for autoimmune thyroid disease, presence of goitre, signs and symptoms suggestive for thyroid dysfunction, personal history for type 1 diabetes mellitus or other autoimmune disease, history of neck irradiation, previous miscarriages, or preterm deliveries.

- A third arm of universal TSH screening of all women irrespective of TPO-Ab status was conspicuous by its absence (as such, how the aforementioned screening strategies compare with this missing universal screening strategy remains unclear).

Follow-up duration was until delivery and adverse maternal and neonatal outcomes were of interest. Longer-term neuro-cognitive-behavioural outcomes were not investigated.

Following outcomes are presented: neuropsychological impairment, preterm birth, low birth weight, perinatal mortality, maternal gestational hypertension and pre-eclampsia. Because trials were heterogeneous in their aims and objectives, comparators, duration, outcomes, and risk of bias, no meta-analysis was attempted. No evidence was found considering overall maternal and perinatal adverse events. For details on quality appraisal and evidence tables, please see Appendices 8 and 9.

The following two comparisons were reported:

- Universal screening compared to no screening for hypothyroidism
- Universal screening compared to targeted TSH screening in TPO-antibody positive pregnant women.

Universal screening versus no screening

Neurological impairment (important outcome)

- Very low quality evidence from the RCT of Lazarus¹¹⁰ suggested that universal screening compared with no screening does not result in improved cognitive function in children at 3 years of age
 - No difference was found for the control standardised **IQ at 3 years** (as measured by Wechsler Preschool and Primary Scale of Intelligence):
 - Mean Difference: -0.8 (95%CI -2.6 to 1.1)
 - IQ < 85: RR 0.85 (95%CI 0.60 to 1.22); Risk Difference: -2.1 (95%CI -5.6 to 3.1)



- No differences were found in IQ for other cut-offs and individual assessment components
- No difference was found for **behaviour** (Child Behaviour Checklist T-score: MD -0.7; 95%CI -2.5 to 1.2) and Behaviour Rating Inventory of Executive Function, preschool T-score: MD= zero).

Preterm birth

- Very low quality evidence from the RCT of Lazarus¹¹⁰ suggested that universal screening compared with no screening does not result in improved fetal morbidity in terms of preterm birth
 - No difference was found for **preterm birth (<37 weeks)**: RR 0.71 (95%CI 0.42 to 1.20)

Universal screening versus targeted TSH screening in TPO-antibody positive pregnant women

Preterm birth

- Moderate quality evidence from the RCT of Negro¹¹¹ suggested that universal screening compared with targeted screening does not result in improved fetal morbidity in terms of preterm birth
 - No difference was found for **preterm birth (<37 weeks)**: RR 0.99; 95%CI 0.80 to 1.24
 - No difference was found for **preterm birth (<34 weeks)**: RR 0.98; 95%CI 0.64 to 1.49

Low birth weight

- Moderate quality evidence from the RCT of Negro¹¹¹ suggested that universal screening compared with targeted screening does not result in improved fetal morbidity in terms of preterm birth
 - No difference was found for **birth weight <2500g**: RR 0.97; 95%CI 0.74 to 1.27

Perinatal mortality (important outcome)

- Moderate quality evidence from the RCT of Negro¹¹¹ suggested that universal screening compared with targeted screening does not result in improved fetal and perinatal mortality

- No difference was found for **perinatal/neonatal death**: RR 0.92; 95%CI 0.42 to 2.02

Maternal outcomes (important outcome)

- Moderate quality evidence from the RCT of Negro¹¹¹ suggested that universal screening compared with targeted screening does not result in improved maternal outcomes
 - No difference was found for **gestational hypertension** (RR 1.02; 95%CI 0.80 to 1.29) and for **pre-eclampsia** (RR 0.87; 95%CI 0.64 to 1.18)

Conclusions

Universal screening versus no screening

- Based on the limited available very low quality evidence, **no clinically important difference** has been shown **between universal screening for hypothyroidism versus no screening** in terms of neonatal morbidity or neurological functioning.

Universal versus targeted TSH screening in TPO-antibody positive pregnant women

- Although longer-term evidence for neurodevelopmental delay and bone growth was not available, moderate quality of evidence suggests that **targeted screening for TPO antibodies and TSH of high risk pregnancies is as effective as, and no more harmful than, universal screening as far as major adverse neonatal and maternal pregnancy outcomes are concerned.**

The GDG acknowledged that although an association between (sub)clinical hypothyroidism and unfavourable neonatal and maternal outcomes has been suggested, evidence on the effectiveness of screening of subclinical hypothyroidism is sparse, especially for screening based on thyrotropin levels.

The GDG mentioned that the diagnostic accuracy is limited. There is a great variability in TSH concentration (during the day because of circadian cycle, depending on the trimester of pregnancy, after vomiting...) which makes difficult to determine an accurate threshold.



The GDG considered the cost of thyrotropin measurements as low. Resource use would not be considered as a major barrier for implementation of generalized screening even if no formal cost assessment was performed.

4.6.2.3 *Benefits-harms of therapy for subclinical hypothyroidism during pregnancy: results*

Among the 98 records screened on full text, eight records met the eligibility criteria. Finally, we included in the synthesis to answer this question: a high quality systematic review (Reid et al. 2013),¹¹² five RCTs and one observational study.

- Restricted to randomized controlled trial evidence, the review by Reid et al.¹¹² was based on two studies in pregnant euthyroid women who were **positive for thyroid peroxidase antibodies**. Negro et al. (2006)¹¹³ [N=115; gestational age at treatment initiation was approximately 10 weeks] investigated levothyroxine versus no treatment. Selenomethionine versus no treatment was evaluated by Negro et al. (2007)¹¹⁴ [N=169; gestational age at the time of treatment initiation was ≥ 12 weeks].
- One randomized controlled trial that was excluded by Reid et al., was included in our updated evidence synthesis of RCT evidence. This was Negro et al. (2010)¹¹¹ randomization of 4 562 pregnancies to universal versus targeted screen guided management of hypothyroidism and hyperthyroidism (only 0.4% of the participants were hyperthyroid). **All thyroid peroxidase antibody positive** (TPO-Ab) women with raised first trimester TSH (> 2.5 mIU/L) were treated with levothyroxine to maintain TSH < 2.5 mIU/L in first and < 3.0 mIU/L in second and third trimesters but only high risk women were managed similarly in the targeted screening group. For effectiveness of levothyroxine treatment of hypothyroidism in pregnancy, the trial data pertain to a unique patient population – low-risk pregnancies with raised TSH and TPO-antibody. Because the data originated in a subgroup analysis we judged the risk of bias as unclear for outcomes of levothyroxine effectiveness.
- In total, five RCTs not included in the review by Reid et al. met our eligibility criteria^{111, 115-118}, of which one that was testing selenomethionine did not provide relevant data.¹¹⁷ The remaining four

trials investigated levothyroxine therapy versus no treatment.^{111, 115, 116,}

¹¹⁸ All trials were judged as unclear risk of bias. Study populations were:

- Euthyroid TPO-Ab positive women (2 trials, total N = 148)^{115, 118}
- (Subclinical) hypothyroid women positive for TPO-Ab (1 trial, N=77)¹¹¹
- (Subclinical) hypothyroid women without TPO-Ab status determination (N analyzed= 29).¹¹⁶
- A high quality systematic review (last search date of Dec 2011) by Vissenberg et al. (2012)¹¹⁹ was used to identify observational studies and to attempt a de novo synthesis of evidence. Only one study was identified.¹²⁰ This study concerns women with subclinical hypothyroidism at no particular risk for hypothyroidism who received levothyroxine versus no treatment during early pregnancy (duration of treatment: ≥ 12 weeks of gestation until birth). The study was judged to be at high risk of bias and grossly underpowered for it to improve our confidence in estimates of effects obtained from RCT evidence. As such, the study data were not considered in our synthesis of evidence (outcome/N of events: miscarriage 28; preterm birth 9; low birth weight less than 2 500 grams 4; gestational hypertension 3).

Following outcomes are presented: preterm birth, low birth weight, NICY admission and maternal hypertension or pre-eclampsia. Evidence was not identified for the neurological impairment in childhood and for adverse events of hypothyroidism treatment. Miscarriages were considered in one study of very low quality concerning the therapy with selenomethionine. More details are available for quality appraisal, evidence tables, GRADE profiles and forest plots in Appendices 8, 9, 10 and 11.

The following two comparisons were reported:

- Levothyroxine compared with no treatment
- Selenomethionine compared with placebo



Levothyroxine versus no treatment

Preterm birth (important outcome)

- Low quality of evidence from four studies^{111, 113, 115, 116} comprising 288 newborns showed a **reduction** in the rate of **preterm birth < 37 weeks** with levothyroxine (RR 0.29; 95%CI 0.15 to 0.56). Besides aforementioned diversity in included patient population, there were clinical differences in terms of definition of preterm birth and treatment dose; however effect estimates were similar raising no major concerns about pooling data.
- Very low level of evidence from two studies^{111, 116} comprising 106 newborns showed no significant difference for **very preterm birth < 34 weeks** (RR 0.43; 95%CI 0.10 to 1.91).

Low birth weight

- Very low level of evidence from one RCT¹¹¹ comprising 77 newborns showed no difference in risk of **birth weight <2500g** with or without levothyroxine (RR 1.05; 95%CI 0.91 – 1.22).

NICU admission

- Very low level of evidence from one RCT¹¹¹ comprising 77 newborns showed no significant difference in risk of **NICU admission** with or without levothyroxine (RR 0.35; 95%CI 0.08 – 1.52).

Maternal outcomes

- Very low level of evidence from two studies^{111, 113} comprising 182 pregnant women showed no significant difference for **gestational hypertension** (RR 0.53; 95%CI 0.20 – 1.38) and for **pre-eclampsia** (RR 0.68 (95%CI 0.19 – 2.47) with or without levothyroxine treatment.

Selenomethionine vs. placebo

- Inconclusive very low quality evidence was found for outcomes of **miscarriage, preterm birth < 37 weeks, hypothyroidism, and pre-eclampsia** from a single RCT for this comparison.¹¹⁴ The study included 151 euthyroid pregnant women positive for thyroid peroxidase antibodies randomised to 200µg/day of selenomethionine or placebo at

12 weeks of gestation. The study was deemed as unclear risk of bias, specifically due to concerns about allocation concealment, performance bias, and selective reporting.

Conclusion

Levothyroxine vs. no treatment

- Low quality evidence suggests levothyroxine treatment early in pregnancy may reduce preterm birth but not low birth weight, NICU admissions, gestational hypertension or pre-eclampsia. Available evidence predominantly investigated euthyroid pregnancies that were positive for antibodies against thyroid peroxidase enzyme; precluding exploration of effect modification by antibody status. As such, **whether benefits and harms of therapy for subclinical hypothyroidism differ by thyroid peroxidase antibody status remains an unanswered equipoise.**
- There are no data from RCTs about long-term (i.e. neuro-cognitive-psychological and behavioural childhood outcomes) benefits of antenatal thyroid hormone replacement as well as important drug related harms.

Selenomethionine vs no treatment

- Inconclusive evidence exists about comparative effectiveness of selenomethionine treatment of subclinical hypothyroidism during pregnancy.

Concerning the treatment by levothyroxine, the GDG underlined that confidence on the result is low. There is high uncertainty about long-term (i.e. neuro-cognitive-psychological and behavioural childhood outcomes) benefits of antenatal thyroid hormone replacement.

4.6.2.4 Recommendation for subclinical hypothyroidism

Based on the retrieved evidence and the discussion with the GDG, we developed one recommendation concerning the screening for hypothyroidism in asymptomatic pregnant women. The considerations that lead to the recommendations are summarized below.



Other considerations

Factor	Comment
Balance between clinical benefits and harms	<p>Evidence on the effectiveness of screening or treatment of subclinical hypothyroidism is sparse, especially for screening based on thyrotropin levels. Furthermore, many questions remain unanswered with currently available evidence, e.g. screening based on antibodies and/or thyrotropin levels, effect of timing of treatment, influence of iodine supplementation, possible harms of treatment etc.</p> <p>Overall, the GDG recommends against universal screening for subclinical hypothyroidism but only as a weak recommendation, as the underpowered available evidence suggests a possible effect and furthermore, risk factors that may warrant evaluation of thyroid function are very frequent (e.g. age > 30 years old) so that screening can be defended.</p>
Quality of evidence	Very low level of evidence
Costs (resource allocation)	No formal cost assessment was performed but the GDG considers the cost of thyrotropin measurements as low. Resource use would not be considered as a major barrier for implementation of generalized screening.
Patients values and preferences	Not applicable.

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> Do not routinely offer screening for hypothyroidism to pregnant women otherwise at low risk for thyroid disease. [new KCE 2015] 	Weak	Very low



4.6.3 Vitamin D deficiency – full search

4.6.3.1 Background

Despite a substantial proportion of pregnant women reporting taking antenatal vitamin D supplements (60% approximately), the prevalence of maternal 25-hydroxyvitamin D deficiency is high (approximately 45%) in Belgium according to a cross-sectional study with a total sample size of 1 311 women in their first and third trimester. The study was conducted in the period from September 2010 to June 2011.¹⁰⁹

Low vitamin D status was reported as:

- Insufficient : <30ng/mL
- Deficient : <20ng/mL
- Severely deficient : <10ng/mL

Table 10 – Prevalence estimates for vitamin D deficiency for pregnant population in Belgium

Prevalence	First trimester %	Third trimester %
Vitamin D insufficiency	82.2	66.7
Vitamin D deficiency	47.0	42.3
Severe vitamin D deficiency	11.6	12.6

It has been suggested that low maternal vitamin D concentrations are associated with several adverse neonatal and maternal outcomes, such as low birth weight, preterm birth, gestational diabetes and pre-eclampsia.¹²¹ This association has prompted the hypothesis that screening for and supplementation of vitamin D insufficiency could be a useful strategy to improve important outcomes for mother and neonate.

To investigate if screening for maternal vitamin D deficiency during pregnancy may be useful, we reviewed the evidence to answer the following questions:

- What are the benefits and harms of routine vitamin D deficiency screening of all low-risk pregnant women compared with no routine screening (or targeted screening of clinically at risk women) (direct evidence)?
- Compared with no or lower dose supplementation, what are the benefits and harms of vitamin D supplementation during pregnancy? Do treatment effects vary by patient risk (i.e. low versus high risk for vitamin D deficiency) or baseline vitamin D levels (i.e. established baseline hypovitaminosis D versus unclear or normal baseline vitamin D levels) (indirect evidence)?

For detailed research question in the PICO format, we refer to Appendix 5.

A search strategy was performed separately for the two questions (see Appendix 6). A total of 1 054 records were identified concerning the screening for vitamin D deficiency, and after de-duplicating, 981 records formed the first screening set. A total of 15 records were screened on full text. Concerning the supplementation on vitamin D, a total of 788 records were screened, and after de-duplicating, 599 records formed the first screening set. A total of 178 records were screened on full text. A description of the study selection (including Prisma flowchart) is available on Appendix 7.

4.6.3.2 Benefits-harms of universal screening for vitamin D deficiency in pregnant women - results

Among the 15 records screened on full text, no systematic review, no randomized clinical trial and no observational evidence met the eligibility criteria.

Conclusions

- There is are no data from randomized or non-randomized comparative studies on the benefits-harms of screening for vitamin D deficiency in pregnant women.



4.6.3.3 Benefits-harms of vitamin D supplementation in pregnant women: results

- A high quality systematic review by De-Regil et al.¹²² was identified for this question. This review was restricted to randomized clinical trials and included six RCTs on healthy pregnant women in their 3rd trimester with or without risk factors for vitamin D deficiency. Five RCTs compared vitamin D versus no treatment/ placebo [N= 621 ranging from 40-200]¹²³⁻¹²⁷ and the other compared vitamin D plus calcium versus no treatment/ placebo [N=400].¹²⁸ Vitamin D type was D2,^{123, 127} D3,^{124, 126} and not reported in two RCTs.^{125, 128} Also treatment dose varied across the studies. All six RCTs were judged to be of high risk of bias. The applicability concern in these RCTs ranged from no concern to very serious due to race, dose of vitamin D and exclusion of women with outcomes of interest.
- We identified seven additional studies in 11 records published since the search date of the systematic review; of which one was a long-term follow-up of participants in Yu 2009¹²⁷ included in the De-Regil 2012 review.¹²⁹⁻¹³⁹ Of these, two did not provide any data on the outcomes of interest and was not included in the evidence table.^{135, 136} The intervention was vitamin D3 versus placebo in three RCTs^{129, 133, 137}, and vitamin D3 plus calcium versus placebo in one RCT.¹³¹ All four RCTs were deemed as having serious concern for applicability due to various factors such as race, ethnicity, low calcium diet, and extensive exclusion criteria. The pregnant women were healthy without vitamin D deficiency risk factor in one RCT,¹³³ healthy with risk factor for vitamin D deficiency in 2 RCTs^{129, 137} and healthy without specific risk factor vitamin D deficiency but with low Ca diet in one RCT.¹³¹ None of the RCTs exclusively included pregnant women with documented vitamin D deficiency.
- No relevant, high quality systematic review including observational studies was identified. We conducted a de novo synthesis of the literature published in the past 15 years - a cut-off mutually agreed by experts on the team to be a relatively confident approximation of current practice and standards of care. A total of 21 studies (25 records) were identified¹⁴⁰⁻¹⁶³ of which 11 studies (12 reports) did not provide data on

the outcomes of interest.¹⁵²⁻¹⁶³ Only one study was exclusively in pregnant women with documented vitamin D deficiency,¹⁴³ five were in healthy pregnant women without risk factors for vitamin D deficiency,^{140, 142, 146, 148, 151} two in healthy women with risk factor for vitamin D,^{150, 164} and two studies, from one birth cohort, were in women without specific risk factor for vitamin D deficiency with infants at increased genetic risk for Type 1 diabetes.^{145, 149} Six studies were deemed as having no applicability concern, three as having serious applicability concerns due to race, exclusion of women with outcomes of interest, or being in low-middle socioeconomic women or strictly in a rural setting, and one as having very serious applicability concerns due to being exclusively in women with term deliveries. All studies judged to be of high risk of bias in at least one of the following domains: selection bias, information bias and confounding. Type of vitamin D administered was mix of D2 and D3 in three studies, D2 in two studies, D3 in one study, and unclear in four studies.

For details on the quality appraisal and evidence tables, we refer in Appendices 8 and 9.

Following outcomes are presented: preterm birth, birth weight- length-head circumference, neonatal mortality, maternal and neonatal adverse events.

Two comparisons are described:

- vitamin D vs. no vitamin D supplementation
- vitamin D + calcium vs. no vitamin D/calcium supplementation.

Vitamin D supplementation vs. no Vitamin D supplementation

Preterm birth

- **Preterm birth**, not clearly defined, was reported in three small trials.^{124, 129, 137} Two of the three trials registered an occasional preterm birth including very preterm birth <34 weeks. The third trial concerned 160 Bangladeshi women. While the trial was judged as low risk of bias, it was underpowered for a precise estimation of preterm birth (defined as birth between 34-37 weeks of gestation) yielding very low quality of indeterminate evidence (RR 0.56; 95%CI 0.24 – 1.33).¹³⁷



- Data for **gestational age at delivery** was reported in 6 studies.^{123, 124, 126, 127, 133, 137} Two studies reported data either as median or narratively; with both indicating no meaningful difference in the durations of pregnancy.^{124, 133} Pooled estimate from the remaining four trials was statistically precise but clinically of borderline precision; it concerned 579 pregnancies; given the 95% confidence intervals around the estimate of effect, it appears that vitamin D supplementation versus no vitamin D may be harmful or ineffective, at best shortening the natural course of gestation by as little as 7 hours to as much as 5 days. However, our confidence in this conclusion is very low.

Low birth weight- length-head circumference (important outcome)

- Pooled results for **birth weight** across 4 trials indicated imprecise inconclusive results possibly explained by heterogeneity and small sample sizes of contributing studies (RR 0.56; 95%CI 0.26 – 1.21). Heterogeneity was mostly as a result of clinical diversity across studies.^{123, 126, 127, 137} Outcome definitions varied and included definitions such as birth weight <2 500g, small for gestational age, or undefined low birth weight.
 - Very low quality evidence provided from a subgroup meta-analysis of 2 studies in which low **birth weight was defined as <2 500g**^{123, 126} showed **benefits** of vitamin D supplementation (RR 0.36; 95%CI 0.14 – 0.91).
 - **Mean birth weight in grams** as a continuous outcome reported across five (mostly high risk of bias) trials showed heterogeneous inconsistent findings with an imprecise and non-significant pooled estimate (MD 35.88; 95%CI -157 – 228).^{123, 125-127, 137} Heterogeneity in findings could be explained by Caucasian versus non-Caucasian ethnicity. As such we graded the quality of evidence from the single RCT conducted in France in Caucasian women. Low level of evidence from this RCT comprising 77 newborns showed a lower birth weight with vitamin D supplementation: 180 grams lower birth weight with vitamin D (from 215 to 145 lower).¹²⁵
- Very low quality evidence from a meta-analysis of three trials of low¹³⁷ to high risk of bias^{123, 126} demonstrated inconclusive findings (MD=0.72; 95%CI -0.33 – 1.76) concerning the **birth length**. Risk of bias did not

explain the obvious heterogeneity in individual study estimates. All trials were conducted in South Asians employing variable vitamin D regimens.

- Concerning **head circumference at birth**, three trials conducted in South Asian populations were meta-analysed yielding non-significant results (MD 0.28; 95%CI -0.11 – 0.67). Study risk of bias (low quality) did not explain between study statistical heterogeneity (I-squared 61%). Confidence intervals of the studies did overlap, however.

Neonatal mortality (important outcome)

- Very low quality evidence from two trials^{127, 137} showed 5 neonatal deaths in 266 randomised pregnancies, yielding to non-significant results (RR 0.33; 95%CI 0.05 – 2.09).

Maternal and neonatal adverse events (important outcome)

- A single RCT comprising 147 births (in South Asian population) showed major adverse event in 4 mothers and 13 neonates (from 23 fewer to 162 more total major maternal adverse events and from 65 fewer to 138 more total major neonatal adverse events).¹³⁷ The level of evidence is very low.
- No study reported occurrence of kidney stones in mothers. Hypercalcemia was reported in 4 trials.^{126, 127, 133, 137} No case of hypercalcemia was observed across trials including a total of 800 patients. One case of hypercalciuria was noted in one study.

GRADE profiles and forest plots are available in Appendices 10 and 11. Also evidence from **non-randomized studies** are summarized in evidence tables in Appendix 9 for the following outcomes: Type I diabetes mellitus in offspring, childhood asthma, pre-eclampsia, NICU admission and APGAR score.



Vitamin D + calcium vs. no vitamin D/calcium supplementation

One study each contributed evidence for the outcomes of pre-eclampsia¹²⁸ and preterm birth.¹³¹ Both studies were conducted in developing countries and either included south Asian women exposed in second trimester¹²⁸ or adolescent Brazilian women exposed in third trimester.¹³¹ No other experimental or observational evidence addressed other outcomes for this particular comparison.

- Very low quality evidence from a trial comprising 400 women showed no risk difference **in pre-eclampsia** with or without vitamin D plus calcium supplementation (RR 0.67; 95%CI 0.33 to 1.35).¹²⁸ Evidence was grossly underpowered to evaluate comparative benefit of vitamin D plus calcium supplementation in pregnancy.
- Zero **preterm births** were observed across 84 participants in Brazilian adolescent women on low calcium diet.¹³¹

Conclusions

- Based on limited evidence of low or very low quality, no clear conclusion can be drawn on whether or not systematic **vitamin D supplementation** is effective in lowering the rate of fetal morbidity and neonatal death.
- Based on limited evidence of very low quality, no clear conclusion can be drawn on whether or not systematic **co-administration of vitamin D and calcium supplementation** is effective in lowering the rate of fetal morbidity and neonatal death.

The GDG underlined that the high prevalence of vitamin D insufficiency and deficiency raises questions about the clinical relevance of the measurements and thresholds used. One can also wonder if the variability of vitamin D concentration according to the season was taken into account. The adverse events of the treatment appeared to be not enough studied.

Nevertheless, the GDG mentioned that some people are particularly at risk of severe vitamin D deficiency (e.g. women who have low or no exposure to the sun, women who cover their skin for cultural reasons, women who have darker skin or women who follow a vegetarian diet). For these women, it is considered useful to provide advises on how they can maintain sufficiently high vitamin D levels.

4.6.3.4 Recommendation for vitamin D deficiency

Based on the retrieved evidence and the discussion with the GDG, we developed two recommendations concerning the vitamin D deficiency during pregnancy. The considerations that lead to the recommendations are summarized below.

**Other considerations**

Factor	Comment
Balance between clinical benefits and harms	<p>There is no direct evidence to support the effectiveness of screening for vitamin D deficiency in pregnant women. Indirect evidence regarding the effectiveness of vitamin D supplementation in women with low vitamin D levels suggests there may be a reduction in birth weight below 2500g but the confidence in that finding is very low. For other important outcomes, there is no proven benefit. Furthermore, the high prevalence of vitamin insufficiency and deficiency raises questions about the clinical relevance of the measurements and thresholds used. There is a great variability of vitamin D concentration between people but also according to the season.</p> <p>The GDG concluded that screening for vitamin D status is thus not of proven benefit and that there is insufficient evidence to recommend vitamin D supplementation in all pregnant women. However, it is considered useful to advise women who are at risk of severe vitamin D deficiency (e.g. women who have low or no exposure to the sun, women who cover their skin for cultural reasons, women who have darker skin or women who follow a vegetarian diet) on how they can maintain sufficiently high vitamin D levels.</p>
Quality of evidence	Very low level of evidence
Costs (resource allocation)	Not applicable
Patients values and preferences	Not applicable

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">Do not offer screening for vitamin D deficiency to pregnant women. [new KCE 2015]	Strong	No evidence
<ul style="list-style-type: none">Do not routinely offer vitamin D supplementation to all pregnant women. [new KCE 2015]	Weak	Very low



4.7 Screening for specific pregnancy related risks

4.7.1 Risk of preterm birth – full search

4.7.1.1 Background

Preterm birth is, in developed countries, the most important cause of neonatal morbidity and mortality. In a subpopulation of pregnant women with a history of preterm birth, a shortened cervix is associated with an increased risk for preterm birth. Follow-up of cervical length with vaginal ultrasound in women who are at increased risk can identify women who possibly benefit from cervical cerclage. A KCE report on prevention of preterm birth in women at risk has recently been published on this topic (Roelens et al. KCE Reports 228. Prevention of preterm birth in women at risk: selected topics).¹⁶⁵

Furthermore, also in women presenting with signs of threatened preterm labour, cervical length is related to the risk of birth within seven days and can be used to identify women who may be eligible for treatment or not.¹⁶⁵ In asymptomatic women at low risk of preterm birth (no history of preterm birth, no history of surgery to the cervix, no multiple pregnancy in the current pregnancy, no uterine malformation), it has also been hypothesised that a short cervix measured in the second trimester (19-24 weeks) indicates an increased risk of preterm birth and that measures such as progesterone or cerclage could decrease the occurrence of preterm birth and improve neonatal outcomes in that group of women.

To investigate whether screening for shortened cervix, followed by preventive measures, would be useful in pregnant women who are otherwise at low risk for preterm birth, we reviewed the evidence to answer the following questions:

- In pregnant women judged to be exclusively or predominantly at low risk for preterm birth based on history, physical exam, or both, what are the comparative benefits and harms of mid-to-third trimester transvaginal ultrasound for cervical length, funnelling, or both, and/or digital vaginal exam in routine patient management (direct evidence)?
- Compared with each other or no active intervention (i.e. expectant management), what is the comparative benefits and harms of progesterone therapy, cerclage, and/or reduced physical activity (e.g.

bed rest) to prevent preterm birth and its sequelae in asymptomatic women with short cervix but either who have **no additional risk factors** for preterm birth (i.e. exclusively low-risk populations as judged on history and physical exam before cervical assessment) or who are **predominantly at low risk** (as judged on history and physical exam before cervical assessment) for preterm birth (indirect evidence)? Specific recommendations related to the use of progesterone, cerclage or reduced physical activity were considered out of scope for this guideline.

For detailed research questions in the PICO format, we refer to Appendix 5.

A search strategy was performed separately for the two questions (see Appendix 6). A total of 787 records were identified concerning the screening for risk of preterm birth, and after de-duplicating, 563 records formed the first screening set. A total of 26 records were screened on full text. Concerning the different interventions, a total of 1862 records were identified, and after de-duplicating, 722 records formed the first screening set. A total of 128 records were screened on full text. A description of the study selection (including Prisma flowchart) is available on Appendix 7.

4.7.1.2 Benefits and harms of screening for risk of preterm birth in pregnant women at low risk of preterm birth - results

Among the 26 records screened on full text, one Cochrane systematic review by Alexander et al. (2010)¹⁶⁶ was retrieved and no primary evidence was identified.

This systematic review of moderate quality investigated repeat digital cervical assessment with internal examination limited to clinical indication or no internal examination. Two randomised controlled trials^{167, 168} was included in the review involving 7 163 women likely to be predominantly at low risk for preterm birth. This review reported odds ratios as the effect estimates and meta-analysed outcomes data using fixed effect mode. For ease of interpretation, we calculated relative risks from the reported n/N in the review. We employed a random effect model in keeping with our systematic review protocol. For routine digital exam, evidence was graded as moderate for all outcomes which we judged was also reasonably applicable to women exclusively at low risk. More details are available for



quality appraisal, evidence tables and GRADE summaries in Appendices 8, 9 and 10.

Screening by routine digital exam versus no screening

Outcomes retrieved in the systematic review of Alexander et al. concerned two categories: perinatal mortality and neonatal morbidity (preterm birth, low birth weight and NICU admission). Evidence was not identified for the neurological damage and for maternal and infants adverse events.

Perinatal mortality (important outcome)

- Moderate level of evidence from one multicenter RCT^{111, 167} suggested that there was no difference in risk of **stillbirth** (n=5490) with systematic digital cervical examination versus no examination unless medically indicated in 5490 pregnancies (RR 1.09; 95%CI 0.61–1.94).
- Moderate level of evidence from one multicenter RCT^{111, 167} that there was no difference in risk of **neonatal death** (n=5 444) with systematic digital cervical examination versus no examination unless medically indicated in pregnancies (RR 1.47; 95%CI 0.76–2.83).

Preterm birth (important outcome)

- Moderate level of evidence from two RCT^{167, 168} suggested that there was no difference in **preterm birth < 37 weeks** (n=6 070) with systematic digital cervical examination versus no examination unless medically indicated (RR 1.05; 95%CI 0.86 to 1.28).
- Moderate level of evidence from one multicenter RCT¹⁶⁷ suggested that there was no difference in **very preterm birth < 34 weeks** (n=5 041) with systematic digital cervical examination versus no examination unless medically indicated (RR 0.93; 95%CI 0.65 to 1.33).

Low birth weight

- Moderate level of evidence from one multicenter RCT¹⁶⁷ suggested that there was no difference in risk of **birth weight <2500g** (n= 5 371) with systematic digital cervical examination versus no examination unless medically indicated (RR 0.86; 95%CI 0.71 – 1.04).
- Moderate level of evidence from one one multicenter RCT¹⁶⁷ suggested that there was no difference in risk of **very low birth weight <1500g**

(n=5 371) with systematic digital cervical examination versus no examination unless medically indicated (RR 0.81; 95%CI 0.53 – 1.23).

NICU admission

- Moderate level of evidence one multicenter RCT¹⁶⁷ suggested that there was no difference in risk of **NICU admission** (n=5 329) with systematic digital cervical examination versus no examination unless medically indicated (RR 1.08; 95%CI 0.94 – 1.23).

Screening by transvaginal ultrasound for cervical length, funneling, or both versus no screening

We did not identify any systematic review or primary study to assess the comparative benefits and harms of transvaginal ultrasound for cervical length, funnelling or both in exclusively or predominantly low-risk pregnant women.

Conclusions

- Moderate level of evidence shows that in pregnancies otherwise at low risk for preterm birth, there is no clinically important benefit or harm of **digital vaginal exam** to screen for increased risk of preterm birth.
- No evidence was identified concerning the screening for risk of preterm birth by **transvaginal ultrasound for cervical length, funeling or both** in low-risk pregnant women.

The GDG acknowledged that, according to evidence of moderate quality, repeat digital exam is not beneficial to improve neonatal outcomes related to preterm birth. Although not harmful, it can be uncomfortable to pregnant women. Concerning the cervical length measurements by transvaginal ultrasound, the lack of direct evidence does not allow to assess the effectiveness of primary screening for the risk of preterm birth with this method.



4.7.1.3 *Benefits and harms of progesterone, cervical cerclage, and reduced physical activity in low-risk pregnant women with short cervix - results*

Among the 128 records screened on full text, no systematic review was identified. For de novo synthesis, a total of 13 studies were identified of which nine were RCTs and 4 observational cohort studies. Eight studies (all RCT design) evaluated benefits and harms of progesterone versus no active treatment, four studies (1 RCT and 3 observational) assessed benefits and harms of cerclage versus no cerclage, and one cohort study compared reduced physical activity versus no activity restriction in the population of interest.

Progesterone vs. no active intervention (placebo or no treatment)

The comparative effectiveness of progesterone vs. no active intervention (placebo or no treatment) was examined in eight RCTs. The intervention was in the form of daily vaginal tablets/capsules or gel in five studies,¹⁶⁹⁻¹⁷³ intramuscular injection in two studies^{174, 175} and oral medroxyprogesterone acetate tablet in one study.¹⁷⁶ All but one¹⁶⁹ compared the intervention to similar or identical placebos, and all but two^{175, 176} were in women with short cervix.

Details of the included RCTs are summarized before the corresponding evidence tables in Appendix 9.

Few studies contributed data for the outcomes of interest. Despite clinical and methodological diversity we pooled studies to arrive at an overall effect for progesterone across studies because inadequacy of data precluded subgroup analyses.

The pooled meta-analytic estimates inform us about the average effect across studies irrespective of progesterone route of administration, duration of therapy, and cervical length eligibility criteria. Most studies, however, included **patients with short cervix** (<30 mm). We graded the quality of evidence for each meta-analytic estimate of effect.

For GRADE profiles and forest plot, we refer to Appendices 10 and 11.

Outcomes are presented on three categories (ante- and peri-natal mortality), preterm birth and maternal and infant adverse events. Other outcomes such as seizure and neonatal free survival without morbidity are available in Appendices 10 and 11. Quantitative data was not reported for total serious or major maternal harms of progesterone therapy.

Ante- and peri-natal mortality (critical outcome)

- Very low level of evidence from two RCTs^{173, 174} comprising 1 115 pregnant women suggested that there was no difference for **perinatal mortality** with progesterone versus no active treatment (RR 0.88; 95%CI 0.47 to 1.65).
- Low level of evidence from four RCTs^{170, 173, 174, 176} comprising 1 560 pregnant women suggested that there was no difference for **neonatal death** with progesterone versus no active treatment (OR 0.52; 95%CI 0.26 to 1.05).
- Very low level of evidence from four RCTs^{170, 173, 174, 176} comprising 1 560 pregnant women suggested that there was no difference for **stillbirth/fetal death** with progesterone versus no active treatment (OR 1.34; 95%CI 0.54 to 3.31).
- Very low level of evidence from one RCT¹⁷⁴ comprising 657 pregnant women suggested that there was more **abortion <20weeks** with progesterone versus no active treatment (OR 7.46; 95%CI 0.15 to 375.83). However, given the wide confidence interval around the point estimate, we cannot be confident in the effect.

Preterm birth (important outcome)

- Very low level of evidence from four RCTs^{171, 173-175} comprising 1 449 pregnant women suggested that there was no difference for **preterm birth <37weeks** with progesterone versus no active treatment (RR 0.88; 95%CI 0.74 to 1.05).
- Low level of evidence from three RCTs^{170, 171, 174} comprising 981 pregnant women suggested that there was a difference in **preterm birth <34weeks** with **less events** with progesterone versus no active treatment (RR 0.71; 95%CI 0.52 to 0.93).



- Very low level of evidence from two RCTs^{173, 174} comprising 1 115 pregnant women suggested that there was a difference in **preterm birth <28 weeks** with **less events** with progesterone versus no active treatment (RR 0.059; 95%CI 0.37 to 0.94).

Maternal and infant adverse events

- Very low level of evidence from four RCTs^{170, 171, 173, 174} comprising 1368 pregnant women suggested that there was a difference for **major neonatal adverse outcomes** (mortality and 4 common morbidities: intraventricular haemorrhage, necrotizing enterocolitis, respiratory distress syndrome, periventricular leukomalacia) with **less events** with progesterone versus no active treatment (RR 0.67; 95%CI 0.48 to 0.93).
- A narrative statement in one RCT¹⁷⁰ comprising 250 pregnant women suggested no significant differences in maternal adverse events.

Cerclage vs. no cerclage

A total of four studies provided evidence pertaining to cerclage vs. no cerclage therapy for preterm birth, of which one was a RCT¹⁷⁷ and three were observational cohort studies.¹⁷⁷⁻¹⁸⁰ Studies varied in co-interventions that were administered as background level of care (i.e. bed rest advice, counselling for preterm labour, corticosteroids with overt preterm labour or premature rupture of membranes, and use of progesterone). Details of the included RCTs are summarized before the corresponding evidence tables in Appendix 9.

For GRADE profiles and forest plot, we refer to Appendices 10 and 11.

Few studies contributed data for the outcomes of interest: there was a qualitative report on 10 pregnancies for neonatal death and major neonatal adverse events, and no study reported important neonatal morbidity. Outcomes are presented on two categories: preterm birth and maternal adverse events.

Preterm birth (important outcome)

- Very low level of evidence from three observational studies¹⁷⁸⁻¹⁸⁰ comprising 483 pregnant women suggested that there was no difference with cerclage vs no cerclage for **preterm birth <37weeks** (RR 0.82; 95%CI 0.57 to 1.18).

- Very low level of evidence from two observational studies^{178, 179} comprising 235 pregnant women suggested that there was no difference for **preterm birth <34weeks** with cerclage versus no cerclage (RR 0.67; 95%CI 0.15 to 3.03).
- Very low level of evidence from two observational studies^{178, 180} comprising 237 pregnant women suggested that there was no difference for **preterm birth <28weeks** with cerclage versus no cerclage (RR 0.68; 95%CI 0.27 to 1.71).

Maternal adverse events

- Very low level of evidence from one observational study¹⁸⁰ comprising 167 pregnant women suggested that there was a difference for **total maternal adverse outcomes** with more events with cerclage (+ modified bed rest +/- progesterone) vs. bed rest (+/- progesterone) (OR 4.52; 95%CI 0.40 to 50.99). However given the wide confidence interval around the point estimate, we cannot be confident in the effect.

Reduced activity vs. no activity restriction

A single observational study, a post-hoc analysis of a randomised controlled trial evaluating progesterone therapy for preterm birth, in 657 nulliparous pregnancies with cervical length <30 cm between 16-22 weeks GA reported findings on reduced activity for the outcome of birth <37 and <34 weeks.¹⁸¹ This study investigated the difference in preterm birth between restriction in physical (work and non-work related) and sexual activities versus no activity restriction. Seventy seven percent of patients were non-white (50% of African descent), 30% reported history of miscarriage, and 16% were smokers. The trial excluded women at very high risk for preterm birth (e.g. bleeding, membrane prolapse, past cervical surgery or planned cerclage, known major fetal anomaly, planned or indicated preterm delivery, those receiving progesterone therapy before 16 weeks or those with a contraindication to IM progesterone injection). The observational cohort study was judged at high risk of bias because of very serious concerns about unmeasured confounding (a post hoc subgroup analysis of an RCT), time-varying nature of adherence to activity recommendation, exposure ascertainment bias (actual physical activity was not measured), and respondent bias.



No other outcome than preterm birth was reported. Quality appraisal and the evidence table are available in Appendices 8 and 9.

Preterm birth (important outcome)

- Very low level of evidence from one observational study¹⁸¹ comprising 646 pregnant women showed a **significant difference** with restriction in physical (work and non-work related) and sexual activities versus no activity restriction for **preterm birth <37weeks** (OR 2.37; 95%CI 1.6 to 3.53).
- The same study of very low level of evidence¹⁸¹ comprising 646 pregnant women showed a **significant difference** with restriction in physical (work and non-work related) and sexual activities versus no activity restriction for **preterm birth <34weeks** (OR 2.28; 95%CI 1.38 to 3.8).

Study findings favoured no activity restriction compared with restricted activities (GRADE results in Appendix 10). When data were analysed comparing any restriction on work and non-work related activity versus no activity restriction (or only sexual activity restriction) the findings did not change.

Conclusions:

- Low to very low quality evidence suggests that **progesterone** may reduce overall adverse neonatal outcomes and preterm birth before 34 weeks in pregnant women with a short cervix on ultrasound. With regards to perinatal mortality, results remain inconclusive.
- Very low quality evidence suggests that **cerclage** in women with a short cervix but otherwise at low risk for preterm birth is not associated with clinically important differences compared to no cerclage in terms of neonatal mortality and major adverse events. Maternal adverse events may be more frequent with cerclage.
- Findings from one observational study at high risk of bias demonstrated that **physical activity restriction** may be harmful for the outcome preterm birth; however, our confidence for this finding is very low. There are no data from comparative studies regarding important neonatal or maternal outcomes.

The GDG acknowledged the lack of evidence regarding the benefit-harm of the cerclage and the restriction in activities. Concerning progesterone, evidence from RCTs suggest that progesterone can reduce neonatal morbidity in women with a short cervix measured during the second trimester but the GDG underlined the heterogeneous inclusion criteria in the studies.

4.7.1.4 Recommendation for screening for preterm birth risk in low-risk pregnant women

Based on the retrieved evidence and the discussion with GDG and stakeholders, we developed two recommendations concerning the screening for preterm birth risk in low-risk pregnant women. The considerations that lead to the recommendations are summarized below.

**Other considerations**

Factor	Comment
Balance between benefits and harms	clinical <p>There is no direct evidence on the effectiveness of primary screening for the risk of preterm birth using cervical length measurements (vaginal ultrasound) and evidence of moderate quality shows that repeat digital exam is not beneficial to improve neonatal outcomes related to preterm birth.</p> <p>Evidence from RCTs suggest that progesterone can reduce neonatal morbidity in women with a short cervix measured during the second trimester. Indirectly, this can be considered an argument in favour of screening, as there is an effective treatment available. However, the GDG mentioned that it remains significant doubt on the effectiveness of progesterone to improve important outcome in Western women with a short cervix who are otherwise at low risk for preterm birth, due to the heterogeneous inclusion criteria in the studies. For example, the FDA has raised questions about the robustness in efficacy in the US subgroup as compared to overall efficacy in the trial of Hassan et al.^{173, 182} Furthermore, the prevalence of a cervix < 20mm at +/- 20 weeks of pregnancy in a Belgian low-risk population is unknown. In a recent pilot project in the US, the prevalence of a shortened cervix in the screened population was 1.1%, which is lower than expected based on the randomized trials and would render primary screening not cost-effective.¹⁸³ Moreover, when implemented in real-world practice, screening may have unintended consequences such as anxiety in women with nearly positive results, unnecessary interruption of working activities and delayed medical-help seeking in falsely reassured women.</p> <p>In Belgian practice, some clinicians believe in the efficacy of progesterone and currently use it. A study published in 2015 (after our systematic review) did not show however a significant benefit of progesterone in reducing adverse neonatal outcome and preterm birth in women with a short cervix, who are otherwise at low risk.¹⁸⁴</p> <p>Given the uncertainty about the effectiveness of progesterone treatment and prevalence of short cervix in a Western low-risk population, the GDG proposes to apply primary screening for the risk of preterm birth within the framework of clinical research only. This screening should preferably be performed by ultrasound measurement instead of repeat digital examination.</p>
Quality of evidence	Very low level of evidence
Costs (resource allocation)	No cost assessment was performed.
Patients values and preferences	No formal assessment of patient values and preferences was performed.



Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> Do not screen for the risk of preterm birth with repeat digital exam. [new KCE 2015] 	Strong	Moderate
<ul style="list-style-type: none"> Primary screening for risk of preterm birth by cervical length measurements in low-risk women should only be performed within the framework of research. [new KCE 2015] 	Weak	Very low

4.7.2 Risk of pre-eclampsia – full search

4.7.2.1 Background

Pre-eclampsia is the third cause of maternal mortality and the first cause of perinatal mortality. Several risk factors are known for pre-eclampsia, such as hypertensive disease during a previous pregnancy, diabetes, age 40 years or older, or a body mass index of 35kg/m² or more. Usually, history taking and clinical examination are the basis for determining the risk and to select women who may benefit from close monitoring and preventive aspirin during pregnancy. However, such a risk factor approach is considered having limited predictive accuracy and other tests have been suggested to early identify women without clinical risk factors who may also benefit from preventive measures. These tests encompass for example the pulsatility index measurement of the uterine arteries or various biomarkers.

To investigate if screening for risk of pre-eclampsia during pregnancy may be useful in women without clinical risk factors, we reviewed the evidence to answer the following question:

- What are the benefits and harms of screening for pre-eclampsia risk with additional tests compared to assessment based on history and physical exam alone, in asymptomatic pregnant women otherwise at low-risk for pre-eclampsia?

According to the GDG, we focused on some specific tests alone or in combination i.e. dipstick for proteinuria; pulsatility index of the uterine arteries measured during a Doppler ultrasound scan; pregnancy-associated plasma protein-A (PAPP-A); placental growth factor (PlGF) in combination with soluble fms-like tyrosine kinase-1 (sFlt-1); fetal DNA and RNA in maternal plasma (may be helpful in the prediction of pre-eclampsia as they

are markers of the trophoblast apoptosis). For detailed research question in the PICO format, we refer to Appendix 5.

A search strategy was performed and found 4 791 records (see Appendix 6). After de-duplicating, 3 554 records formed the first screening set. A total of 79 records were screened on full text. A description of the study selection (including Prisma flowchart) is available on Appendix 7.

4.7.2.2 Benefits and harms of screening for pre-eclampsia risk by additional tests compared with usual history and physical exam in asymptomatic healthy pregnant women - results

Among the 79 records screened on full text, one systematic review by Stampalija et al. (2010)¹⁸⁵ met the eligibility criteria. The high quality review had not identified any primary studies on the intervention of interest that it covered (pulsatility index). No systematic reviews of other relevant interventions were identified and no primary evidence was identified. As such, this question remained unanswered.

Conclusions

- There is no evidence from randomized or non-randomized comparative studies on the effectiveness of screening for increased risk for pre-eclampsia in asymptomatic women otherwise at low risk for pre-eclampsia.



The GDG acknowledged there are no comparative studies giving evidence on the benefit and harms of pre-eclampsia screening in a low-risk population and advised that before implementing a screening strategy, evidence on the effect of screening and subsequent interventions on important clinical outcomes should be available.

4.7.2.3 Recommendation for screening for pre-eclampsia risk in low-risk pregnant women

Based on the retrieved evidence and the discussion with GDG and stakeholders, no recommendation could be developed concerning the screening for pre-eclampsia risk in low-risk women. The considerations that lead to this proposition are summarized below.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	No comparative studies provided evidence on the benefit and harms of pre-eclampsia screening in a low risk population. Additional costs of the different tests are not currently justified, except within a research framework.
Quality of evidence	No evidence identified.
Costs (resource allocation)	NA
Patients values and preferences	NA

Recommendations	Strength of Recommendation	Level of Evidence
There is insufficient evidence to recommend additional screening (compared with usual routine assessment based on history and physical exam) for increased risk of pre-eclampsia in low-risk women. Primary screening for risk of pre-eclampsia in low-risk women should only be performed within the framework of research. [new KCE 2015]	NA	No evidence



4.7.3 Surveillance of pregnancies that passed their due date – full search

4.7.3.1 Background

Late-term pregnancy is defined as a pregnancy that has reached between 41 0/7 weeks and 41 6/7 weeks of gestation from the last menstrual period (LMP) and postterm pregnancy refers to one that has reached or extended beyond 42 0/7 weeks of gestation.^{186, 187, 188}

Late-term and postterm deliveries have been associated with increased neonatal morbidity (e.g. neonatal convulsions, meconium aspiration syndrome, 5-minute Apgar scores <4).¹⁸⁶⁻¹⁸⁸ An increased risk of macrosomia, oligohydramnios, stillbirth and neonatal mortality is described with postterm pregnancies. There are also maternal risks associated with late-term and postterm deliveries such as caesarean delivery, perineal laceration, infection and, postpartum hemorrhage.¹⁸⁶

In Belgium, a close follow-up of pregnancy is often proposed from the 40th week of pregnancy with a variability of different strategies in practice. After discussion with the GDG, two examinations appeared to be particularly interesting in this context: the cardiotocography and the amniotic fluid measurement by ultrasound.

Thus, we reviewed the evidence to answer the following question:

- In low-risk (for adverse consequences of prolonged pregnancy) asymptomatic pregnant women who remain undelivered past 40 weeks of gestation, compared with each other or no intervention/routine clinical follow up, what are benefits and harms of nonstress test cardiotocography (CTG) and ultrasound estimation of amniotic pool depth/volume/index?

For detailed research question in the PICO format, we refer to Appendix 5.

A search strategy was performed and found 1143 records (see Appendix 6). After de-duplicating, 722 records formed the first screening set. A total of 80 records were screened on full text. A description of the study selection (including Prisma flowchart) is available on Appendix 7.

4.7.3.2 Benefits-harms of specific surveillance in low-risk pregnant women who have passed their due date - results

Among the 80 records screened on full text, no systematic review was found for updating. Seven unique primary studies were identified of which one¹⁸⁹ did not provide outcome data, so six studies were ultimately included in the synthesis: three RCTs,¹⁹⁰⁻¹⁹² two cohort studies (one prospective¹⁹³ and one retrospective¹⁹⁴) and one prospective study (where it was unclear whether participants were 'allocated' to their intervention or not)¹⁹⁵. The description of the interventions and the nomenclature for tests (e.g. non-stress test, cardiotocography, biophysical profile) were often not consistent within or across reports.

- Two RCTs compared the effectiveness of monitoring by CTG plus ultrasound measurement of amniotic fluid index (AFI) versus CTG plus ultrasound measurement of amniotic fluid depth (AFD).^{190, 192} Both enrolled women with uncomplicated singleton pregnancies at approximately 41 weeks 3 days (290 days) gestation.
- The third RCT¹⁹¹ compared a modified biophysical profile test (consisting of measurement of fluid volume, fetal movement, fetal tone, fetal breathing and CTG versus CTG plus AFD). Herein we referred to as the first intervention as modified BP. All tests were performed twice a week from 42 weeks of gestation.
- A prospective cohort from the United States¹⁹³ compared CTG plus fetal movements versus CTG, fetal movement and ultrasound amniotic fluid volume (AFV) measurement, both with different protocols for patient management. All tests were performed 2 times per week from 42 weeks to delivery apart for AFV in group 2 (1/week). In both groups, a non-reactive CTG + fetal movement test (based solely on fetal heart rate (FHR) accelerations and fetal movement) was indication for another test (real time ultrasound for fetal breathing movement, fetal movement, AFV, general survey of intrauterine contents, fetal presentation and position, biparietal diameter and FHR) that we referred to it as partial biophysical profile (BP). Abnormal results for partial BP were an indication for induction. In group 2, labour was also induced if fetal heart rate decelerations or abnormal AFV were noted in the first tests.



- A retrospective cohort study from Sweden¹⁹⁴ compared management by clinically indicated fetometry to routine fetometry plus AFI at 41 weeks gestation. Abnormal fetometry results in either group or abnormal AFI in Group 2 led to assessment of umbilical artery blood flow. An abnormal flow was an indication for induction or caesarean. Women with an estimated small for gestational age fetus were not scheduled to continue into 42 weeks gestation. Analysis for this study was presented for women delivering from 32 weeks gestation onward, from 37 to 41 weeks, and from 42 weeks onward. The outcome for this study was defined as 'severe adverse fetal outcome in the post-term (> 42 weeks) period.
- Finally, a study of unclear design from Egypt¹⁹⁵ compared biophysical profile (AVF, fetal movement, fetal tone + fetal breathing + heart rate) versus non-stress test (NST) versus NST+AFV. All tests appear to have been conducted 2 times per week from >42 weeks gestation until delivery if results were normal. Abnormal BP (Group 1), NST (Group 2) or AFV (Group 3) were indications for induction.

Outcomes considered by these studies encompassed neonatal and perinatal death, stillbirth, NICU admission, Apgar score, meconium aspiration syndrome, hypoxic ischemic encephalopathy grades 2 and 3, cerebral palsy, neonatal convulsion, cerebral haemorrhage/intracranial haemorrhage, cerebral damage (includes HIE23, cerebral palsy and cerebral haemorrhage), instrumental delivery, caesarian-section. A Table in Appendix 9 summarizes by outcome the concerned studies and their different interventions. Quality appraisal and evidence tables are also available in Appendices 8 and 9.

No evidence was retrieved on the following maternal and fetal outcomes: miscarriage, obstetrical complications (analgesia used, maternal lesions as perineal trauma, chorioamnionitis, postpartum haemorrhage, and endomyometritis), shoulder dystocia, and maternal anxiety.

These six studies with different comparison and intervention groups yielded imprecise estimates of effects precluding meaningful conclusions. For all relevant outcomes, RCTs were considered to have an unclear risk of bias due to missing information concerning important study-level variables. When the effect could be estimated, it demonstrated statistically non-

significant differences across all of the outcomes except for neonatal intensive care unit admission (shown below). For the non-significant results we refer to the GRADE profiles and Forest plots in Appendices 10 and 11.

NICU admission

- Very low level of evidence from one prospective cohort study¹⁹³ comprising 507 pregnant women showed a significant difference with intervention [Test 1: (CTG+ fetal movement) +/- Test 2: partial BP* if non-reactive Test 1] versus comparator {[Test 1: (CTG+ fetal movement) + Test 2: AFV] +/- Test 3: partial BP* if non-reactive Test 1} for **NICU admission** (RR 22.33; 95%CI 1.38 to 360.26).

Conclusions

- Six studies comparing various fetal distress monitoring tests/strategies provided data for the outcomes of interest, not showing meaningful difference for important outcomes except for NICU admissions. Very low quality evidence suggests that **adding routine measurement of amniotic fluid volume to CTG and fetal movement assessment in the surveillance of postterm pregnancies may reduce the number of NICU admissions**. The confidence in the overall results remains very low however.

The GDG acknowledged that evidence were of very low quality and rarely conclusive. Furthermore, studies differed from the Belgian practice, as the tested follow-up strategies started only at 41 weeks or later, period where an induction of labour is often performed in our country and assessed as acceptable in the KCE 2010 guideline on delivery (Mambourg F. et al. KCE Reports 139: Guideline relative to low-risk birth, 2010).¹⁹⁶

4.7.3.3 Recommendation for pregnancies that passed their due date

Based on the retrieved evidence and the discussion with GDG and stakeholders, no recommendation could be developed concerning the surveillance of pregnancies that passed their due date. The considerations that lead to this proposition are summarized below.



Other considerations

Factor	Comment
Balance between clinical benefits and harms	None of the identified studies provided an answer to the question if the use of cardiotocography (CTG) or ultrasound (such as amniotic fluid index or biophysical profile) in the follow-up of prolonged uncomplicated pregnancies leads to better outcomes compared to follow-up without routine CTG or ultrasound. Additional costs and risk of stress induced in low-risk women by CTG and ultrasounds examinations (such as amniotic fluid index or biophysical profile) are not balanced by evidence. Furthermore, even studies in women at increased risk of complications have shown no benefit of antenatal CTG. ¹⁹⁷
Quality of evidence	Very low level of evidence
Costs (resource allocation)	Not applicable
Patients values and preferences	Additional examinations in prolonged pregnancies could induce stress in women.

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> Routine use of antenatal electronic fetal heart rate monitoring (cardiotocography) or ultrasound (e.g. amniotic fluid measurements, biophysical profile) is not supported by evidence for fetal assessment in women with an uncomplicated pregnancy who have passed their due date, for less than one week. [new KCE 2015] 	NA	Very low



5 IMPLEMENTATION AND UPDATING OF THE GUIDELINE

5.1 Implementation

5.1.1 *Actors of the implementation of this guideline*

The dissemination and implementation of this guideline at a national level but also at regional levels will be ideally performed in collaboration with partners whose mission is the improvement of the quality of care. The coordination could be organised by the College Mother and Baby (FPS Public Health) or a platform installed at the NIHDI (CNPQ) responsible for the monitoring and the improvement of the quality of care. The involvement of additional partners is of course desirable since it increases the probability of a guideline to be disseminated and implemented.

This guideline should be disseminated through diverse channels such as websites or programmes of continuing education. The dissemination of this guideline can further be supported by transforming this material into attractive and user-friendly tools tailored to specific caregiver groups and patient associations. The algorithm proposed in the synthesis can be used as a guide for the management and the follow-up of pregnant women.

This guideline is intended to be used by care providers involved in the care for pregnant women and their babies, especially obstetricians/gynaecologists, midwives, neonatologists and general practitioners. It is also of interest for parents-to-be, pregnant women and their partners.

The target organisations (high schools for midwives and nurses, university teachers, scientific associations – ISP/WIV, Superior Council of Health Promotion), professional organisations (VVOG, GGOLF, UPSFB, VLOV vzw, AFsF, UVV, Domus Medica, SSMG...), sickness funds, organisations of birth and childhood (e.g. ONE and its College of gynaecological advisors and midwives, Kind & Gezin, Dienst für kind und familie/kaleido-dg), prenatal

centres, policy makers (Federal Public Service Public Health, Vlaamse Agentschap Zorg & Gezondheid^c, Direction Générale de la Santé en Fédération Wallonie-Bruxelles^d), contribute to the dissemination of these updated recommendations towards the target users previously cited. In majority, their websites already proposed a link towards the KCE guideline 2004. The update will be easily transferred to these organisations.

5.1.2 *Barriers and facilitators for implementation of this guideline*

Potential barriers and facilitators for the implementation of this guideline can be related to the pregnant woman herself, the health practitioners, the health system as a whole or to the level of evidence underlying the clinical recommendations.

Examples of how pregnant woman factors may influence an early entry into prenatal care include:

- Age: Teenagers are more likely to have unplanned or unwanted pregnancies and be less aware of the importance of beginning prenatal care, which may cause their delay in seeking care.¹⁹⁸
- Cultural differences: Immigrant women may have practices or beliefs in their native countries that do not view early prenatal care as a priority; cultural differences have to be taken into account when preventive information is delivered (e.g. weight control and diet for gestational diabetes).¹⁹⁸
- Health literacy: Women unaware of the importance of positive health behaviours are less likely to enrol in early prenatal care. Literacy and language may be barriers to understanding health information (e.g. precautions to avoid infection by CMV or toxoplasmosis).¹⁹⁸
- Work status: Women working in marginalized employment, with no flexibility for time off, may not make prenatal care a priority.¹⁹⁸
- Comorbid diagnosis: Homelessness, drug use, or mental health disease may negatively have an impact on the timing of entry into care.¹⁹⁸

^c Agency for Care and Health develops and implements the health policy of the Flemish community. It is part of the Flemish Ministry for Welfare, Public Health and Family

^d General Direction for Health in Wallonia-Brussels



- Socioeconomic status: Limited financial resources may be a barrier to accessing care.¹⁹⁸
- Anxiety: desire of anxious parents-to-be to ask for more exams than required to be reassured, and wish to undergo diagnostic procedures (particularly if these exams have the ability to detect structural anomalies or infections that can impact the normal development of their baby).

Some factors can be related to the individual practitioners, the care team or the quality of their relationship with their patients:

- Obstetricians and midwives can claim more freedom in how they screen and follow-up their patients.
- Diagnostic tests that are easy to perform and cheap at an individual level, practitioners may be more reluctant to change clinical practice, especially if tests were recommended in the past.
- Patient-clinician relationship: When recommendations intend to correct deleterious lifestyle factors (e.g. smoking, drugs use, alcohol intake, sex with multiple partners during pregnancy), they might be perceived as being offensive. Pregnant women may not accept recommendations and advice about their life-style and they may decide to stop prenatal care or direct towards a less interventionist practitioner.

Health system factors often involve financial and operational issues. Health system factors that may influence early entry into prenatal care and regular follow-up include:¹⁹⁸

- Cost and payment:
 - uninsured or underinsured women may have difficulty finding a provider willing to provide care;
 - expensive interventions that are not adequately reimbursed by the Belgian sickness funds can also impair the follow-up of pregnant women;
 - providing all necessary information, counselling and obtaining informed consent can be viewed by healthcare practitioners as time-consuming activities not adequately financed or reimbursed, resulting in a loss of income (these services would take time away

from seeing other patients). Such perception may lead to unsatisfactorily communications and care.

- Patient materials: to avoid a disrupted follow-up due to women' negligence, automated reminders sent one day in advance can be useful. Providing patient materials such as immunization cards, a booklet with a quarterly calendar reminding all interventions to be performed, flyers and booklets with schemes and figures to render the scientific and technical information easy to understand can be considered as a helpful support to remind the essential information.
- Availability of modern equipment: some recommended interventions that require up-to-date equipment (e.g. automation of the immunoassay in the laboratories) can be replaced by non-recommended interventions due to old-fashioned equipment in some hospitals/prenatal centres.
- Scheduling systems: availability of evening and weekend appointments and wait time may have an impact on access.
- Location: no transportation or an unsafe location may present barriers.
- Inconsistency of recommendations between various clinical preventive services proposed to pregnant women: the plethora of guidelines, advice and information e.g. on websites form different organisations dedicated to the management of the pregnancy can lead to inconsistent messages that are not always evidence-based. The contradictory opinions communicated to health care providers and pregnant women can hurdle the implementation of evidence based practice.

The level of evidence underlying the clinical recommendations can be a facilitator or a barrier for the implementation of the clinical guidelines. It is more difficult to motivate health practitioners and pregnant women to adopt specific constraining behaviours or abandon diagnostic interventions where a low level of scientific evidence leads to the formulation of 'weak' recommendations. On the contrary, a high level of evidence and strong recommendations are incentives to change a current practice.



5.2 Monitoring the quality of care

In the context of the development of indicators to provide an overview of the global care pathway of the (future) mother, both during the period of pregnancy, the delivery and the postnatal period, the InterMutualistic Agency (IMA) has already produced two reports, one relating to prenatal care (2010 data) and one relating to the period of delivery (inpatient only; data 2008-2012). A report on postnatal care (data 2012 or 2013) is currently in preparation.

For the report related to prenatal care, the IMA evaluated the implementation of the KCE guideline 2004 the year after its publication (IMA report based on data 2005) and 5 years later (data 2010).⁴

Three main aspects of antenatal care were examined in both reports: consultations with various care providers (general practitioners and specialists, midwives, physiotherapists), common laboratory tests and technical examinations. Compared to 2005, the detection of Down syndrome, vaccination against flu and the delivery of contraceptives in the six months prior to pregnancy have been added to the 2010 analysis; these issues were not covered by the KCE guideline 2004.

Process indicators were developed by the IMA and measured using the administrative database of all Belgian sickness funds:

1. Proportion of low-risk pregnant women
2. Antenatal visits
 - a. Mean number of antenatal visits during the pregnancy according to the level of risk (low risk vs. high risk)
 - b. Proportion of antenatal visits performed by general practitioners / midwives / obstetricians/gynaecologists / other medical specialists
3. Laboratory analyses
 - a. Proportion of pregnant women who have underwent haematological assessments during their pregnancy
 - b. Proportion of pregnant women who have underwent screening for infectious diseases during their pregnancy (bacteriuria / Group B Streptococcus / CMV / hepatitis B / hepatitis C / rubella / syphilis / HIV / toxoplasmosis)
- c. Proportion of pregnant women who have underwent screening for gestational diabetes during their pregnancy
- d. Proportion of pregnant women who have underwent screening for allergies or hypercholesterolemia during their pregnancy (not relevant screening that captures overconsumption of diagnostic tests)
- e. Mean number of laboratory analyses performed per pregnant woman during her pregnancy
4. Technical procedures
 - f. Proportion of pregnant women who have undergone ultrasound examinations (gestational age / fetal development / fetal abnormalities / transvaginal ultrasound)
 - g. Proportion of pregnant women who have undergone invasive prenatal diagnostic procedures (chorionic villus sampling, amniocentesis, percutaneous umbilical cord blood sampling and fetal biopsy)
 - h. Proportion of pregnant women who have undergone cardiotocography (CTG)
 - i. Mean number of technical procedures performed per pregnant woman during her pregnancy
 - j. Proportion of pregnant women who have undergone exams for detecting Down syndrome (triple test and PAPP-A)
5. Use of physiotherapy during pregnancy
6. Proportion of pregnant women who were vaccinated against flu
7. Proportion of pregnant women who were hospitalized during their pregnancy

This updated clinical guideline will be transmitted to the working Group at IMA in order to monitor the implementation of the current recommendations.



5.3 Guideline update

Clinical guidelines need a periodic evaluation of scientific literature that may impact the formulation of the recommendations for clinical practice (quality of the evidence, balance between benefits and harms, patients' values and preferences, or resource use and cost).¹³ Any decision to update a guideline must balance the need to reflect changes in the evidence against the need for constancy, because regular changes to guideline recommendations would make implementation difficult.¹⁹⁹

KCE clinical guidelines are updated as needed so that recommendations take into account important new information. This guideline would ideally be reviewed at 5 years after publication to determine whether all or part of it should be updated. If important new evidence is published earlier, we may decide to do a more rapid update of some recommendations.



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