

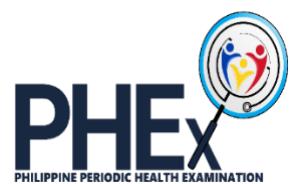


PHILIPPINE GUIDELINES on PERIODIC HEALTH EXAMINATION (Phase 3)



Prenatal Disorders

PERIODIC HEALTH EXAMINATION TASK FORCE 2022-2023



Disclaimer and Contact Information

This guideline is intended to be used by general practitioners, specialists and health professionals who are primary care providers. Although adherence to this guideline is encouraged, it should not restrict the primary care providers in using their sound clinical judgment in handling individual cases. Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but this document should not be the sole basis for evaluating insurance claims. Recommendations from the PHEX app and the guidelines therein should also not be treated as strict rules on which to base legal action.

Contact Us

Send us an email at mjvgermar@gmail.com for any questions or clarifications on the outputs and process of this CPG.

Acknowledgments

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The Task Force members undertook extensive technical work in (1) searching and synthesizing the evidence while ensuring objectivity in each stage of the process, (2) presenting the evidence in the panel discussion, and documenting and writing the final report. They were also indispensable in carrying out the legwork, coordinating among various individuals, groups, and committees, and facilitating the en banc meeting. The CPG Central Steering Committee and the Task Force Steering Committee were responsible for overall organization and management and were accountable for the quality of the CPG.

Lastly, this guideline was completed through the invaluable contribution and participation of panelists from different sectors of healthcare who committed their time and effort, their knowledge, experience, and expertise in analyzing the scientific evidence and their values and preferences were crucial in formulating the recommendations.

We thank all in contributing to this endeavor.

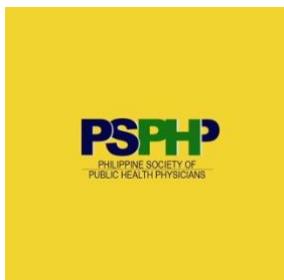
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Participating Societies, Organizations, Agencies and/or Institutions



List of Abbreviations and Acronyms

ACOG	American College of Obstetrician and Gynecologists
ACP	Antenatal Care Package
ADHD	Attention-Deficit/Hyperactivity Disorder
AOG	Age of gestation
AUC	Area under the ROC (Receiver Operating Characteristic) curve
BMI	Body mass index
CBC	Complete blood count
CHD	Congenital heart disease
COI	Conflict of interest
CP	Consensus Panel
CPG	Clinical Practice Guideline
CVS	Chorionic villus sampling
DALYs	Disability-adjusted life years
DOH	Department of Health
EON-GBS	Early onset Group B Streptococcus
ERE	Evidence Review Experts
EtD	Evidence to Decision
FT4	Free T4; Free thyroxine
GBS	Group B Streptococcus
GDM	Gestational diabetes mellitus
HELLP	Hemolysis, elevated liver enzymes and low platelets
IAP	Intrapartum antibiotic prophylaxis
IDA	Iron deficiency anemia
IVF	In vitro fertilization
LGA	Large for gestational age
MUAC	Mid-upper arm circumference
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NT	Nuchal translucency
OB-GYN	Obstetrician-gynecologist
OGTT	Oral glucose tolerance test
PAPP-A	Pregnancy associated plasma protein-A
PIGF	Placental growth factor
POGS	Philippine Obstetrics and Gynecology Society
QALY	Quality-adjusted life year
RCOG	Royal College of Obstetricians and Gynecologists
SC	Steering Committee
SOGC	Society of Obstetricians and Gynecologists of Canada
TPO-Ab	Thyroid peroxidase antibodies
TSH	Thyroid Stimulating Hormone
USPSTF	U.S. Preventive Services Task Force
WHO	World Health Organization

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Executive Summary

Among the top 10 pregnancy associated conditions in the Philippines are Gestational Diabetes Mellitus, Hypertension, Thyroid diseases, Anemia and malnutrition. These conditions can be detected antenatally and can have a significant impact on maternal and neonatal outcomes. These conditions contribute significantly to the maternal and neonatal burden of disease. Notably, low and middle-income countries, bear a disproportionate share of this burden. Hence, it is imperative to detect these conditions during its early stages in order to mitigate the impact of prenatal disorders on Filipino mothers, their infants and families.

This CPG on prenatal disorders aims to provide recommendations to prioritized clinical questions and improve health outcomes of pregnant Filipino women. The consensus statements look at the asymptomatic, pregnant Filipino woman as an individual who does not have any symptoms or devoid of modifiable risk factors of the disease. The critical outcomes include preterm birth, perinatal or neonatal mortality, infant mortality, maternal mortality, and pregnancy outcomes. It does not aim to address every facet of prenatal or neonatal care, but it is intended to be used by general practitioners, specialists, other healthcare professionals, and policymakers involved in the health service deliveries of pregnant Filipino women, who are the target beneficiaries.

This guideline is based on the current best available evidence (literature search up until September 2022), local resources, infrastructures, and the practice context in the country. Guideline recommendations were developed following a standard methodology for guideline development outlined in the DOH CPG Manual in 2018. Various working groups were established. Existing guidelines and clinical studies were comprehensively searched and reviewed to address 11 key questions. A multi-sectoral panel of representatives and experts collaborated to develop and finalize a set of recommendations that were agreed upon by consensus. The GRADE method was used to determine the direction and strength of each recommendation.

Table 1 shows the summary of 11 questions and recommendations for screening for prenatal disorders.

Table 1. Summary of questions and recommendations for screening for prenatal disorders

Recommendations	Strength of recommendations	Certainty of Evidence
Question 1. Should screening for thyroid disease using biochemical tests be offered to all asymptomatic pregnant Filipino women to improve maternal and perinatal outcomes?		
1.1 We recommend risk-based TSH and/or FT4 antenatal screening among asymptomatic pregnant Filipino women to detect maternal hypo-/hyperthyroidism and to prevent perinatal morbidity and mortality.	STRONG	Low
Question 2. Should routine measurement of cervical length during the second trimester be offered to all asymptomatic pregnant Filipino women to prevent perinatal morbidity and mortality?		
2.1 Among asymptomatic pregnant Filipino women, we suggest against routine measurement of cervical	WEAK	Very Low

length during the second trimester to prevent perinatal morbidity and mortality.

Question 3. Should screening for gestational diabetes mellitus (GDM) using oral glucose tolerance test (OGTT) be offered to all pregnant Filipino women to decrease perinatal mortality and morbidity?

3.1 We suggest screening for GDM among pregnant women using a 75-g OGTT in the second trimester (24-28 weeks) to decrease perinatal mortality and morbidity.

WEAK

Very Low

Question 4. Should screening for group B Streptococcus using culture be offered to all pregnant Filipino women to improve perinatal outcomes?

4.1 We suggest screening pregnant women for risk factors for group B *Streptococcus* followed by intrapartum antibiotic prophylaxis for those who screen positive and have a planned vaginal delivery to prevent early onset neonatal GBS sepsis.

WEAK

Very Low

Question 5. Should first trimester ultrasound be offered to all pregnant Filipino women to improve maternal and perinatal outcomes?

5.1 We suggest first trimester ultrasound in all pregnant Filipino women to improve maternal and perinatal outcomes.

WEAK

Very Low to Low

Question 6. Should screening for fetal aneuploidy using nuchal translucency be offered to all pregnant Filipino women in the first trimester?

6.1 We suggest nuchal translucency measurement at 11-14 weeks AOG be offered to all pregnant Filipino women to screen for Down syndrome; and be offered to pregnant women at high risk for fetal anomaly, to screen for major CHD.

WEAK

Very Low to Low

Question 7. Should second trimester ultrasound be offered to all pregnant Filipino women to improve maternal and perinatal outcomes?

7.1 We suggest routine second trimester ultrasound for all pregnant Filipino women to improve maternal and perinatal outcomes.

WEAK

Low

Question 8. Should the risk for pre-eclampsia be assessed in the first trimester for all pregnant women?

8.1 We suggest assessing the risk for preeclampsia in the first trimester in all pregnant women.

WEAK

Very Low

Question 9. Should multimarker screening rather than maternal factors alone be used to screen for pre-eclampsia among pregnant women?

9.1 We suggest using multimarker screening rather than maternal risk factors alone to assess the risk for preeclampsia in the first trimester in all pregnant women.

WEAK

Low

Question 10. Should screening for iron deficiency anemia using complete blood count be offered to all asymptomatic pregnant Filipino women to improve maternal and perinatal outcomes?

10.1 We suggest against screening for iron deficiency anemia using complete blood count among all asymptomatic pregnant Filipino women to improve maternal and perinatal outcomes.

WEAK

Very Low

Question 11. Should screening for undernutrition via measurement of mid-upper arm circumference be offered to all pregnant Filipino women to improve maternal and perinatal outcomes?

11.1 We suggest screening for undernutrition via measurement of mid-upper arm circumference in all pregnant Filipino (adolescent and adult) women to improve perinatal outcomes.	WEAK	Very Low
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1. Introduction

The Philippine Guidelines on Periodic Health Examination (PHEX), which was first published in 2004 (1), aimed to provide early prevention services among apparently healthy Filipinos. The publication offered evidence-based recommendations for screening tests that was tailored to the Philippine setting.

This 2023 version of the Philippine Guidelines will support the objectives stated in the Universal Health Care Act (2) that all Filipinos are given access to quality and affordable medical services, including primary care benefits. In the guideline development, evidence-based recommendations for the prioritized health screening were crafted using the GRADE Evidence-to-Decision (EtD) framework (3,4). The EtD framework facilitated the adaptation of recommendations and decisions of experts and stakeholders based on specific contexts, essential health outcomes, benefits, and harms while taking into consideration the concerns on equity, applicability, and feasibility.

The evidence collated to answer the research questions on screening tests are used in formulating the recommendations that can be classified into two: (a) screening for a risk factor, which is directed towards determining effective management of the condition as a risk factor, and (b) screening for early disease that is focused on the performance of the tests that will be used to detect and eventually treat early disease and prevent it from further progression.

Nonetheless, health screening also carries potential harm, particularly if a person is falsely labeled as being ill. This poses a threat to the psychological, social, or physical well-being and even to the individual's financial stability. Because of these probable adverse effects of screening, criteria are set to determine if screening for a particular condition can be beneficial and pragmatic. The voting panel members used these items aligned with the EtD framework: (a) burden of illness must be high, (b) screening tests must be accurate enough, (c) early treatment must be more effective than late treatment, (d) confirmatory tests and early management must be safe and available, and (e) costs of screening must be proportional with the potential benefit.

Aside from the regulatory agencies and policymakers in the national government, the target users of this guideline on screening strategies include primary care providers, general physicians, specialists, training institutions, payors, patients, the general public, and industry partners.

According to the World Health Organization, congenital disorders or conditions that develop prenatally and may be identified before, at birth, or later in life are one of the primary causes of the global burden of disease affecting low and middle-income countries disproportionately (5). In the country, it is among the top 5 causes of neonatal deaths, accounting for 14% of deaths for children under 5 in 2019 (6). Although more than 7,000 birth defects from genetic or partially genetic sources have been identified, there is still a substantial proportion that is unknown, with risk factors and preventive approaches not yet

confirmed (7).

It is therefore significant to detect these conditions at an earlier stage so as to reduce the burden of prenatal disorders among Filipino mothers, their infants, and their families. The consensus statements look at the asymptomatic, pregnant Filipino woman as an individual who does not have any symptoms or is devoid of modifiable risk factors for the disease. The critical outcomes include preterm birth, perinatal or neonatal mortality, infant mortality, maternal mortality, and other pregnancy outcomes.

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2. Objective, Scope, Target Population and Target Users

2.1. Objectives

The overall objective of this guideline is to present evidence-based recommendations for screening for prenatal disorders among asymptomatic, pregnant women through a comprehensive evaluation of the benefits, harms, costs, feasibility, acceptability and equity associated with screening in the local context.

2.2. Scope and Purpose

This CPG provides evidence-based recommendations for screening for prenatal disorders among pregnant Filipino women.

2.3. Target Population

These guideline questions and recommendations target health outcomes of all pregnant Filipino women and/or newborn, such as detection of maternal disease, stillbirth, preterm birth, maternal hospitalization, neonatal birth injuries and disorders, and admission to NICU.

2.4. Target Users

The recommendations contained in this guideline assist various stakeholders in making informed decisions. These stakeholders include general practitioners, obstetrician-gynecologists, family physicians, neonatologists, endocrinologists, midwives, allied healthcare students and professionals, trainees, patients, and policymakers. Academic medical institutions may use this CPG as a reference to educate doctors-in-training on the best practices in screening for prenatal disorders. In addition, the CPG aims to equip policymakers, labor force administrators, regulatory agencies, and both government and private financial and healthcare delivery institutions in the Philippines with essential tools and strategies that will enable them to facilitate prompt healthcare access for pregnant women.

3. CPG Development Methodology

3.1 Organization of the Process

With regards the guideline development process, it was divided into four phases (1), namely: 1) preparation and prioritization, 2) CPG generation, 3) CPG appraisal, and 4) implementation in the Manual for CPG Development (2).

During the first phase of preparation and prioritization, the Steering Committee set the CPG objectives, scope, target audience, and clinical questions. The members identified and formed the working groups involved in creating the evidence base and finalizing the recommendations for each clinical question included. SC members had no direct participation in assessing and synthesizing the evidence, generating the evidence summaries and evidence-based draft recommendations of the evidence review experts (ERE), and voting on final recommendations during the en banc consensus panel review. They SC invited the relevant

organization to nominate individuals who can become part of the consensus panel.

The Steering Committee convened the Consensus Panel (CP), in consideration of possible conflicts of interests of each member. Each nominee was required to fill out and sign a declaration of interest form and submit their curriculum vitae. The SC and the COI Committee screened the nominees for any possible conflict of interest that may bias their decisions. Those with significant potential COI based on the decision of the COI Committee were not allowed to vote during the *en banc* meeting but were allowed to fully participated in the panel discussions. To ensure fairness and transparency, the composition was guided by the DOH Manual (1), with content experts and other key stakeholders being invited to join the panel. The key stakeholders included policymakers, patient advocates, allied medical practitioners, and physicians from different settings (e.g., public primary care, private practice, and public health). The physicians were members of the different medical societies, such as, Philippine Obstetrical and Gynecological Society, Philippine Society of Maternal Fetal Medicine, Philippine Academy of Family Physicians, Philippine Society of Public Health Physicians, Philippine Society of Newborn Medicine, Philippine Society of Endocrinology and Metabolism, and Philippine Society of Ultrasound in Obstetrics and Gynecology. The patient advocate is from the Management Collective of Action for Economic Reforms.

The Evidence Review Experts (ERE) or the technical working group were tasked to review existing CPGs, appraise and summarize the evidence, and draft the initial recommendations. The evidence summaries were then presented to the Consensus Panel members to finalize the recommendations.

The Consensus Panel that was comprised of representatives from various sectors, were assigned to assess the evidence summaries and create recommendations during the *en banc* meeting. In the said meeting, outcomes were prioritized as to ‘critical’ and ‘important,’ while necessary considerations were discussed about the recommendations, and agreement on each recommendation and its strength were voted upon by the members.

This guideline guaranteed that patients’ views and preferences were considered in all the recommendations by including studies about these in the evidence summary and by ensuring the participation of a patient representative from the Management Collective of Action for Economic Reforms .The patient advocate provided input on the reasons for, barriers to, and facilitators of seeking care. She had specific inputs on cost and feasibility of certain screening modalities. These were considered and clarifications were made in the discussions.

The Steering Committee facilitated the whole CPG development process, but the members had no direct participation in assessing and synthesizing the evidence, generating the evidence summaries and evidence-based draft recommendations of the Evidence Review Experts, and voting on final recommendations during the *en banc* Consensus Panel review. The relevant organizations or societies were asked to nominate individuals who can become a part of the Consensus Panel.

3.2. Evidence Summaries

Two evidence reviewers were assigned to work on each guideline question that was posed by the steering committee. Research questions in the PICO (population, intervention, comparator and outcome) format were framed from the guideline questions to guide the evidence review. Any concerns on the population(s) of interest, interventions, comparators, and outcomes were clarified with the steering committee. The clinical questions of the PHEX for prenatal disorders were about thyroid disease, cervical length, gestational diabetes mellitus, group B streptococcus, fetal aneuploidy, pre-eclampsia, iron deficiency anemia, and undernutrition among pregnant women.

Recent local and international clinical practice guidelines relevant to the topic of the guideline question were searched, retrieved, and critically appraised by two independent reviewers using the AGREE-II tool. Clinical practice guidelines that were rated at least 75% overall AGREE rating and at least 80% for scaled domain score for "Rigor of development" were considered for possible adoption/adaptation. Evidence profiles and summaries of eligible CPGs were adapted and updated. Systematic reviews and meta-analyses were performed for questions where existing CPGs were not adapted.

Search Strategy and Study Inclusion

Two independent reviewers searched various electronic databases for studies relevant to their assigned research question. Search results (titles and abstracts) were screened for relevance to the question. Full text articles of relevant studies were retrieved. Disagreements regarding study inclusion were resolved through a consensus or arbitrated by a third reviewer.

The ERE searched and appraised international practice guidelines related to periodic health screening, including but not limited to those of the American College of Obstetrician and Gynecologists, National Institute for Health and Care Excellence, Royal College of Obstetricians and Gynecologists, Society of Obstetricians and Gynecologists of Canada, U.S. Preventive Services Task Force, and World Health Organization. If the CPG was deemed to be of good quality and done within 5 years, the evidence summaries of the CPG were adopted.

The results of the appraisal of existing CPGs and their evidence summaries determined whether a systematic search in electronic databases should be done (MEDLINE via PubMed, CENTRAL, Google Scholar) and for the need to do de-novo systematic reviews and meta-analysis for each question. Relevant local databases and websites of medical societies were also covered in the search. Keywords were based on PICO (MeSH and free text) set for each question. The ERE also contacted authors of related articles to verify details and find other studies for appraisal, if needed.

Appraisal of Studies and Creation of Evidence Summaries

Two independent reviewers critically appraised eligible studies based on directness, methodological validity, results, and applicability using validated critical appraisal tools. Disagreements were discussed and resolved by consensus or consultation with a third reviewer. Tools such as RevMan, STATA, and GRADEPro were used for the quantitative synthesis of important clinical outcomes for each question. Evidence summaries were

generated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (2). Table 2 shows the rating of certainty of evidence.

The ERE generated evidence summaries for each of the eleven (11) questions, with every summary discussing the evidence on the burden of the problem, and diagnostic performance, benefits, harm, and social and economic impact of the screening test/intervention. Evidence/information that will facilitate in the decision (i.e. cost of screening test, cost-effectiveness studies, qualitative studies) were also included in the summaries.

Table 2. Basis for assessing the quality of the evidence using GRADE approach

Certainty of Evidence	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect.
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.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Factors that lower quality of the evidence are:

- Risk of bias
- Important inconsistency of results
- Some uncertainty about directness
- High probability of reporting bias
- Sparse data/Imprecision
- Publication bias

Additional factors that may increase quality are:

- All plausible residual confounding, if present, would reduce the observed effect
- Evidence of a dose-response gradient
- Large effect

3.3 Formulation of the Recommendations

Draft recommendations were formulated by the evidence reviewers according to the certainty of evidence and presented to the CP for discussion. The CP finalized the recommendations after consideration of all factors, such as trade-offs between benefit and harm based on the evidence, cost-effectiveness, applicability, feasibility, equity, resources and uncertainty due to research gaps.

Prior to virtual CP meetings, the members received the draft recommendations together with evidence summaries based on the Evidence-to-Decision (EtD) framework in Table 4.

Box 1. Detailed considerations based on the EtD framework (3)

1. Is the problem a priority?
2. How accurate is the test?
3. How substantial are the desirable anticipated effects?
4. How substantial are the undesirable anticipated effects?
5. What is the certainty of the evidence of test accuracy?
6. Is there important uncertainty about or variability in how much people value the main outcomes, including adverse effects and burden of the test and downstream outcomes of clinical management guided by the test results?
7. Does the balance between desirable and undesirable effects favor the test or the comparison?
8. How large are the resource requirements (costs)?
9. What is the certainty of the evidence of resource requirements (costs)?
10. Does the cost-effectiveness of the test favor the test or the comparison?
11. What would be the impact on health equity?
12. Is the test acceptable to key stakeholders?
13. Is the test feasible to implement?

The strength of each recommendation (i.e. strong or weak) was decided upon by the Panel considering all the factors mentioned in Table 4. Strong recommendation means that the Panel is “confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects” while weak recommendation means that the “desirable effects of adherence to a recommendation probably outweigh the undesirable effect but is not confident” (4).

The recommendation for each question and its strength was determined through voting. A consensus decision was reached if 75% of all CP members who were eligible to vote agreed (2); however, if consensus was not reached in the first round of voting, then members were encouraged to have questions and discussions; and, another 2 rounds of voting on an issue were conducted.

This CPG also ensured that patients’ views and preferences were considered by including a patient advocate who actively participated during the discussion of each question and voting on recommendations. Research studies capturing the views of stakeholders, if available, were also presented during the CP meetings.

3.4 Planning for Dissemination and Implementation

All recommendations will be incorporated in a web-based and mobile application that is user-friendly and accessible to the public through <https://phex.ph>. Upon entry of individual patient

demographic data (e.g., age, sex, weight, height), into this application, the user can generate a list of the recommended screening strategies.

The evidence summaries and the full CPG manuscript will be posted online in the DOH Website once approved. The CPG will undergo quality screening by the DOH Evidence Generation and Management Division for recognition and implementation as a National Practice Guideline by DOH and the Philippine Health Insurance Corporation (PHIC).

A summarized version of the manuscript of the CPG will be published in the Acta Medica Philippina. The CPG will also be published in the official websites of the participating organizations like the POGS. The CPG will be presented to doctors and other health professionals through lectures, symposia, and small group discussions during continuing medical education meetings of academic institutions and medical societies. The recommendations of the CPG will also be discussed in health forums disseminated through the radio, television, and social media.

3.5 External Review

Two independent reviewers examined the CPG manuscript. The SC invited 2 experts on content and research methodology from the University of the Philippines College of Medicine engaged in prenatal disorders to compose the External Review Panel. They were asked to share their insights on the completeness and relevance of the evidence, the processes, clarity of the output (the recommendations and the manuscript), and the planned methods of dissemination of the CPG. They used the AGREE II tool for the methodological assessment. In response to their feedback and comments, the SC revised portions of the Methodology (description of the GRADE methodology, certainty of evidence, and strength of recommendation) and the consensus discussions to improve clarity.

3.6. Editorial Independence

Funding Source

This CPG on periodic screening for prenatal disorders received financial support from the Department of Health. The DOH neither imposed any conditions nor exerted any influence on the procedures and final recommendations and output.

Management of Conflicts of Interest

Prior to the start of guideline or the formulation of consensus statements, all task force members (including the task force chair, steering committee members, technical coordinator, evidence review experts, technical writer, and potential consensus panelists) were required to submit a complete disclosure. These included financial, intellectual, or other

personal interests that could be perceived by others to influence their judgment on issues addressed by this CPG. The members were also entrusted with disclosing immediate family members' potential COIs. The panelists' disclosures and contributions to the field were reviewed both individually and collectively to create a balanced panel.

The scope of disclosure included a two-year period. All Task Force members were asked and reminded to avoid any new financial conflicts for a year after the completion of the guideline recommendations.

The Conflict of Interest Review Committee (COIRC) evaluated the COIs of the Task Force members throughout the entire process of developing the guideline. Conflicts that relate directly to the disease, diagnostic techniques, intervention, or management were said to be primary; those that do not relate directly were characterized as secondary.

The algorithm for COI management is shown in Figure 1. In general, those relationships and activities that are (1) intellectual in nature and lacking direct and indirect financial benefit or (2) unrelated to the content area and focus of the PICO question or recommendation with a company that has no products in that specific topic area are allowed. Where intellectual conflicts exist, relationships should be disclosed to the group of panelists throughout the development process and included in the final publication.

Based on the disclosures, the specific terms of management were set forth by the COIRC for each Task Force member and limited participation in this way: (1) broadcast conflict (B), (2) cannot vote (C), and (3) disallowed relationships and activities (D).

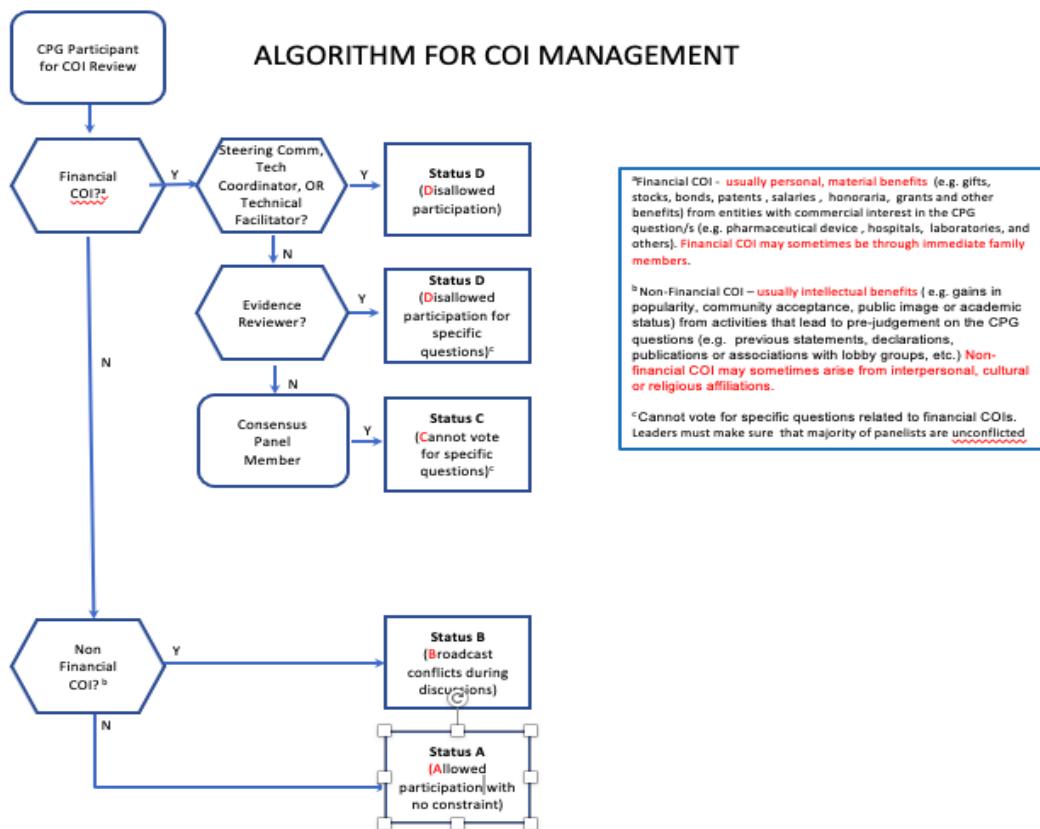


Figure 1. COI management algorithm

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4. Recommendation and Evidence Summaries

4.1 Screening for Thyroid Disease

RECOMMENDATION

We recommend risk-based TSH and/or FT4 antenatal screening among asymptomatic pregnant Filipino women to detect maternal hypo-/hyperthyroidism and to prevent perinatal morbidity and mortality. (*STRONG recommendation, low level of evidence*)

Thyroid Disease risk factors include the following:

- Family history for autoimmune thyroid disease
- Presence of goiter
- Personal history of type 1 Diabetes Mellitus or any autoimmune disease
- History of neck irradiation
- Previous miscarriages or preterm deliveries
- Signs/symptoms suggestive of thyroid dysfunction

Considerations

The Consensus Panel considered the following when formulating this recommendation:

- The evidence presented focused on the detection of maternal hypothyroidism or hyperthyroidism, miscarriage, neonatal respiratory distress syndrome, and perinatal or neonatal death. Based on the evidence, universal screening, when compared with risk-based screening, led to a higher number of detected maternal thyroid dysfunctions. However, the evidence on miscarriage, which was deemed critical by the Panel, was inconclusive. The investigations into important outcomes such as neonatal respiratory distress syndrome and perinatal or neonatal death were also inconclusive.
- The Panel also asked about effects on infants later in life. Based on the RCTs, there was no difference in children's intelligence quotient measured at 3 years of age between the groups of pregnant women who underwent universal screening or risk-based screening. Thyroid dysfunction in these children was not examined in these RCTs.,
- There are research gaps as prevalence of thyroid disease among pregnant women was unknown, and local studies are lacking about this condition leading to concerns on applicability. One panelist then proposed to include maternal hypo-/hyperthyroidism in the research agenda for further studies that will strengthen evidence among Filipino women and neonates.
- The timing of testing was not included due to possible inaccuracy of biochemical assessment in the first trimester.
- There were major issues regarding universal screening namely, a) feasibility of implementation and resource requirements at the primary level, and b) inaccuracy of thyroid function tests in laboratories leading to false positive results or unnecessary referrals/work-ups, hence risk-based screening was preferred.

- Although the level of evidence was rated to be low, the Panel decided to place it as a strong recommendation due to the impact of hypothyroidism in newborns, and it is deemed of utmost importance to address prevention and rehabilitation of neonatal thyroid disorders.

4.1.1 Burden of disease

Epidemiology, Natural Course, Management, Economic impact, and Social impact of the Disease

A large body of evidence suggests that thyroid dysfunction during pregnancy is associated with adverse perinatal outcomes. In a Danish population-based study of more than one million pregnancies, it was found that spontaneous abortion was more likely to occur among those diagnosed with hyperthyroidism either before or during pregnancy compared to those without hyperthyroidism (aHR: 1.28, 95% CI: 1.18 to 1.40) (1). An individual patient data meta-analysis of 48,145 mother-child pairs found that maternal subclinical hypothyroidism was associated with higher risk of small for gestational age offspring compared to euthyroidism (OR: 1.24, 95% CI: 1.04 to 1.48) (2). Thyroid dysfunction also appears to affect neurocognitive development beyond pregnancy. A systematic review and meta-analysis of 29 observational studies representing more than seven million patients found associations between maternal hyperthyroidism and attention deficit hyperactivity disorder (OR: 1.18, 95% CI: 1.04 to 1.34, $I^2 = 0\%$) and epilepsy (OR: 1.19, 95% CI: 1.08 to 1.31, $I^2 = 0\%$) in the offspring (3).

Moreover, the prevalence of maternal thyroid dysfunction varies widely. The Philippine Thyroid Diseases Study 1 estimated the national prevalence of thyroid disorders in Filipinos (4), which involved conducting a survey among 4,897 Filipino adults 20 years and older who were non-pregnant and non-lactating. The overall prevalence of thyroid function abnormalities was 8.53%, with subclinical hyperthyroidism (5.33%) being the most commonly occurring type. Prevalence estimates were 2.18% for subclinical hypothyroidism and <1% each for both overt hyperthyroidism and overt hypothyroidism.

On the other hand, thyroid replacement therapies are considered safe in pregnancy, while anti-thyroid medications are associated with potential risks for adverse outcomes. The said associated risks for treatment of thyroid disorder during pregnancy varies – both levothyroxine and liothyronine are classified under US Food and Drug Administration (FDA) Pregnancy Category A, meaning adequate and well-controlled studies have failed to demonstrate fetal risk (5). On the other hand, both propylthiouracil (PTU) and methimazole (MMI) are classified under US FDA Pregnancy Category D, meaning there is positive evidence of human fetal risk that must be weighed against potential clinical benefits (6,7). The most recent meta-analysis on the use of antithyroid drugs (ATD) in pregnancy (7 cohort studies, 1 case control study, n = ~6 million pregnancies) found that both MMI and PTU were associated with increased risk of birth defects (aRR: 1.51, 95% CI: 1.02-1.29) (8).

In summary, current evidence suggests that maternal thyroid dysfunction, both hypothyroidism and hyperthyroidism, may have negative repercussions to the pregnancy, fetal growth, and future neurocognitive development of the offspring. Treatment of maternal subclinical hypothyroidism with levothyroxine appears beneficial with no clear evidence of

harm on the fetus. Treatment of maternal hyperthyroidism with either PTU or MMI appears beneficial but with some evidence of harm on the fetus. The evidence is unclear whether universal antenatal screening for thyroid function leads to improved maternal and neonatal outcomes.

4.1.2 Benefits, Harms and Diagnostic Performance of Screening Tests

Screening Cascade

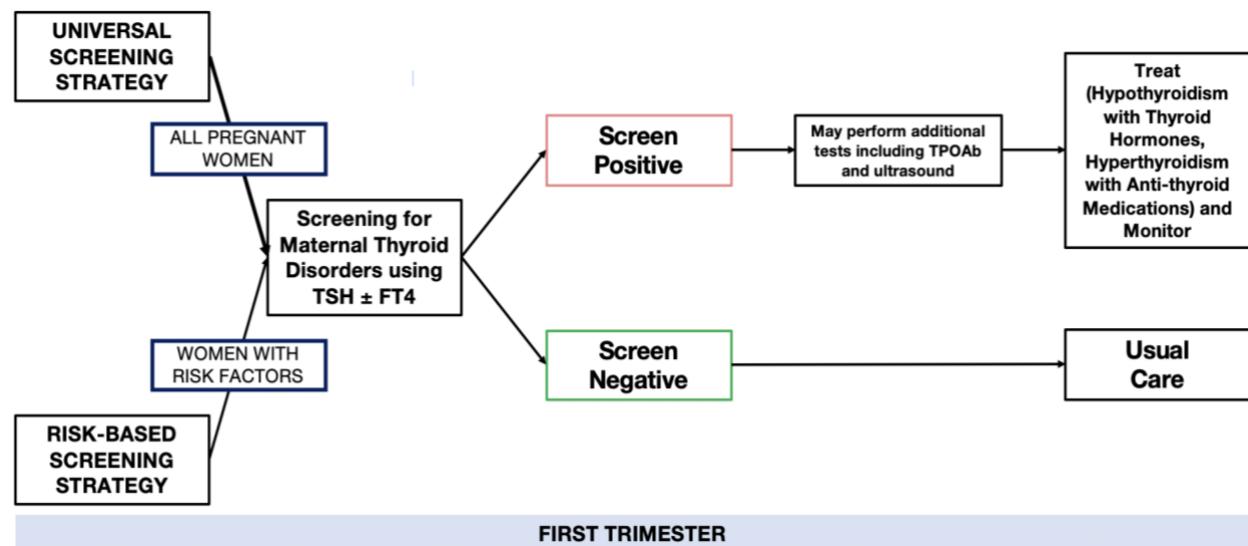


Figure 2. Screening Cascade for Thyroid Disease

As shown in Figure 2, the screening for thyroid dysfunction takes place during the first trimester. The universal screening strategy requires all pregnant women to undergo screening for maternal thyroid disorders using TSH and/or FT4, whereas only those with risk factors shall undergo screening in a risk-based strategy. If a woman screens positive, additional tests may be performed including neck ultrasound and TPO antibodies. Those with hypothyroidism may undergo treatment with thyroid hormone replacement, while those with hyperthyroidism may be prescribed anti-thyroid medications. Pregnant women are then monitored to term; and if a woman screens negative for thyroid disorder, she receives usual care.

Detection of Maternal Hypothyroidism or Hyperthyroidism

Only one RCT (Negro 2010, n = 4,562) collected data on the detection rate of either hypothyroidism or hyperthyroidism among mothers who underwent universal screening versus case finding (or risk-based screening) for thyroid disease. In this RCT, case finding was performed by screening participants for high-risk features including at least one of the following: family history of autoimmune thyroid disease, presence of goiter, signs and symptoms suggestive of thyroid dysfunction, personal history of T1DM or other autoimmune disease, history of neck irradiation, previous miscarriages, or preterm deliveries. All women underwent blood extraction for testing for TSH, FT4, and TPO-Ab. Participants belonging to the universal screening group had their sera immediately run while those in the case-finding group had their sera frozen at -70°C and assayed in the postpartum period.

Because the study only presented the proportion of participants in the case finding and universal screening groups who were later classified according to thyroid status and respective outcomes, secondary analysis of published data was performed. From the extracted incidence data, comparison of event rates on maternal hypo/hyperthyroidism between the universal screening and case finding groups was done. Summary of effect sizes using relative risk and 95% confidence intervals was generated using RStudio. (14)

Participants belonging to the universal screening group were then more likely to be diagnosed with either hypothyroidism or hyperthyroidism compared to those in the case finding group (RR: 3.28, 95% CI: 2.04 to 5.26).

Perinatal Morbidity including Miscarriage and Respiratory Distress Syndrome and Perinatal Death

Two RCTs (Negro 2010, n = 4,562 and Ma 2015, n = 1,671) collected data on perinatal outcomes among those belonging to universal screening for thyroid function group versus case finding or usual care group.

In Ma 2015, cluster randomization was performed whereby pregnant women from one center were assigned to the screening group while the participants from the other center were assigned to the control group. Blood specimens were extracted from all participants for testing for TSH, FT4, FT3, and TPOAb. Sera in the control group were kept in a -20° C freezer for analysis postpartum.

The incidence between treatment groups of the following outcomes were compared, as reported from one RCT (Negro 2010): neonatal respiratory distress syndrome and perinatal/neonatal death. For the outcome on miscarriage that was stated by both RCTs, meta-analyses was done using random-effects models and reported pooled relative risks, 95% CI, and I^2 statistic in Review Manager (15). The cluster randomization of Ma 2015 was adjusted using the effective sample size estimation method (16). An intracluster correlation coefficient of 0.05 was then used, on the basis of the WHO Global Survey on Maternal and Perinatal Health (17). The results are summarized in Table 3.

Table 3. Effect of universal screening on perinatal morbidity and mortality outcomes compared to risk-based screening or usual care

Outcomes	No. of Studies	RR	95% CI	I^2 Statistic
Miscarriage	2	0.90	0.68 to 1.19	0%
Neonatal respiratory distress syndrome	1	0.79	0.48 to 1.31	-
Perinatal or neonatal death	1	0.92	0.42 to 2.02	-

In summary, there was no statistically significant difference in the occurrence of perinatal morbidities including miscarriage and respiratory distress syndrome and perinatal deaths between universal screening and case finding or usual care group.

Fetal Congenital Anomalies

No study was found that assessed the effect of universal screening for maternal thyroid function tests, on the occurrence of fetal congenital anomalies.

Overall Certainty of Evidence

The certainty of evidence for the use of universal thyroid function screening for the outcome detection of either maternal hypothyroidism or hyperthyroidism is high. However, the certainty of evidence for the perinatal morbidity outcome including miscarriage, neonatal respiratory distress syndrome and perinatal mortality were moderate due to issues in imprecision. The overall certainty of evidence for these critical outcomes is moderate.

4.1.3 Cost Implication

There were four economic evaluation studies, three from the US (18,19,20) and one from Spain (21), on the use of the universal screening versus risk-based or no screening strategy for thyroid function in pregnancy. No economic evaluation was found in settings with comparable socioeconomic conditions as in the Philippines.

The analyses used a societal perspective in their costing and expressed utilities using quality-adjusted life-years (QALYs). Studies from the US used a cost-effectiveness threshold of below USD 50,000 per QALY gained, and the study from Europe used a below GBP 30,000 per QALY gained threshold. In contrast, the cost-effectiveness threshold used in economic evaluations in the Philippines is typically pegged at the latest gross domestic product per capita per disability-adjusted life years lost which is around USD 3,400 (22).

All the studies assessed either subclinical hypothyroidism or autoimmune hypothyroidism, and none assessed screening for hyperthyroidism. Hence, these evaluations required testing for TSH, FT4, and TPO-Ab. The primary economic outcomes involved long-term costs associated with caring for offspring with low intelligence quotient. Additionally, Candil and collaborators also assessed short-term perinatal morbidity hospitalization costs. Finally, the studies used maternal hypothyroidism prevalence estimates of around 2% in their analyses.

Overall, these economic evaluations found that universal screening was cost-effective compared to risk-based or case-finding screening strategies. Moreover, universal screening was deemed a dominant strategy (i.e., both cost-effective and less costly) compared to no screening strategy (i.e., no risk assessment strategy). However, cost-effectiveness was found to be sensitive to extreme changes in the assumed prevalence of hypothyroidism as well as the assumed effect size of hypothyroidism on perinatal and childhood outcomes.

4.1.4 Equity, Acceptability, and Feasibility

While there were no studies obtained that were assessing patient preference specific to universal thyroid function screening during pregnancy, the diagnosis of thyroid dysfunction using TSH and FT4 through blood specimens has a long history of use and acceptability. (23)

The tests themselves are well-established, and guidelines and recommendations on the use of trimester-specific cut-offs are in place. Moreover, diagnostic and treatment facilities exist in many contexts.

If universal screening were to be implemented and for the said strategy to be truly accessible to all, it must be included in the antenatal care package (ACP) within the maternity care package of PhilHealth. According to PhilHealth Circular No. 025-2015, the ACP shall cover services to screen, detect, and manage complications of pregnancy. (24) PhilHealth recognizes the importance of preventative and anticipatory services; hence, ACP was created distinctly from delivery packages. However, the whole package covers only PHP 1,500, which will likely make it insufficient to cover the existing essential prenatal services, let alone the inclusion of thyroid function assays.

4.1.5 Recommendations from Other Groups

The recommendations from other professional bodies are summarized in Table 4 below.

Table 4. Summary of existing guideline recommendations (thyroid Disease)

Guideline	Recommendation	Strength of Recommendation	Level of Evidence
Polish Guidelines 2021 (10)	<p>It is recommended that TSH is routinely determined in women at 4-8 weeks of pregnancy.</p> <p>It is not recommended that FT3/FT4 is routinely determined.</p>	Strong	Moderate
ACOG Practice Bulletin 2020 (9)	<p>Which pregnant patients should be screened for thyroid disease?</p> <ul style="list-style-type: none"> • Personal or family history of thyroid disease • Type 1 diabetes mellitus • Clinical suspicion of thyroid disease • Significant goiter or with distinct thyroid nodules <p>What laboratory tests are used to diagnose thyroid disease during pregnancy?</p> <ul style="list-style-type: none"> • First line screening test – TSH level 	None	None
Australian Pregnancy Care Guidelines 2020 (25)	Do not routinely test pregnant women for thyroid dysfunction.	None	None
American Thyroid Association 2017 (11)	<p>There is insufficient evidence to recommend for or against the universal screening for abnormal TSH concentration in early pregnancy.</p> <p>Universal screening to detect low FT4 concentrations in pregnant women is not recommended.</p>	No recommendation	Insufficient
		Weak	Moderate

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4.2 Screening for Cervical Length

RECOMMENDATION

Among asymptomatic pregnant Filipino women, we suggest against routine measurement of cervical length during the second trimester to prevent perinatal morbidity and mortality. (*WEAK recommendation, very low level of evidence*)

Considerations

The Consensus Panel considered the following when formulating this recommendation:

- Clarifications during the discussion centered on the outcomes of the clinical question and the population investigated in the review. Preterm birth is a critical outcome because cervical length measurements are supposedly performed for its prevention. Although the clinical question appears to encompass broad outcomes, a separate analysis on preterm birth was done and it shows that routine measurement of cervical length has an inconclusive effect on its prevention. It was also clarified that preterm birth is subsumed under the perinatal period (between 28 gestational weeks and 28 gestational days). No evidence looked into routine screening of cervical length among pregnant women with a history of prior spontaneous preterm birth, which is currently practiced. Among high-risk groups (twin pregnancies but no history of prior preterm birth or cervical insufficiency), there was no definite benefit shown with the use of screening.
- Apart from considering the large to moderate costs entailed by this procedure, the Panel perceived the evidence of benefit and harm to be inconclusive, and the balance between the two effects was uncertain. Due to the very low certainty of evidence, one CP member voted for a strong recommendation.

4.2.1 Burden of disease

Epidemiology, Natural Course, Management, Economic impact, and Social impact of the Disease

Preterm birth is defined as birth before the completion of 37 weeks of gestation. It is considered the most important cause of perinatal and neonatal morbidity and mortality globally. Infants born prematurely are at risk for a plethora of life-threatening conditions that adversely impact their survival and growth as well as predispose them to a lifetime of disability (1).

According to global data from WHO, 15 million infants are born prematurely every year and this number continues to rise annually. Of these children, more than 1 million die due to their prematurity. In the Southeast Asia and Oceania regions, more than 1 million cases of preterm birth were recorded in 2010, with a prevalence of 13.5% of births (2). Data from the Philippine General Hospital in 2014 showed that preterm births comprised 24% of all live births in the institution, with 73% of neonatal deaths occurring among preterm infants (3).

The National Statistics Authority report in 2017 pegged the national prevalence of preterm birth at 3% (4).

Risk factors for preterm birth include history of prior preterm birth, young or advanced maternal age, multiple-gestation pregnancy, genitourinary infection, and cervical insufficiency (2). Current research in the field is focused on using these factors to predict those at risk and to provide disease-modifying treatment. Available studies have explored the efficacy of tertiary prevention but the benefit of primary and secondary prevention strategies remains to be discovered (5). While guidelines from various societies agree that progestogens and cerclage are effective in preventing preterm birth among singleton pregnancies, the evidence for multiple gestation pregnancies is less definitive. Meta-analyses of randomized controlled trials have shown that cerclage did not prevent preterm birth among twin gestations with short cervix < 25 mm (6), and that progestogens did not reduce adverse perinatal outcomes (including preterm birth) among unselected women with twin pregnancies (7).

One of the known tests for the prediction of preterm birth is the measurement of cervical length through ultrasound. The most recent guideline on preterm labor released by the Philippine Obstetrics and Gynecology Society (POGS) recommends sonographic cervical length measurement for high-risk women with or without prior preterm birth at 14 to 22 weeks and 18 to 24 weeks of gestation, respectively. Due to the lack of studies in the local setting as well as the dearth of international studies on the screening of low-risk women, these guidelines did not recommend universal cervical length screening (3).

More recent studies have led to the generation of larger data sets to evaluate the utility of sonographic cervical length screening for predicting preterm birth among asymptomatic women. Screening strategies involving cervical length are now being evaluated in randomized clinical trials. The impact of cervical length measurement beyond that of predicting preterm birth, such as on the prevention of preterm birth and perinatal morbidity and mortality, remains to be ascertained.

4.2.2 Benefits, Harms and Diagnostic Performance of Screening Tests

Screening Cascade

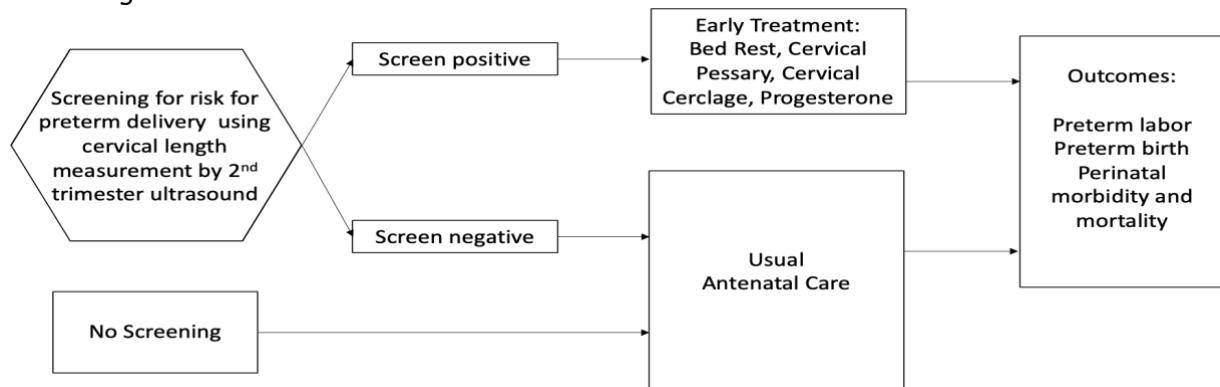


Figure 3. Screening for risk for preterm birth

The diagram (Figure 3) shows the care pathway for preterm birth. Those who screen positive for a shortened cervix via ultrasound measurement during the 2nd trimester are given early treatment. In a 2022 Cochrane meta-analysis, it was found out that among singleton pregnancies with a short cervix, only vaginal progesterone has shown to prevent perinatal death and preterm birth. In another 2021 meta-analysis among multiple gestation pregnancies with short cervix, pessary, progesterone, or cerclage did not reduce the rate of preterm birth or perinatal mortality. Those who screened negative or did not undergo screening received usual antenatal care. (37,38)

Prevention of preterm birth

Two RCTs ($n = 421$) reported the impact of cervical length (CL) screening on the incidence of preterm birth. At the end of the studies, incidence of preterm birth among women in the screened group did not differ from those in the unscreened group (RR: 1.04, 95% CI: 0.67 to 1.63, $I^2 = 0\%$). Results of the outcome in both low risk and high risk groups with multiple gestation were inconclusive. (Figure 4)

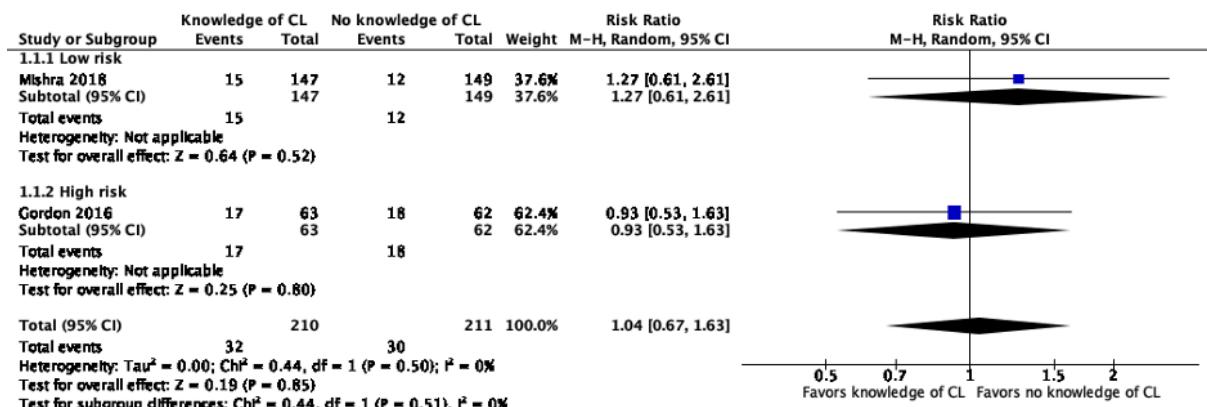


Figure 4. Comparison of knowledge of cervical length (CL) versus no knowledge of CL with preterm birth as outcome

Neonatal death

One RCT on low-risk women ($n = 296$) reported neonatal death as an outcome. Two neonatal deaths occurred in the unscreened group while none died in the screened group. One premature neonate died from respiratory distress after 24 hours despite receiving surfactant and ventilatory support while the other term neonate expired after 2 hours due to birth asphyxia. The incidence of neonatal death was not statistically different between the screened and unscreened groups (RR: 0.20, 95% CI: 0.01 to 4.19). There were no studies on high-risk women that reported neonatal death as an outcome.

Maternal hospitalization for preterm labor

One RCT on high-risk women with multiple gestation ($n = 125$) reported the rate of maternal hospitalization due to preterm labor. There was no statistically significant difference in maternal hospitalization for preterm labor between the screened and unscreened groups

(RR: 1.29, 95% CI: 0.75 to 2.23). There were no studies on low-risk women that reported maternal hospitalization for preterm labor as an outcome.

Gestational age at delivery

Two RCTs ($n = 421$) reported age of gestation (in weeks) at delivery. The pooled mean difference of gestational age in weeks between the screened and unscreened groups was not statistically significant (MD: -0.24, 95% CI: -0.61 to 0.12, $I^2 = 0\%$). Results of the outcome in both low risk and high risk groups with multiple gestation were inconclusive.

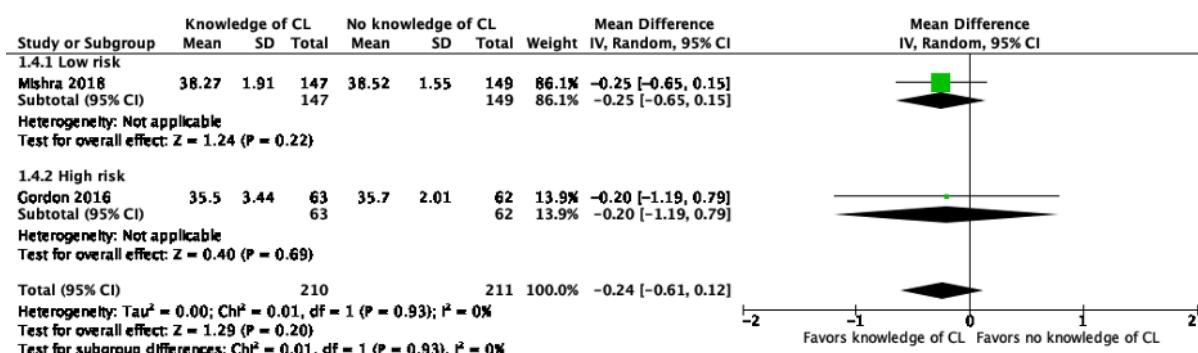


Figure 5. Comparison of knowledge of cervical length (CL) versus no knowledge of CL with gestational age at delivery in weeks as outcome

Neonatal respiratory distress syndrome

One RCT on low-risk women ($n = 296$) reported incidence of neonatal respiratory distress syndrome. There was no statistically significant difference between the screened and unscreened groups (RR: 2.03, 95% CI: 0.38 to 10.90). There were no studies on high-risk women that reported neonatal respiratory distress syndrome as an outcome.

Overall Certainty of Evidence

For all outcomes, certainty of evidence was rated down twice for moderate risk of bias from lack of blinding of study participants and the physicians managing them and imprecision. The overall certainty of evidence is very low.

4.2.3 Cost Implication

The cost-effectiveness of universal screening of cervical length (i.e. including both low-risk and high-risk populations) has been investigated in four studies from the United States. These studies assumed that any short cervix defined as 20 mm or shorter (measured transvaginally in three studies, first-line trans-abdominally in one study) would receive consequent therapy to prevent preterm labor, such as progesterone or cerclage. This strategy was considered cost-effective if there was a willingness to pay up to 100,000 USD for every quality-adjusted life year gained. All four studies concluded that universal

screening was cost-effective under the base scenarios in high-income settings depending on the prevalence of short cervix in the population. Cut-offs below which the universal screening strategy would cease to be cost-effective vary among the studies, ranging from prevalence of 0.31% to 1.71% (13-16). Data sets from a study done in Indonesia in 2020 showed the prevalence of cervical length 20 mm or shorter to be 2.25% (17).

A more recent cost-effectiveness analysis done in Sweden in 2022 evaluated various screening strategies of cervical length screening, including universal strategy (i.e. all patients screened and those with short cervix are treated with progesterone), low-risk strategy (i.e. low-risk patients screened, while high-risk patients received progesterone outright), and high-risk strategy (i.e. only high-risk patients screened). Results showed that all interventions produced a better outcome than 'no screening.' With the assumption that vaginal progesterone would reduce the risk of preterm labor <33 weeks by 30% and preterm labor 33-36 weeks by 10% and that willingness-to-pay was at 56,000 US dollars per QALY, the most cost-effective intervention was the low-risk strategy at either 18 to 20 6/7 weeks or 21 to 23 6/7 weeks of gestation (18).

Despite the cost-effectiveness shown in studies done in high-income countries, barriers to access in low-resource settings impair the recommendation and implementation of universal cervical length screening. Antenatal clinics in local government units generally lack the equipment and trained personnel needed to perform prenatal ultrasound, with ultrasound machines only being available in secondary or tertiary hospitals (19). Due to the lack of local studies on the prevalence of the condition, availability of ultrasound, and cost-effectiveness studies for lower-resource settings, a statement on the feasibility of the intervention is difficult to make.

4.2.4 Equity, Acceptability, and Feasibility

Socioeconomic status is an emerging risk factor for preterm birth; women with lower educational attainment and lower quintiles of income were found to have a higher risk for poorer outcomes (8). Due to corresponding complications, preterm birth exacts a great toll psychosocially and financially on the infants and their families. With the rising prevalence of assisted reproductive technology, the increase in multiple gestation pregnancies is also leading to increases in preterm birth rates among the higher socioeconomic brackets.

Direct costs associated with preterm births are correlated with the rising degree of neonatal intensive care required with earlier births and lower birth weights. A cost analysis study done in New South Wales in Australia showed that more than 145 million Australian dollars was used for neonatal care in 1998, with 55.1% being used for the care of infants greater than 2.5 kilograms in weight (9).

In 2007, the US Institute of Medicine reported the total cost of preterm birth was 26.2 billion USD annually, including the indirect costs of disabilities and continuing health needs of children who survive prematurity. Of the budget for preterm birth, 71.8% or 18.8 billion USD is attributed to neonatal intensive care and labor and delivery costs. The remaining 7.4 billion was used for early intervention and special education services for

children with developmental delays as well as the opportunity cost from lost work and pay for people born prematurely (1).

Observational studies done in the United States describing the acceptability of a universal cervical length screening program yielded that it was acceptable to 75% to 99.9% of women surveyed. (20-23) Studies on the use of transvaginal ultrasound also show that it is generally safe, even among women with premature rupture of membranes (24).

In two studies, the acceptability of vaginal and intramuscular progesterone as preventive treatments for preterm labor among women at risk is high (25,26). However, a survey of 311 pregnant women (85.2% response rate) at a median of 32-weeks of gestation done in Canada showed that most (65.8%) preferred not to use any prevention if told by their healthcare provider that they were at increased risk for preterm birth. Of these, 93.4% preferred close monitoring only and 6.6% preferred neither monitoring or prevention. Almost all women rated concerns about the effectiveness and safety of the preventive measures (progesterone, cerclage, and pessary) to both the mother and infant as important. The highest proportion of women who reported that they would not follow their healthcare provider's recommendation was for cervical cerclage (50.2%), followed by pessary (28.7%), then progesterone (10.9%) (27).

4.2.5 Recommendations from Other Groups

The recommendations from other published guidelines are presented in Table 5 below.

Table 5. Summary of existing guideline recommendations (cervical length)

Guideline	Recommendation	Strength of Recommendation	Level of Evidence
Philippine Society of Maternal Fetal Medicine with the Philippine Obstetrical and Gynecological Society, 2015 (3)	Routine screening for preterm birth in low risk women is not recommended.		
	Sonographic cervical length measurement should be done at 18-24 weeks of gestation on women with no prior preterm birth.		
	Sonographic cervical length measurement done at 20 to 24 weeks in twin gestations may lead to better prediction of preterm birth.	Not reported	Not reported
Society for Maternal-Fetal Medicine (US), 2016 (28)	Universal cervical length screening is not recommended until local studies are available.		
	We recommend routine transvaginal cervical length screening for women with singleton pregnancy and history of prior spontaneous preterm birth.	Grade 1A High quality of evidence	Strong recommendation
	The issue of universal cervical length screening of singleton gestations without prior PTB for the prevention of preterm birth remains an object of debate. CL screening in singleton	Grade 2B	Weak recommendation

	<p>gestations without prior PTB cannot yet be universally mandated. Nonetheless, implementation of such a screening strategy can be viewed as reasonable, and can be considered by individual practitioners. Practitioners who decide to implement universal cervical length screening should follow strict guidelines.</p> <p>We recommend routine transvaginal CL screening not be performed for women with cervical cerclage, multiple gestation, PPROM, or placenta previa.</p> <p>We recommend sonographers and/or practitioners receive specific training in the acquisition and interpretation of cervical imaging during pregnancy.</p>	Moderate quality of evidence Grade 2B Moderate quality of evidence Grade 2B Moderate quality of evidence	Weak recommendation Weak recommendation	
American College of Obstetricians and Gynecologists, 2016 (Practice Bulletin) (29)	<p>Although this document does not mandate universal cervical length screening in women without a prior preterm birth, this screening strategy may be considered.</p> <p>Practitioners who decide to implement universal cervical length screening should follow one of the protocols for transvaginal measurement of cervical length from the clinical trials on this subject.</p>	Limited or inconsistent evidence Consensus and expert opinion	Level B	Level C
International Society of Ultrasound in Obstetrics and Gynecology, 2022 (30)	<p>When feasible, transvaginal cervical length measurement should be performed at the second-trimester scan to screen for preterm birth.</p> <p>CL measurement for the prediction of preterm birth should be performed using transvaginal sonography.</p> <p>CL measurement is the preferred method for screening for preterm birth in twins; 25 mm is a pragmatic cut-off between 18 and 24 gestational weeks.</p>	Not reported Not reported Not reported	Grade C Grade B Good practice point	
Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2021 (31)	Acknowledging the challenges and continued debate surrounding universal cervical length screening, RANZCOG currently supports the use of initial transabdominal screening of low risk women with singleton pregnancies at the mid trimester scan, with additional transvaginal assessment for those with a short cervical length (<35 mm) or full cervical length unable to be clearly viewed.	Not reported	Consensus-based recommendation	
National Institute for Health and Care Excellence (NICE), 2008 (32)*	Routine screening for preterm lab our should not be offered.	Not reported	Not reported	

*2021 update no longer mentions screening for preterm labor

French College of Gynaecologists and Obstetricians, 2017 (33)	Data in the literature are insufficient to justify recommending the routine or repeated measurement of cervical length by transvaginal ultrasound except in women with a history of preterm delivery. Although universal cervical length screening by transvaginal ultrasound at 18-24 weeks can be considered by individual practitioners, this screening cannot be universally recommended.	Level of Evidence 2 LE 2	Professional consensus Professional consensus
International Federation of Gynecology and Obstetrics (FIGO), 2015 (34)	Sonographic cervical length measurements should be performed in all pregnant women at 19–23 6/7 weeks of gestation using transvaginal ultrasound. This can be done at the same time as the ultrasound performed for the anatomical survey. Universal cervical length screening and vaginal progesterone treatment (90 mg vaginal gel or 200 mg micronized vaginal soft capsules) is a cost-effective model for the prevention of preterm birth.	Not reported	Not reported
Society of Obstetricians and Gynaecologists of Canada, 2019 (35)	Universal cervical length screening in isolation of quality assurance audit is not recommended. Therefore, the committee cannot fully recommend standalone universal cervical length screening across Canada until such time as the incidence of short cervix in a Canadian population is determined and more data on the value of a 2-step approach are available, both of which are needed to inform an accurate economic analysis.	Not reported	Not reported
Guideline on Preterm Labor and Delivery by the Society of Specialists in Perinatology, Turkey 2020 (36)	If possible, cervical length measurement by transvaginal ultrasonography is recommended for all pregnant women, especially for those in the risk group at the time of the second trimester fetal anatomic scan at 18-24 weeks.	Not reported	Not reported

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4.3 Screening for Gestational Diabetes Mellitus

RECOMMENDATION

We suggest screening for GDM among pregnant women using a 75-g OGTT in the second trimester (24-28 weeks) to decrease perinatal mortality and morbidity. (*WEAK recommendation, very low level of evidence*)

Considerations

The Consensus Panel considered the following when formulating this recommendation:

- The direct evidence comparing oral glucose tolerance test (OGTT) screening to no screening and the indirect evidence on linked treatment for GDM had mixed results, especially with regard to some critical outcomes like LGA, macrosomia, and NICU admissions. This may be attributed to the study designs. The direct evidence consisted of retrospective studies with unclear methods of event tracking and reporting. In contrast, albeit indirect, the studies that looked into the effectiveness of treatment for GDM subsequent to screening were more recent randomized controlled trials, and these showed better outcomes. The screening strategies used in these trials also varied and included procedures such as risk-based evaluation and OGTT.
- The decision to suggest the use of a 75-gram OGTT as the preferred strategy to screen for GDM in the second trimester, despite lack of head-on comparisons and variability in dosage and approach in the evidence review, was considered appropriate by the Consensus Panel. This recommendation aims to establish a standardized practice and provide comprehensive guidance to healthcare practitioners regarding the recommended course of action. Furthermore, the strategy currently endorsed by the majority of international guidelines is the 1-step 75-gram oral glucose tolerance test (OGTT) procedure.

4.3.1 Burden of disease

Epidemiology

The worldwide prevalence of gestational diabetes is unknown, but estimates vary from 0.6 to 15% (1). In a 2022 meta-analysis, pooled global standardized prevalence was estimated at 14%, with the highest regional standardized prevalence found in South East Asia (20.8%) and in the Middle East and Northern Africa (27.6%) (2). In the Philippines, gestational diabetes has a prevalence of 14%, based on a survey of 1,203 pregnancies from the Asian Federation of Endocrine Societies Study Group on Diabetes in Pregnancy (ASGODIP) (3). Additional data from the ASGODIP showed that around 40% of high-risk Filipino women were diagnosed with GDM when screening was done after 26 weeks of gestation (4).

Natural Course of the Disease

Pregnant women with gestational diabetes are at an elevated risk for caesarean section and (5) pre-eclampsia for the mother, and admission to the neonatal intensive care unit, macrosomia, shoulder dystocia, birth injuries, neonatal hypoglycemia (6,7) and perinatal mortality for the offspring (7). In Southeast Asian countries, macrosomia is noted to be one of the most cited complications of GDM, which in turn increases the risk for cesarean deliveries and neonatal birth trauma (7). Previous gestational diabetes also places women at increased risk for developing type 2 diabetes after pregnancy, with an incidence of 7.3%. This is also reported to be more associated among high-risk women with obesity, multigravida and increased maternal age (7,8). They are also at increased risk of cardiovascular disease postpartum (1). International studies also suggest that patients with GDM had a significantly lower short-term and long-term quality of life compared to women without GDM (9).

Management

Once diagnosed with GDM, it is recommended that patients do self-monitoring of blood glucose pre-meals and 1 hour or 2 hours postprandially. Target blood glucose levels are less than 95 mg/dL, 140 mg/dL and 120 mg/dL for fasting blood glucose, one-hour postprandial blood glucose and two-hour postprandial blood glucose respectively. Medical nutrition therapy is also advised, in the form of caloric restriction of 1800 kcal/day minimum intake up to 2,500 kcal/day as well as subscription to a DASH (Dietary Approaches to Stop Hypertension) diet. In cases where medical nutrition therapy and lifestyle changes are not sufficient to achieve target blood glucose levels, subcutaneous insulin should be used. Fetal surveillance is also done in patients with GDM, in the form of fetal movement counting, nonstress test, pelvic ultrasound for fetal growth monitoring, biophysical profile scoring, and congenital anomaly scan, depending on maternal glycemic control (10).

Economic and Social impact of the disease

There is no local data analyzing the economic burden of gestational diabetes. In a US study, researchers found that the cost for GDM reached as high as US\$1.6 billion in 2017 (11). In India, pregnant women with GDM had more direct medical costs compared to women without GDM (12).

4.3.2 Benefits, Harms and Diagnostic Performance of Screening Tests

Figure 6 presents the screening pathway for GDM. Pregnant women with no symptoms and no prior diabetes mellitus undergo screening for GDM, and those confirmed to have the disease are managed with glucose monitoring, medical nutrition therapy, and, in cases where this is insufficient, insulin therapy. On the other hand, those who screen negative and those who do not receive screening will receive usual prenatal care.

These interventions are instituted because effective treatment for GDM has been shown to improve perinatal outcomes

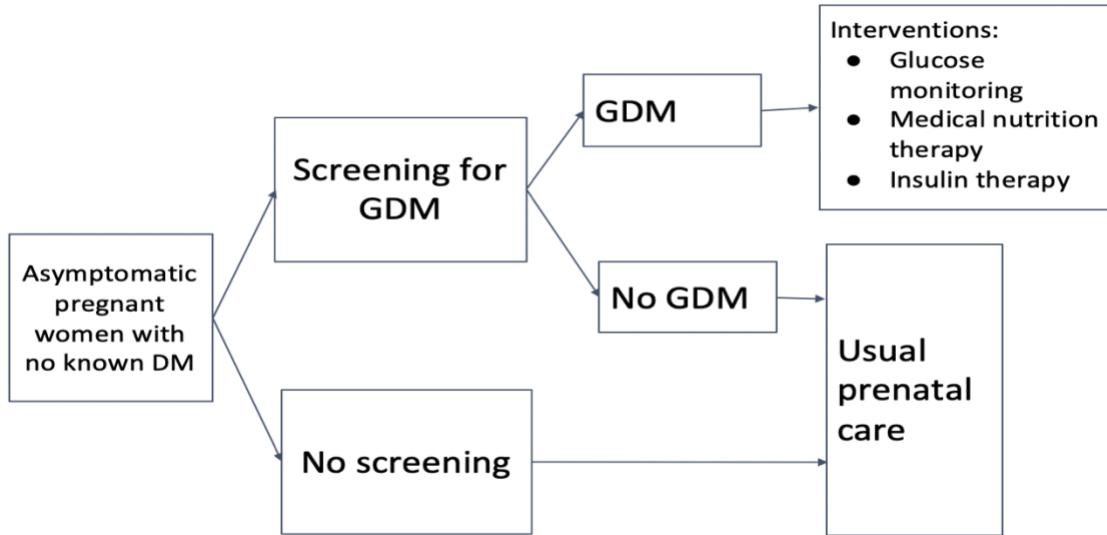


Figure 6. Screening cascade for GDM

Stillbirth

One case control study (22) done in the United Kingdom ($n = 1,012$) assessed late stillbirth rates at 28 weeks of gestation between pregnant women who were screened for GDM versus patients who were not screened. The study was a secondary analysis of the data from another case control (23) that looked at the association between the risk of late stillbirth in the UK and maternal going-to-sleep position. There was no direct involvement of the study participants in the secondary analysis. Cases were defined as singleton non-anomalous late-stillbirths (28 weeks age of gestation and above) while the controls were randomly selected women with ongoing pregnancies matched by age of gestation with the cases. The screening method for GDM was not clearly reported by the study but assumed by the USPSTF 2021 guidelines on GDM to have followed the 2015 NICE guidance, where screening was done at 24-28 weeks among at-risk women via fasting plasma glucose (FPG) or 2-hour 75g OGTT. Screening was offered earlier for women who had previous history of GDM at the first visit in the first or 2nd trimester. At-risk women were defined as women of South Asian or Black Caribbean ethnicity, body mass index $\geq 30\text{kg}/\text{m}^2$, or previous pregnancy affected by GDM or macrosomia (birth weight $\geq 4.5\text{kg}$) (22).

The study showed that at-risk women who underwent screening for GDM were less likely to deliver stillbirths compared to those who did not undergo screening (aOR: 0.68, 95% CI: 0.47 to 0.97) (22).

Certainty of evidence was downgraded to very low due to moderate risk of bias for non-reporting of response rates (22).

Neonatal Hypoglycemia

One retrospective cohort study (22) ($n = 2,780$) assessed the rates of hypoglycemia in neonates born to pregnant women who were screened for GDM via OGTT versus women who were not screened. The results showed that those neonates whose mothers were screened for GDM were twice as likely to experience neonatal hypoglycemia (OR: 2.00, 95% CI: 1.42 to 2.82). The certainty of evidence was assessed to be low.

Gestational hypertension or pregnancy-induced hypertension

One retrospective cohort study (20) ($n = 998$) showed that pregnant women screened for GDM using OGTT were 3.39 times more likely to have gestational hypertension or pregnancy-induced hypertension compared to those who were not screened for GDM (OR: 3.39, 95% CI: 1.65 to 6.97). Certainty of evidence was very low due to risk of bias.

Large for Gestational Age (LGA)/Macrosomia

Three retrospective cohort studies (19-21) ($n = 3,871$) assessed the outcome of neonatal LGA or macrosomia. Pooled results show that women screened for GDM were more likely to deliver neonates that were LGA compared to those who were not screened (OR: 1.93, 95% CI: 1.02 to 3.64). Certainty of evidence is very low due to risk of bias. (See Figure 7 below).

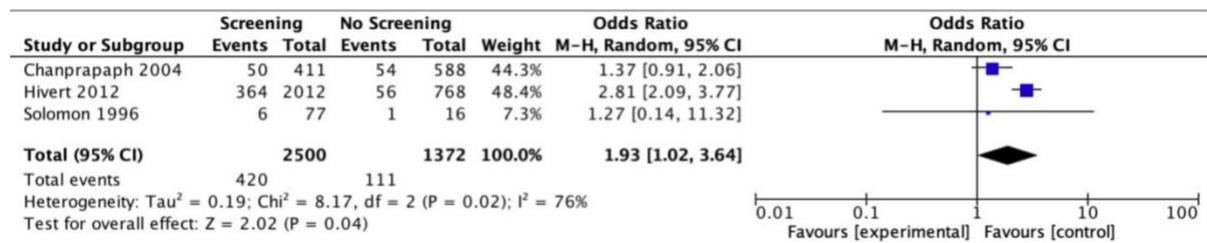


Figure 7. LGA/Macrosomia rates among patients screened for GDM versus patients not screened

Admission to NICU

One retrospective cohort study (21) ($n = 2,780$) assessed the rates of ICU admission among neonates born to pregnant women who were screened for GDM via OGTT versus women who were not screened. No information on indications for ICU admission were reported by the study. Results showed that neonates delivered by women who underwent screening for GDM were more likely to be admitted in the neonatal ICU compared to those delivered by women who were not screened (OR: 1.55, 95% CI: 1.29 to 1.86). The certainty of evidence was very low.

Preterm Delivery

One retrospective cohort study (20) ($n = 998$) assessed preterm delivery rates of pregnant women screened for GDM versus women who were not screened. The study showed that there was no difference in the likelihood of preterm delivery between the two

groups (OR: 1.22, 95% CI: 0.79 to 1.88). Certainty of evidence is very low due to risk of bias and imprecision.

Neonatal Birth Injuries

One retrospective cohort study (21) ($n = 2,780$) assessed the rates of neonatal birth injuries (fracture and shoulder dislocation) between pregnant women who were screened for GDM via OGTT versus women who were not screened. Results showed no significant difference in the likelihood of birth injuries among neonates delivered by women screened and not screened for GDM (OR: 0.94, 95% CI: 0.49 to 1.80). The certainty of evidence was very low.

Overall Certainty of Evidence

The overall certainty of evidence was very low due to moderate risk of bias for nonreporting of response rates for stillbirth; and for imprecision due to wide confidence intervals for the outcomes of preterm delivery and neonatal birth injuries.

4.3.3 Cost Implication

There is currently no local evidence on the cost-effectiveness, cost-utility, or cost benefit of screening for GDM. In a cost-effectiveness analysis in an urban Chinese setting (24), it was found that a total of \$1,329,671 was saved in the GDM screening group compared with no screening group, and a total of 277.4 DALYs. In a 2019 meta-analysis, neither screening nor treatment was found to be cost-effective, but the authors recognize that most research done on the subject were done in high-income countries, which have different health systems from low to middle-income counterparts, wherein screening may still be worthwhile (25).

4.3.4 Equity, Acceptability, and Feasibility

A systematic review by Craig (26) found that women believed the diagnosis of GDM leads to behavioral benefits, i.e. making healthy eating changes. However, women also identified emotional (e.g. self-blame, fear, guilt, uncertainty), financial (due to cost of food, medical expenses), and cultural (due to alternative eating practices, lack of information on traditional food) harm from the diagnosis of GDM. Daneshmand (27) also noted that pregnant women are more likely to make healthier choices after GDM diagnosis. There are currently no local studies available.

On the other hand, Daneshmand, et al (27) found that a diagnosis of GDM becomes a burden to those with financial, cultural, psychological, or social difficulties. In the absence of standardized systems for GDM care, women from minority and low-income groups become at higher risk for perinatal morbidity and mortality. In a qualitative study by Sinha (28), identified barriers to screening include insurance issues, unemployment, lack of transportation, childcare, safe housing, food access, care fragmentation, scheduling policies, and time constraints, while facilitators to care

include government programs, community organizations, care coordination, pregnancy support groups, and education materials.

An international study found that after initial diagnosis of GDM, most women reported emotions of self-blame, failure, fear, sadness and concern, expressing anxiety about the prognosis of the disease. Some also felt lost and guilty, while there were others who felt that the diagnosis of GDM was an opportunity for lifestyle modifications so they can potentially improve maternal and fetal outcomes. Diet-related stress was reported by both insulin and non-insulin requiring patients, citing the frustrations of obtaining elevated blood glucose levels despite dietary restrictions. Some women were even reported to falsify blood glucose readings, starve themselves, and eventually feel the guilt of noncompliance with the prescribed diabetes management. These emotional stressors are further complicated by pressures from factors outside their pregnancy, like work, childcare and other daily responsibilities and routines at home (26).

4.3.5 Recommendations from Other Groups

The recommendations from other groups are summarized in Table 6 below.

Table 6. Summary of existing guideline recommendations (GDM)

Guideline	Recommendation	Strength of Recommendation	Level of Evidence
National Institute for Health and Care Excellence	<p>Assess the risk of gestational diabetes using risk factors in a healthy population. At the booking appointment, check for the following risk factors:</p> <ul style="list-style-type: none">• BMI above 30• Previous macrosomic baby weighing 4.5kg or more• Previous gestational diabetes• Family history of diabetes (first-degree relative with diabetes)• An ethnicity with a high prevalence of diabetes <p>Offer women with any of the above risk factors testing for GDM</p> <p>Use the 75-g 2-hour oral glucose tolerance test (OGTT) to test for gestational diabetes in women with risk factors.</p> <p>Diagnose gestational diabetes if the woman has either:</p>	No level reported	No level reported

		<ul style="list-style-type: none"> • Fasting plasma glucose of 5.6 mmol/L or above OR • 2-hour plasma glucose level of 7.8 mmol/L or above 		
American College of Obstetricians and Gynecologists: Practice Bulletin	All pregnant women should be screened for GDM (generally performed at 24-28 weeks of gestation) with a laboratory-based screening test(s) using blood glucose levels.	Level B	Level C	Level B
	<p>In the absence of clear evidence that supports one cut-off value over another (130mg/dL, 135mg/dL or 140mg/dL) for the 1-hour glucose screening test, obstetricians and obstetric care providers may select one of these as a single consistent cutoff for their practice, using factors such as community prevalence rates of GDM when making their decision.</p> <p>In the absence of clear comparative trials, one set of diagnostic criteria for the 3-hour OGTT cannot be clearly recommended over the other.</p>			
American Diabetes Association	<p>Screen for gestational diabetes mellitus at 24-28 weeks of gestation in pregnant women not previously found to have diabetes or high-risk abnormal glucose metabolism detected earlier in the current pregnancy.</p> <p>GDM diagnosis can be accomplished with either of two strategies:</p> <ol style="list-style-type: none"> 1. One-step 75-g OGTT from the IADPSG Criteria 2. Two-step approach with a 50-g nonfasting screen followed by a 100-g OGTT for those who screen positive, based on 	Level A	No level reported	Level A

Carpenter-Coustan criteria.

Australian CPG	Between 24 and 28 weeks of gestation, advise testing for hyperglycemia to all women who have not previously been tested in the current pregnancy. Advise repeat testing to women who were tested early in pregnancy due to risk factors and who had a normal result on an initial test. Use the WHO/IADPSG tests and criteria to diagnose diabetes and gestational diabetes in pregnancy.	CBR (Recommendation formulated in the absence of quality evidence (where a systematic review of the evidence was conducted as part of the search strategy)):	—
Qatar MOPH	Perform a 75g OGTT at 24-28 weeks in all women to screen for gestational diabetes. Early screening is required for high risk women.	No level reported	No level reported
Canadian Task Force on Preventive Health Care	The quality of available evidence cannot support a recommendation to include universal screening for gestational diabetes; however, a decision on screening must be made on other grounds.	No level reported	No level reported
Philippine Obstetrical and Gynecological Society (Foundation) Inc.	For women with risk factors <ul style="list-style-type: none"> • immediate screening at the first prenatal visit is recommended • If values are elevated beyond the cut-off values (FBS >92mg/dL, 1st hour plasma glucose > 180mg/dL, 2nd hour plasma 	Strong	Moderate

glucose >200 mg/dL), these women are diagnosed with GDM. Should results be Strong normal, a repeat test at 24-28 weeks age of gestation is recommended.

Moderate

- A woman with previously normal results should be retested at 32 weeks or earlier if clinical signs and symptoms of maternal and fetal hyperglycemia are observed

For women with no risk factors

- Testing is performed at 24-28 weeks age of gestation
- A woman with previously normal results should be retested at 32 weeks or earlier if clinical signs and symptoms of maternal and fetal hyperglycemia are observed

A 75 g OGTT is recommended for screening after an overnight fast of at least 8 hours (but not exceeding 14 hours), without restriction of carbohydrate intake in the preceding days. The patient should be seated during the testing, and smoking is prohibited. The glucose solution should be consumed within 5 minutes. Any single plasma glucose determination above the cut-off level would lead to a diagnosis of GDM.

UNITE 2014	All pregnant women should be screened for gestational diabetes.	Grade B Grade C	Level 2 Recommendation Level 4 Recommendation
	All pregnant women should be evaluated at the first prenatal visit for risk factors for diabetes.	Grade B	Level 3 Recommendation
	<p>High-risk women should be screened at the soonest possible time. Risk factors for diabetes among pregnant women include:</p> <ul style="list-style-type: none"> • Prior history of GDM • Glucosuria • Family history of diabetes • First-degree relative with type 2 diabetes • First-degree relative with type 1 diabetes • Prior macrosomic baby • Age > 25 years old • Diagnosis of polycystic ovary syndrome • Overweight/obese before pregnancy • Macrosomia in current pregnancy • Polyhydramnios in current pregnancy • Intake of drugs affecting carbohydrate metabolism <p>Routine testing for gestational diabetes is recommended at 24 to 28 weeks age of gestation for women with no risk factors. An OGTT, preferably the 75g OGTT (using the IADPSG criteria) should be used to screen for gestational diabetes.</p>		

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4.4 Screening for Group B Streptococcus

RECOMMENDATION

We suggest screening pregnant women for risk factors for group B *Streptococcus* followed by intrapartum antibiotic prophylaxis for those who screen positive and have a planned vaginal delivery to prevent early onset neonatal GBS sepsis. (*WEAK recommendation, very low level of evidence*)

Considerations

The Consensus Panel considered the following when formulating this recommendation:

- Despite the seemingly low prevalence of GBS locally due to limited studies, the panel deemed the high probability of neonatal mortality from GBS sepsis as very important. More studies are needed to establish local prevalence of GBS.
- The panel acknowledged that the universal screening test for GBS (requiring rectovaginal swab culture) is not readily available in many hospitals or health centers and is expensive. It may also require trained healthcare worker to perform the test. Due to accessibility and equity issues, screening without the need for culture (screening for risk factors only such as preterm labor, prolonged rupture of membranes, and history of previous GBS infection) was considered in the recommendation.
- Intrapartum antibiotic prophylaxis is only indicated in women who will undergo vaginal delivery.

4.4.1 Burden of disease

Epidemiology, Natural Course, Management, Economic impact, and Social impact of the Disease

Group B *Streptococcus* (GBS) colonization in pregnant women may lead to infection of the newborn via vertical transmission, with an estimated risk of about 1% (1). Evidence suggest that vertical transmission is reduced with antibiotic use. GBS infection is associated with significant morbidity and mortality once it proceeds to early onset neonatal GBS (EON-GBS) sepsis. The risk of mortality reaches 2-10% for term infants and 20-30% in preterm infants (2). Historically, mortality rates reached up to 55% when EON-GBS sepsis first emerged in the 1970s (3).

Studies investigating the prevalence of GBS in either mothers or newborns are limited in the Philippines. A single center cross-sectional study of 40 pregnant women found that only one (2.5%) tested positive for GBS using either Lim broth or Strep B carrot broth as culture media (4). A prospective cohort study that enrolled patients suspected to have neonatal infections in Bohol found very rare occurrence of GBS (5). Over a six year period, only one case out of 767 tested positive for GBS. The study even suggested that Gram negative bacteria were the most important community acquired pathogens affecting young

infants in rural areas. Finally, a recent multicenter study in Manila and Bohol estimated the incidence of neonatal GBS infection to be 0.3 per 1,000 live births (6). There were three cases of GBS sepsis among newborns, wherein two of the three cases died, with both mothers not receiving intrapartum antibiotics.

In clinical practice, pregnant women may be screened for GBS at 35-37 weeks AOG (7). If they test positive, intrapartum antibiotic prophylaxis (IAP) is administered using penicillin, first generation cephalosporin, or clindamycin. All of these drugs are considered acceptable for use during pregnancy (8). If women test positive, they continue to be assessed throughout the remainder of their pregnancy. At the time of delivery, risk factors such as preterm labor, prolonged rupture of membranes, and history of previous GBS infection may necessitate antibiotic use without need for culture studies. At present it is unclear whether universal screening for GBS improves maternal and neonatal outcomes.

4.4.2 Benefits, Harms and Diagnostic Performance of Screening Tests

Screening Cascade

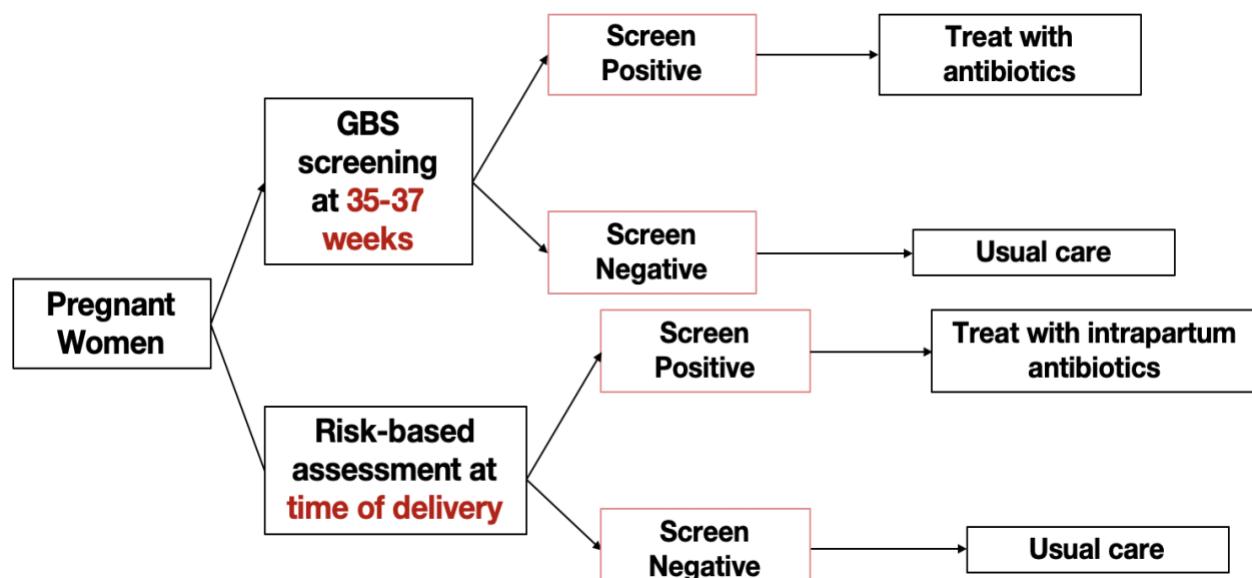


Figure 8. Screening cascade for GBS

Pregnant women may be screened at 35-37 weeks AOG (Figure 7). If positive for GBS, they will be given antibiotics. Alternatively, they may be assessed for presence of risk factors such as preterm labor, intrapartum fever, and prolonged membrane rupture, and history of having an infant with early onset GBS sepsis at the time of delivery. If with risk factors, intrapartum antibiotic prophylaxis is given.

Universal Screening

To estimate the impact of universal screening on critical and important outcomes, random effects meta-analyses was performed using Mantel-Haenszel method in Review Manager version 5 (34). Pooled estimates were reported using odds ratio with 95% CI and

used I^2 statistic as a measure of heterogeneity. For outcomes EON-GBS mortality and bacterial resistance, we performed statistical adjustments to enable inclusion of studies with rare events where both arms had zero events (BAOE). The inclusion of BAOE studies in meta-analyses resulted in less biased estimates compared to study exclusion (35). The altmeta package (36) in R and Rstudio (37) was utilized to perform bivariate meta-analysis using logit link and bootstrapping of confidence intervals through 10,000 iterations.

In summary, direct evidence was found to support universal screening to prevent EON-GBS sepsis. The evidence for the critical outcome of EON-GBS mortality and important outcomes of preterm delivery, GBS pneumonia, and bacterial resistance were inconclusive. (Table 7)

Table 7. Summary of Results (GBS)

Outcome	Importance	Certainty of Evidence	Relative Effects	Absolute Effects	Direction of Association
Early onset GBS sepsis 13 cohort, n = 426,445	Critical	Very Low	OR 0.51 (0.29 to 0.89)	83 fewer cases of early onset GBS sepsis per 100,000 live births (95%CI: 120 fewer to 19 fewer)	Favors screening
EON-GBS Mortality 3 cohort, n = 71,116	Critical	Very Low	OR 0.28 (0.01 to 11.60)	3 fewer deaths from early onset GBS sepsis per 100,000 live births (95%CI: 4 fewer to 48 more)	Inconclusive
Preterm birth 1 cohort, n = 22,574	Important	Very Low	OR 1.05 (0.97 to 1.16)	436 more preterm deliveries per 100,000 live births (95%CI: 264 fewer to 382 more)	Inconclusive
GBS Pneumonia 1 cohort, n = 22,574	Important	Very Low	OR 0.10 (0.01 to 1.66)	47 fewer cases of GBS pneumonia per 100,000 live births (95%CI: 52 fewer to 35 more)	Inconclusive
Bacterial resistance 2 cohort, n = 115,625	Important	Very Low	OR 3.52 (0.41 to 30.18)	5 more cases of bacterial resistance per 100,000 live births (95%CI: 1 fewer to 61 more)	Inconclusive
Early neonatal death	Critical				No evidence
NICU stay	Important				No evidence

Early onset GBS sepsis

Based on the available evidence from 13 cohort studies (16-28) (n = 426,445), universal screening is associated with reductions (OR 0.51, 95%CI 0.29 to 0.89) in EON-GBS sepsis. In absolute terms, the use of universal screening is associated with 83 fewer cases of EON-GBS sepsis per 100,000 live births compared to risk-based screening (95% CI: 120 fewer to 19 fewer). We downgraded the certainty of evidence to very low for inconsistency, which we attributed to methodological heterogeneity, and serious risk of bias.

EON-GBS mortality

Results from 3 cohort studies were pooled (21,22,27) ($n = 71,116$) and showed that universal screening is associated with 72% reduction in odds of mortality from EON-GBS. However, the results are inconclusive due to imprecision. The certainty of evidence was downgraded to very low for risk of bias and imprecision.

Preterm from all causes

One cohort study (24) ($n = 22,574$) was identified for the outcome of preterm birth from all causes, with inconclusive results. The certainty of evidence was downgraded to very low for risk of bias and imprecision.

GBS pneumonia

One cohort study (24) ($n = 22,574$) was found for the outcome of GBS pneumonia, with inconclusive results. The certainty of evidence was downgraded to very low for risk of bias and imprecision.

Bacterial resistance

There were two cohort studies (17,18) ($n = 115,625$) with inconclusive results on bacterial resistance. Among the studies which reported bacterial resistance, the majority had resistance to penicillin or ampicillin. In one setting (17), five cases had resistance to erythromycin where three of which also had concomitant resistance to clindamycin. The certainty of evidence was downgraded to very low for risk of bias and imprecision.

Early neonatal death, length of NICU stay

No evidence was found for the critical outcome of early neonatal death, and the important outcome of NICU stay.

Overall Certainty of Evidence

Only one critical outcome, early onset GBS sepsis, was found to favor screening, with very low certainty of evidence. All other outcomes were either inconclusive or had no available evidence. There is very low certainty of evidence to recommend GBS screening using recto-vaginal swab culture at 35-37 weeks among pregnant Filipino women to prevent early onset neonatal GBS sepsis.

4.4.3 Cost Implication

Prior economic evaluation done in 2007 for the UK context favored the use of GBS screening in the absence of a vaccine, and found it to be cost-effective (40). In the United States, screening at 36-37 weeks with re-screening for those with GBS-negative results five weeks later was cost effective compared to screening at 35-37 weeks alone (41). Economic

evaluations in the 1990s done in the US setting had conflicting results regarding the cost-effectiveness of universal screening at 35-37 weeks (42–44).

4.4.4 Equity, Acceptability, and Feasibility

Currently no agreement exists in universal screening of pregnant women for GBS or if a risk based approach is more appropriate (12).

RCOG 2017 does not recommend universal bacteriological screening in pregnant women with the rationale that a significant number of women are carriers and yet the majority of resulting births have been born safely and without infections. Further reasons against universal testing include subjecting women to receive treatment that they do not need with potential harm to mother and infant, the question on the accuracy of the test to determine persistence of infection at time of delivery, and that infants at risk of being severely affected by GBS are born prematurely and were delivered prior to the recommended time for screening (9,12).

Optimal screening time should be considered in the capacity of cultures to adequately detect GBS. A systematic review of the timing of GBS screening in pregnancy provides evidence for testing at 35-37 weeks of gestation for evaluation of colonization (38). However, 6% of GBS carriers during delivery remain undetected in antenatal cultures. High risk groups may benefit at earlier screening and repeat testing near term.

Using a pragmatic deterministic model, Bevan and collaborators evaluated the effect of GBS screening in antenatal women in the United Kingdom (39). In the model, screening was offered at 36 weeks AOG to women not identified as being at risk for colonization. There was low likelihood (0.2 per 1000 live births) of having an infant affected by EOGBS in women delivering at term with no known risk factors, which coincide with those eligible for screening.

4.4.5 Recommendations from Other Groups

The recommendations from other guidelines are presented in Table 8 below.

Table 8. Summary of existing guideline recommendations (GBS)

Guideline	Recommendation	Strength of Recommendation	Level of Evidence
ADULTS			
ACOG Community opinion 2019, updated 2020	Prevention of Group B streptococcal early-onset disease in newborns: Regardless of planned mode of birth, all pregnant women should undergo antepartum screening (vaginal-rectal swab) for GBS at 36 0/7 – 37 6/7 weeks of gestation, unless intrapartum antibiotic prophylaxis for GBS is indicated because of GBS bacteriuria during the pregnancy or because of a previous GBS-infected newborn.	None	None

	Provides a 5-week window for valid culture results that includes births that occur up to a gestational age of at least 41 0/7 weeks		
	GBS cultures should note a penicillin allergy in the patient, to ensure specimen is tested for clindamycin susceptibility.		
Royal College of Obstetrics and Gynecology 2017	Universal bacteriological screening is not recommended for pregnant women. If performed, bacteriological testing should ideally be carried out at 35-37 weeks of gestation or 3-5 weeks prior to anticipated delivery date Clinicians should be aware of the clinical risk factors that place women at increased risk of having a baby with early-onset GBS disease	None	Low
Australian Pregnancy Care Guidelines 2020	Offer either routine antenatal testing for Group B streptococcus colonisation or a risk factor-based approach to prevention, depending on organizational policy. If offering antenatal testing for Group B streptococcus, arrange for testing to take place at 35-37 weeks gestation. Encourage women to self-collect vaginal-rectal specimens for culture testing for Group B streptococcus and offer information about how to do this.	None	None
Qatar MOPH National Clinical Guidelines 2020	Perform a vaginal swab examination to screen for GBS in all women at 35 weeks or anytime thereafter, if not performed at 35 weeks.	None	None

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4.5 Screening using First Trimester Ultrasound

RECOMMENDATION

We suggest first trimester ultrasound in all pregnant Filipino women to improve maternal and perinatal outcomes. (*WEAK recommendation, very low to low level of evidence*)

Considerations

The Consensus Panel considered the following when formulating this recommendation:

- The Panel members were divided in formulating the statement on first trimester ultrasound in all pregnant Filipino women. This division stemmed from differing views on whether to make a strong or weak recommendation. The main factors influencing this decision were the weight of importance of fetal aging as a critical outcome with moderate to high certainty of evidence, pragmatic considerations, resource requirements, and equity issues.
- The research suggests that ultrasound, unlike reports of last menstrual period, is very accurate in determining fetal aging in the first trimester. Although there is no evidence found linking the knowledge of fetal aging at first trimester to improved maternal and perinatal outcomes, the specialists' clinical experience and high level of evidence on the accuracy of first-trimester ultrasound factored in the discussion. Determining accurate fetal aging through the use of ultrasound guides the clinicians in providing other tests and interventions expected at a certain gestational age to improve other important outcomes (i.e., post-maturity labor induction, fetal congenital anomaly detection, intrauterine growth restriction detection) at later stages of pregnancy. Other outcomes deemed critical by the panel, such as detection of non-viable pregnancy, ectopic pregnancy evaluation or detection, and multiple pregnancy detection, have inconclusive evidence, thus garnering a very low to low level of certainty.
- The recommendation statement faces barriers related to feasibility and resource requirements. These challenges arise from the absence of ultrasound machines in rural health units, the financial burden on patients who must travel to the nearest hospital with ultrasound capabilities, and the scarcity of skilled practitioners, specifically ultrasonographers, in various rural areas of the country.
- Another point raised by those who favored weak recommendation was inequity that may arise from the aforementioned accessibility issues and resource constraints (i.e., lack of trained personnel to perform ultrasound due to prioritization of other medical conditions, infrastructures and systems for the use of technology in certain areas) in spite of the possible coverage of future Philhealth packages.

4.5.1 Burden of disease

Epidemiology, Natural Course, Management, Economic impact, and Social impact of the Disease

Ultrasound as Routine Antenatal Care

Obstetric ultrasound is often performed in the first trimester to confirm the presence of intrauterine pregnancy and estimate gestational age. Diagnostic obstetric ultrasound can also be performed to evaluate pregnancy complications as well as fetal well-being, such as screening for intrauterine growth restriction or congenital anomalies. This is usually done during the second trimester. Although prenatal ultrasound may be routine in other countries such as in the United States, there are no local clinical practice guidelines which recommend its routine use in antenatal care (1). Controversies also exist as to which part of pregnancy it should be done and which outcomes should be checked.

Antenatal Ultrasound in the Philippines

According to the latest available Philippine Health Statistics, there were 1,673,923 live births in the country during the year 2019. Majority of these live births were attended by health professionals (95.3%). These include physicians, midwives, and public health nurses. Only a minority (4.4%) was attended by traditional birth attendants. No local data exists on how many of these pregnant women had ultrasound as part of their antenatal care. The Department of Health released an Administrative Order (2019-0026) ensuring all primigravids and multigravids receive antenatal care from a specialist in a CeMONC (comprehensive emergency obstetric and newborn care) provider facility (level II or III hospital) but implementing guidelines do not include an ultrasound in routine antenatal care (2,3).

4.5.2 Benefits, Harms and Diagnostic Performance of Screening Tests

Screening Cascade

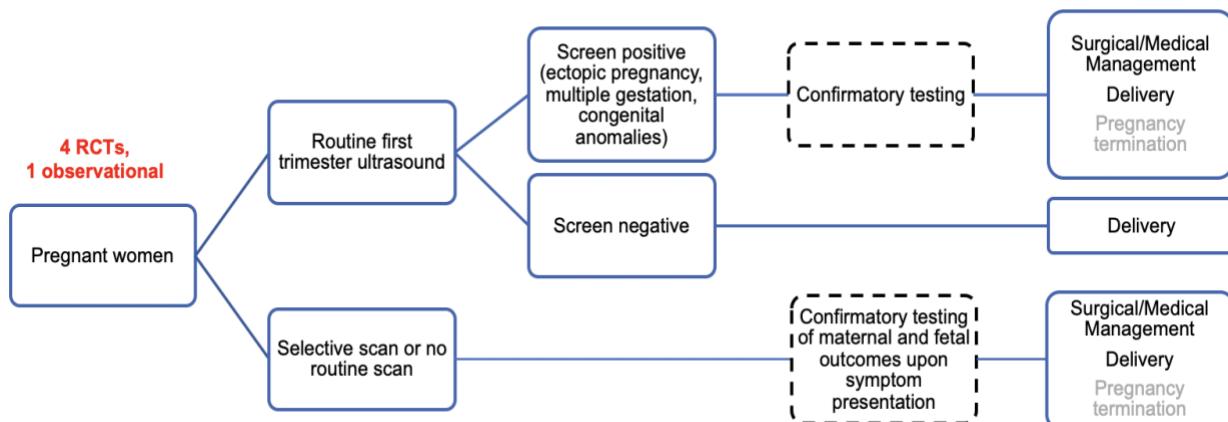


Figure 9. Screening cascade using first-trimester ultrasound

Figure 9 presents the screening cascade using routine first trimester ultrasound. For this review, the sources for direct evidence were 4 RCTs, and 1 retrospective cohort study, which followed up both screened and unscreened groups. Conditions such as ectopic

pregnancy, multiple gestation, and congenital anomalies may be detected early on among screened patients undergoing routine first trimester ultrasound. Such patients may either undergo further testing or proceed to definitive surgical or medical management, delivery, or pregnancy termination. Patient with negative screening or unremarkable first trimester ultrasound may proceed with usual antenatal care in preparation for delivery.

For the unscreened group undergoing either selective scan, or no scan at all, confirmatory testing or scan may be done upon presentation of any indication or symptoms, leading to late diagnosis and management.

Detection of Non-viable Pregnancy

One RCT ($n = 648$) that reported the number of non-viable pregnancies among recruited patients was used for this outcome (8,9). Analysis revealed inconclusive evidence on the detection of non-viable pregnancies using first trimester ultrasound versus no ultrasound (RR: 0.97, 95% CI: 0.52 to 1.8). The certainty of evidence was downgraded to low due to serious risk of bias from lack of blinding due to the nature of the intervention, and imprecision issue from confidence interval straddling the line of no effect.

Accurate Fetal Aging

One observational study ($n = 218$, 104 singleton, 81 twin, 33 triplet gestations) done among patients who underwent in vitro fertilization investigated the accuracy of ultrasound in fetal aging (12). First trimester ultrasound (11-14 weeks of gestation) was seen to slightly overestimate the gestational age by the following mean days: 1.3 ± 0.2 days ($p < 0.0001$) for singletons, 1.4 ± 0.2 days ($p < 0.0001$) for twins, and 0.8 ± 0.4 days ($p = 0.027$) for triplets. Certainty of evidence was high because although it was unclear if the ultrasonographer was aware of the IVF dating, this was judged to be unlikely so risk of bias was not rated down.

Evaluation of Ectopic Pregnancy

One RCT with a total of 218 participants revealed no significant difference in ectopic pregnancy detection between first trimester ultrasound group and control (RR: 2.74, 95% CI: 0.11 to 66.51) (10). The group who underwent a second trimester ultrasound was designated as the control for this analysis. This outcome had very low certainty of evidence due to very serious imprecision issues (very wide confidence interval crossing the line of no effect, single study with small sample size), and risk of bias (lack of blinding due to the nature of intervention).

Diagnosis or Evaluation of Multiple Gestations

Data from two RCTs ($n = 1,136$) showed no significant difference (RR: 1.13, 95% CI: 0.16 to 8.08, $I^2 = 66\%$) between the use of routine first trimester ultrasound versus selective ultrasound or no ultrasound on detecting multiple pregnancies or gestations, particularly before 18 to 26 weeks (9,11). Certainty of evidence was downgraded to very low due to study design limitations (unclear randomization and allocation concealment, and lack of blinding),

inconsistency of studies, and serious imprecision issues from the wide confidence interval crossing the line of no effect. The moderate heterogeneity may be explained by the variation in control groups, wherein one study used no ultrasound, while another study employed selective ultrasound. (Figure 10)

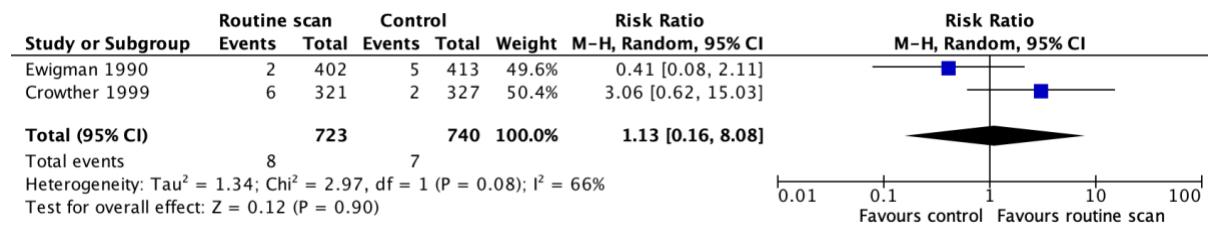


Figure 10. Forest plot on the use of first trimester routine versus selective ultrasound/no ultrasound to diagnose multiple gestations

Incidence of Post-term Pregnancies

The evidence on post-maturity labor induction was used as a surrogate marker for post-term pregnancy outcomes. Three RCTs ($n = 1,474$) investigated the frequency of post-maturity labor induction among pregnant patients who either underwent routine first trimester ultrasound or selective scan (control) were the basis for this outcome (8,10-11). Pooled analysis showed no significant difference between groups in terms of decreasing the incidence of post-term labor induction (RR: 0.83, 95% CI: 0.50 to 1.37, $I^2 = 42\%$). Downgrading of certainty of evidence to very low was done due to very serious risk of bias (unclear randomization and allocation concealment, and lack of blinding), and imprecision (confidence intervals crossing the line of no effect).

Analysis 1.11. Comparison 1: First trimester routine versus selective ultrasound, Outcome 11: Induction of labour for post maturity

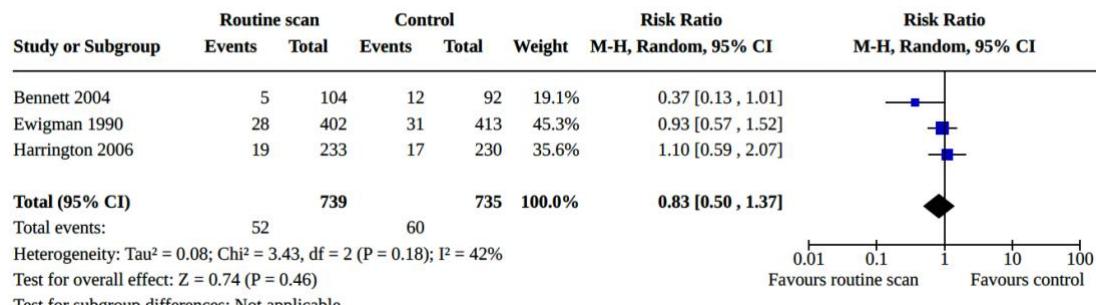


Figure 11. Forest plot on the use of first trimester routine versus selective ultrasound/no ultrasound to evaluate induction of labor for post maturity (adapted from Kaelin-Agten 2021)

Detection of Fetal Congenital Anomalies

One RCT ($n = 648$) revealed inconclusive results on fetal congenital anomaly detection with first trimester ultrasound compared to no scan (RR: 3.06, 95% CI: 0.12 to 74.74) (9). Downgrading the certainty of evidence to very low was done due to risk of bias from study limitations, and imprecision issues from very wide confidence intervals.

Intrauterine Growth Restriction

Outcomes from two RCTs ($n = 681$) showed no significant difference in terms of intrauterine growth restriction detection among patients who underwent first trimester scan compared to those who either had no first trimester ultrasound or had usual care (second trimester scan) (RR: 0.43, 95% CI: 0.13 to 1.44, $I^2 = 0\%$) (8,10). Certainty of evidence was downgraded to low due to risk of bias from study limitations, and imprecision from wide confidence intervals straddling the line of no effect.

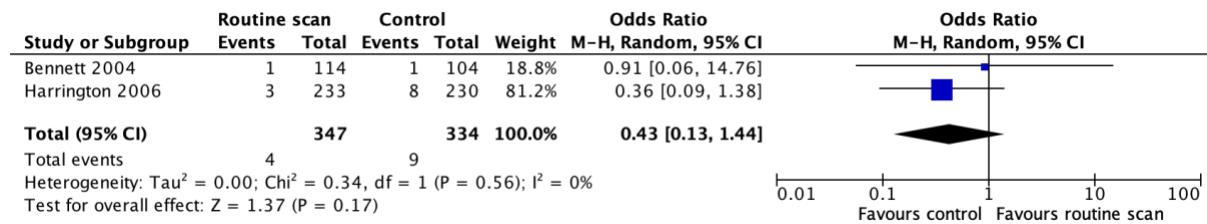


Figure 12. Forest plot on the use of first trimester routine versus usual care (second trimester ultrasound)/no ultrasound to detect growth restriction

Confirm Cardiac Activity

Evidence on the use of first trimester ultrasound to confirm cardiac activity was not analyzed in the adapted systematic review.

Overall Certainty of Evidence

The overall certainty of evidence was rated down to very low due to 1) serious risk of bias from lack of blinding among participants and outcome assessors, which is attributable to the nature of the intervention, 2) imprecision issues from wide confidence intervals that crossed the line of no effect, and 3) inconsistency issue in one outcome with moderate heterogeneity.

4.5.3 Cost Implication

The cost of routine antenatal ultrasound in government facilities ranges from PhP 250 to 500 as of 2021 (13,14). Special tests such as biophysical profile scoring, congenital anomaly scanning, and placental doppler may each cost around PhP 500 on top of the usual routine first and second trimester ultrasound. For private institutions, clinics or diagnostic centers, regular ultrasound and special procedures may range from PhP 700 to 5,500 (15,16). (Table 9)

Table 9. Cost of ultrasound procedures in a Tertiary Government Hospital in the NCR as of September 28, 2021

Procedure	Cost (PhP)
Transvaginal Sonography (1st trimester)	250.00
Transabdominal Sonography (2nd trimester)	250.00
Biophysical Profile Scoring	490.00
Congenital Anomaly Scanning	500.00
Placental Doppler	500.00
OB Doppler (Doppler Velocimetry)	500.00
First Trimester Ultrasound Screening	500.00
Markers	
OB 3D/4D	600.00
Fetal Echo	700.00

4.5.4 Equity, Acceptability, and Feasibility

One study by Kelly-Hedrick (2023) done in the US ($n = 289$) explored the views of pregnant women on receiving abnormal ultrasound findings, and the effect of these abnormal findings on decision-making and whether or not to terminate pregnancy (17). Pregnant patients above 18 years old who presented to Johns Hopkins Hospital for scheduled antenatal ultrasounds (any trimester) were recruited in the study. Participants were given a questionnaire containing close-ended and open-ended items regarding their desire to know abnormal results, if abortion is an option if results are not normal, and reasons behind their responses. Results showed that 95% of the participants wanted information on abnormal ultrasound results, but only half would consider abortion or terminating the pregnancy due to congenital anomalies. Some of the reasons for desiring abnormal finding disclosure included preparedness, valuing knowledge, and for informed decision-making. Cited perspectives on termination were mostly about weighing harms and benefits, maternal duties, and deeming termination as morally impermissible or permissible.

Moreover, based on the 2015 circular of the Philippine Health Insurance Corporation (PHIC/PhilHealth) on the benefits for women about to give birth, the case rate for the antenatal package is worth PhP 1,500 (18). Requirements include updated contributions to the social health insurance, at least four prenatal check-ups with the last one during the third trimester, and proper documentation and referral for delivery. However, this amount shouldered by PhilHealth is not enough to cover for the expenses incurred by any patient seeking private consultation and imaging.

No cost-effectiveness or economic evaluation studies were found on doing routine, first trimester or second trimester ultrasound.

4.5.5 Recommendations from Other Groups

The recommendations from other groups are shown in Table 10 below.

Table 10. Summary of existing guideline recommendations (first-trimester ultrasound)

Guideline	Recommendation	Strength of Recommendation	Level of Evidence
National Institute for Health and Care Excellence (NICE) Antenatal Care (NICE 2021)	Examinations and Investigations <ul style="list-style-type: none"> - Offer pregnant women an ultrasound scan to take place between 11+2 weeks and 14+1 weeks to: <ul style="list-style-type: none"> - determine gestational age - detect multiple pregnancy - and if opted for, screen for Down's syndrome, Edwards' syndrome and Patau's syndrome 	N/A	N/A
The Society of Obstetricians and Gynaecologists of Canada (SOGC) Guideline No. 375: Clinical Practice Guideline on the Use of First Trimester Ultrasound (SOGC 2019)	Fetal aging <ul style="list-style-type: none"> - First trimester ultrasound is not recommended to diagnose pregnancy but is recommended to date a pregnancy (ideally at 7-12 weeks) 	III*	A**
American College of Obstetrician and Gynecologists (ACOG) Practice Bulletin #175: Ultrasound in Pregnancy (ACOG 2016)	First trimester: <ul style="list-style-type: none"> - Screening for fetal anomalies 	N/A	N/A
International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) Practice Guidelines (updated): performance of 11–14-week ultrasound scan (ISUOG 2023)	Performing a routine first-trimester ultrasound examination at 11 + 0 to 14 + 0 weeks' gestation is of value for confirming viability and plurality, accurate pregnancy dating, screening for aneuploidies, identification of major structural anomalies and screening for preterm pre-eclampsia.	N/A	N/A

*Opinion of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

**There is good evidence to recommend the clinical prevention action.

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4.6 Screening for Fetal Aneuploidy

RECOMMENDATION

We suggest nuchal translucency measurement at 11-14 weeks AOG be offered to all pregnant Filipino women to screen for Down syndrome; and be offered to pregnant women at high risk for fetal anomaly, to screen for major CHD. (*WEAK recommendation, very low to low level of evidence*)

Fetal anomaly risk factors include the following:

- Advanced maternal age (>35 years old)
- Positive serum screen
- Other congenital anomalies on ultrasound
- History of prior fetus with birth defects or aneuploidy
- Intrauterine fetal death
- Neonatal death

Considerations

The Consensus Panel considered the following when formulating this recommendation:

- The intervention specified by the Steering Committee in the question was “nuchal translucency (NT) measurement alone,” excluding biomarkers, mostly due to affordability and accessibility issues. Hence, the evidence review focused on the effectiveness of using nuchal translucency measurement as a standalone method for screening chromosomal disorders and congenital disorders. However, the term “alone” was omitted by the Panel in order to avoid limiting the tests (e.g., biomarkers) that clinicians can offer to their patients.
- The Panel also weighed several factors prior to casting their vote in favor of this statement and deciding on the strength of recommendation. First, there is no direct evidence available for the screening cascade of the said conditions. The indirect evidence focused on the diagnostic accuracy of using NT measurement as standalone measure.
- Second, the number of false positives in using NT alone in screening for chromosomal and congenital disorders that can induce anxiety during pregnancy is regarded as undesirable effect of the screening process. However, it is worth noting that the anxiety experienced after the women were screened positive was transient and is typically not sustained beyond the first trimester, as supported by available evidence. Furthermore, similar to other guidelines, further criteria may be established to ensure that counseling services are provided by trained health workers and that quality assurance mechanisms are implemented in this screening cascade.
- Third, feasibility, resource, and equity concerns revolve around the recommendation statement due to the unavailability of confirmatory testing (invasive sampling) in the country. Nevertheless, many mothers or families may be able to afford the screening tests and the necessary means to pursue further tests and subsequent treatments that may be advantageous for both the mother and the

developing fetus.

- Fourth, the implications of suggesting against the screening can have an impact on both the mother and the infant. The failure to identify the problem during early pregnancy may cause detrimental consequences in later stages (e.g., the formation of excess amniotic fluid that may lead to preterm labor) or the birth of the baby with a condition that will have health, economic, and social implications.

4.6.1 Burden of disease

Epidemiology, Natural Course, Management, Economic impact, and Social impact of the Disease

Down syndrome or trisomy 21, the most common chromosomal disorder, results from the presence of a third copy of chromosome 21. The risk of Down syndrome increases with increasing maternal age and manifests as mild to moderate intellectual disability, growth retardation, congenital heart defects, gastrointestinal abnormalities, and characteristic facial features (1). As many as 40% of infants with Down syndrome present with at least one cardiac defect; and among the cardiac defects, major congenital heart disease (CHD) is a subset considered not compatible with postnatal life and would require intervention from birth to one year of life to ensure survival (2). Other less common chromosomal disorders are Edwards syndrome and Patau syndrome due to an extra copy of chromosome 18 and 13, respectively. They share risk factors such as increased maternal age and overlapping characteristic features.

The estimated worldwide incidence of Down syndrome is between 1 in 1,000 to 1 in 1,100 live births which translates to 3,000 to 5,000 cases annually (3). In the Philippines, 1 out of 800 babies is born with Down syndrome (4). In fact, it is the top reason for genetic consultation locally (5). Due to recent medical advancements, there has been a significant increase in the life expectancy of patients with Down syndrome. Between 1979 and 2003, the rate of death among infants with Down syndrome during the first year of life decreased from 8.5% to 5.0% (6). Furthermore, their median life expectancy is 58 years old compared to only about 10 years old during 1960 (7). Meanwhile, CHD, the most commonly diagnosed congenital disorder in newborns, occurs in approximately 0.8 to 1.2% of live births worldwide (8). Edwards syndrome and Patau syndrome are less common with an incidence of 1 in 5,000 live births (9,10).

Several methods have been used for the prenatal diagnosis of Down syndrome, Edwards syndrome, and Patau syndrome. Ultrasound between 11 to 14 weeks of gestation can evaluate soft markers such as nuchal translucency (NT), a transient subcutaneous collection of fluid behind the fetal neck (11). If NT exceeds a set cut-off value, the screen is positive and further diagnostic tests including chorionic villus sampling (CVS) and amniocentesis are done, followed by karyotyping (7). NT is often used in combination with serum biomarkers to increase the diagnostic performance for fetal aneuploidy. Once diagnosis is confirmed, parents receive counselling and are offered the option of pregnancy termination where available. The newest type of screening called non-invasive prenatal testing involves measurement of circulating cell-free DNA in the maternal blood during 10

weeks of gestation; and it estimates the likelihood of Down's syndrome reducing the need for a confirmatory CVS or amniocentesis due to its high accuracy (12,13).

Although the most accurate diagnostic tests are CVS and amniocentesis, they are invasive and carry between 0.5 to 1% risk of miscarriage (11). For CHDs, fetal echocardiogram is used as the primary tool to evaluate and diagnose fetal cardiovascular pathology (14). However, in limited resource settings, only measurement of NT via ultrasound can be performed since combined first trimester tests with serum biomarkers are unavailable or inaccessible. The diagnostic accuracy of nuchal translucency measurement alone has been investigated in several observational studies, but there is no consensus on its use as the sole diagnostic tool to screen for fetal aneuploidy and congenital heart defects.

4.6.2 Benefits, Harms and Diagnostic Performance of Screening Tests

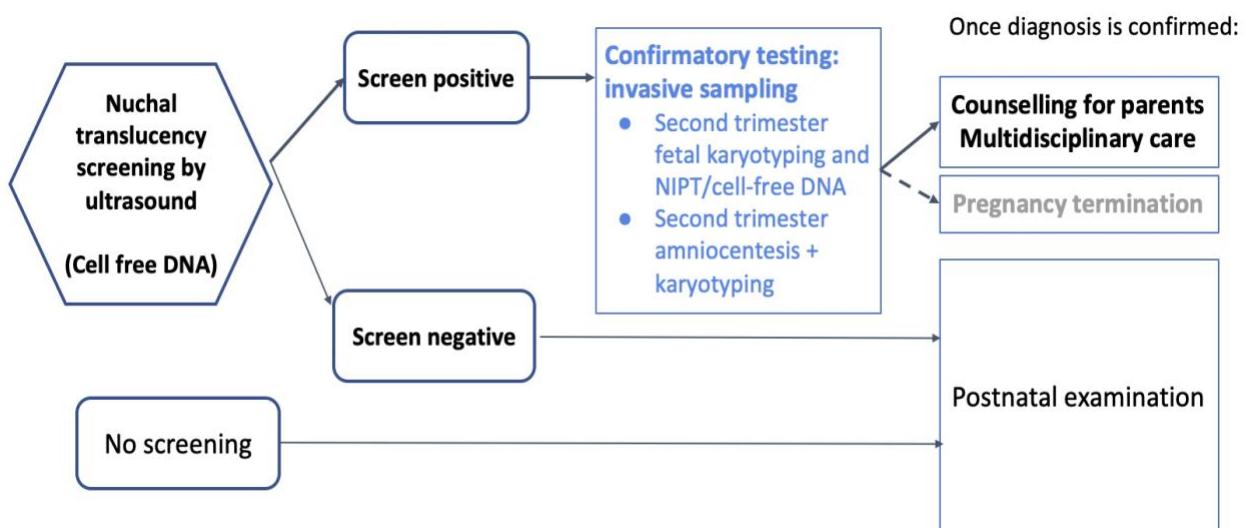


Figure 13. Screening cascade for fetal aneuploidy

If NT exceeds a set cut-off value, the screen is positive and further diagnostic tests including chorionic villus sampling (CVS) and amniocentesis, followed by karyotyping (7). Once the diagnosis is confirmed, parents receive counselling and are offered the option of pregnancy termination where available. If the screen is negative, pregnant women undergo routine prenatal care and postnatal examination at delivery. (Figure 13)

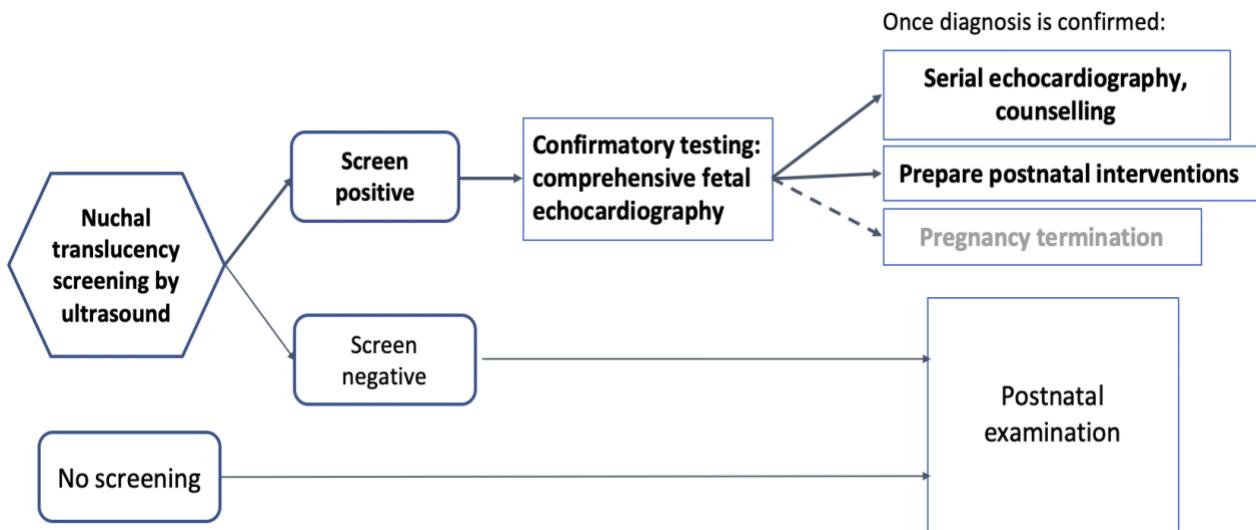


Figure 14. Screening for major CHD with NT

If NT exceeds a set cut-off value, the screen is positive and comprehensive fetal echocardiography is done to confirm CHD. Once the diagnosis is confirmed, the pregnant women receive serial fetal echocardiography and counselling regarding the need for postnatal interventions such as surgery as well as the option of pregnancy termination where available. If the screen is negative, pregnant women undergo routine prenatal care and postnatal examination at delivery. (Figure 14)

Down syndrome

Low-risk population

Twenty-two cohort studies ($n = 225,846$) recruited participants at low risk for fetal anomaly. Of these studies, 14 studies were prospective and eight studies were retrospective. The studies recruited pregnant women at 10 to 14 weeks age of gestation who underwent NT screening at various cut-offs (Figure 15). Performance of NT measurement was standardized among the studies through Fetal Medicine Foundation (FMF) certification of the sonographers. The pooled sensitivity was 67.8% (95% CI: 61.4 to 73.6, $I^2 = 70.4\%$) and specificity was 96.3% (95% CI: 95.5 to 96.9, $I^2 = 96.7\%$). Additional subgroup analysis based on cut-off points is available in the Appendix.

Low risk

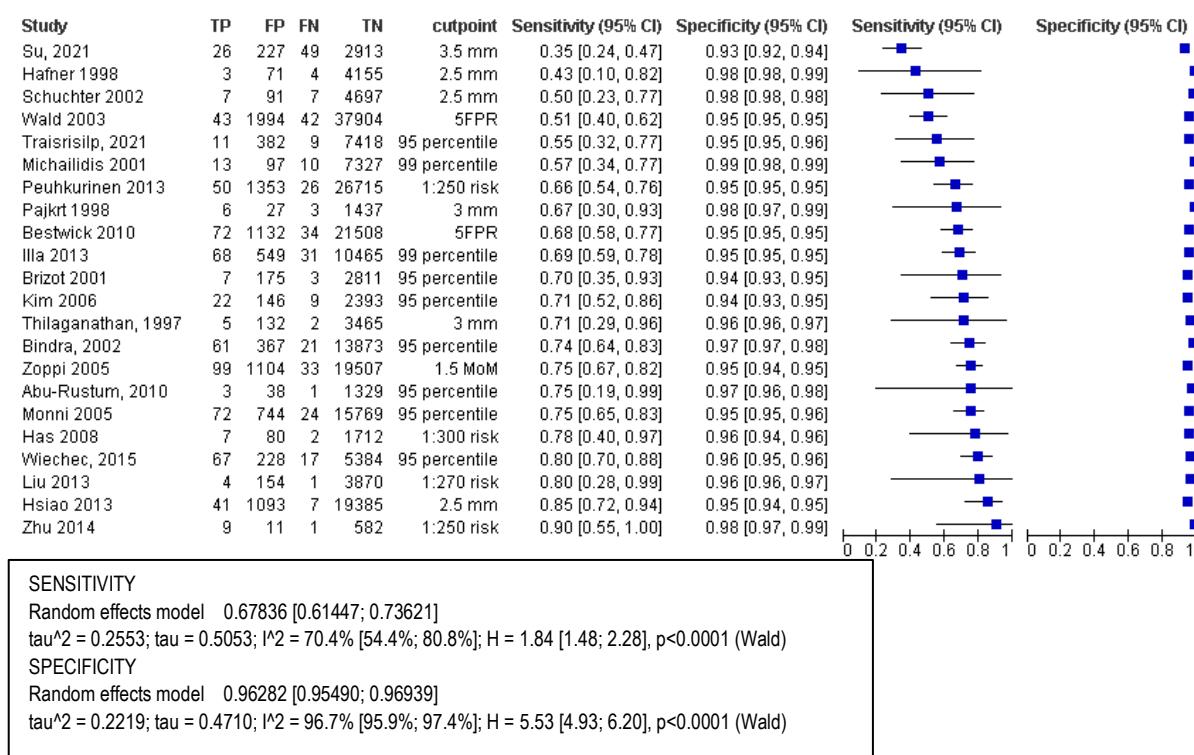


Figure 15. Forest plot of diagnostic characteristics for low-risk pregnant women for the outcome of Down syndrome

High-risk population

Seven studies ($n = 9,197$) recruited participants with risk factors for fetal anomaly, such as advanced age, positive serum screen, presence of other ultrasound anomalies, and history of previous fetus with anomaly. Of these cohort studies, five studies were prospective and two studies were retrospective. The pooled sensitivity was 62.2% (95% CI: 54.1 to 69.7, $I^2 = 38.8\%$) and specificity was 96.5% (95% CI: 93.6 to 98.1, $I^2 = 95.5\%$) (Figure 16). Sensitivity analysis was done by excluding the outlier Acacio et al., but heterogeneity remained substantial with sensitivity values at 61.2% (95% CI: 53.1 to 68.9, $I^2 = 44.2\%$) and specificity at 97.2% (95% CI: 95.7 to 98.2, $I^2 = 91.7\%$).

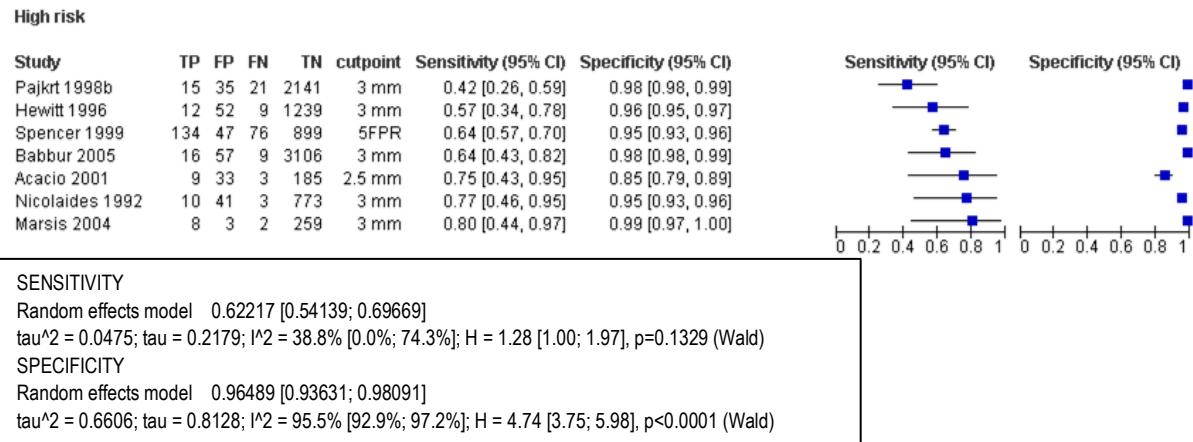


Figure 16. Forest plot of diagnostic characteristics for high-risk pregnant women for the outcome of Down syndrome

Edwards syndrome

Low-risk population

Four studies ($n = 481,252$) were performed among pregnant women at low risk for fetal anomaly. Of these, three studies were prospective and one was retrospective. The studies recruited pregnant women at 10 to 14 weeks age of gestation who underwent NT screening at various cut-offs (Figure 17). Performance of NT measurement was standardized among the studies through FMF certification of the sonographers. The pooled sensitivity was 63.0% (95% CI: 43.5 to 79.1, $I^2 = 76.7\%$) and specificity was 97.4% (95% CI: 94.9 to 98.6, $I^2 = 99.9\%$).

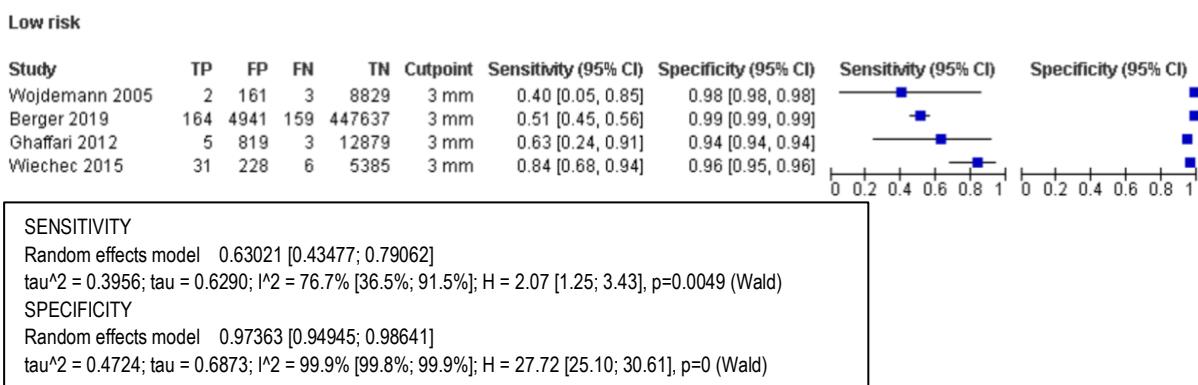


Figure 17. Forest plot of diagnostic characteristics for low-risk pregnant women for the outcome of Edwards syndrome

High-risk population

One prospective study ($n = 1,053$) was performed among pregnant women at high risk for fetal anomaly. In this study, the sensitivity was 71.0% (95% CI: 29.0 to 96.0) and specificity was 97.0% (95% CI: 96.0 to 98.0).

Patau syndrome

No primary studies were found that investigated the diagnostic accuracy of NT alone for Patau syndrome.

Major congenital heart disease

Low-risk population

Thirteen cohort studies ($n = 197,270$) were performed on pregnant women at low risk for fetal anomaly. Of these, there were nine prospective studies and four retrospective studies. The studies recruited pregnant women at 10 to 14 weeks age of gestation who underwent NT screening at various cut-offs (Figure 18). NT measurement was done by FMF-certified sonographers. The pooled sensitivity was 25.0% (95% CI: 17.0 – 35.1, $I^2=76.8\%$), while specificity was 97.2% (95% CI: 95.3 – 98.4, $I^2=99.6\%$).

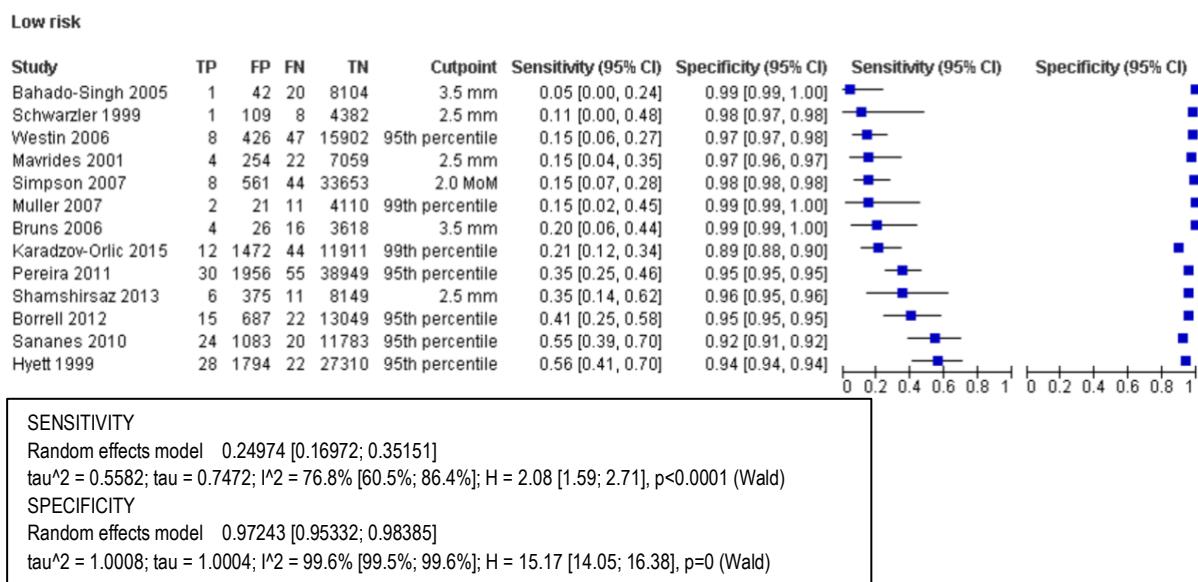


Figure 18. Forest plot of diagnostic characteristics for low-risk pregnant women for the outcome of major CHD

High-risk population

There was one prospective cohort study performed among women at high risk for fetal anomaly. In this study, the sensitivity was 90.0% (95% CI: 55.0 to 100.0) and specificity was 91.0% (95% CI: 89.0 to 93.0).

Overall Certainty of Evidence

For the outcome of Down syndrome among pregnant women at low risk, the evidence was rated down twice: once for different modes of verification and once for

heterogeneity not completely explained by variability in baseline risk or cut-points, hence the certainty of evidence was low. For the outcome of Down syndrome among women at high risk, the evidence was rated down once for differential verification and was assigned moderate certainty.

For the outcome of Edwards syndrome among pregnant women at low risk, the evidence was rated down three times: once for differential verification, once for unexplained heterogeneity, and once for imprecision due to wide confidence interval, leading to a very low certainty of evidence. For women at high risk, evidence was rated down twice for imprecision due to wide confidence interval and small sample size and was assessed to have low certainty.

For the outcome of major CHD among pregnant women at low risk, evidence was rated down twice: once for differential verification and once for unexplained heterogeneity, leading to a low certainty of evidence. For women at high risk for fetal anomaly, evidence was rated down thrice, once for differential verification and twice for imprecision due to wide confidence interval and small sample size, leading to a very low certainty of evidence.

4.6.3 Cost Implication

A cost-effective analysis study found that it would cost USD 98,381 for each additional Down syndrome case diagnosed by NT alone compared to second trimester expanded maternal serum alpha-fetoprotein (AFP) test alone. With a benefit-to-cost ratio of 5.21, this is considered to be cost-effective (69). Meanwhile, a more recent study comparing Down syndrome screening strategies found integrated serum-only screen (beta-hCG, PAPP-A, AFP, unconjugated estriol, dimeric inhibin-A) to be the most cost-effective. Although NT screening costs less, it has a lower Down syndrome detection rate and higher number of procedure-related losses (70).

Another cost-effectiveness analysis by Gilbert et. al. done in the UK last 2001 similarly compared the cost-effectiveness of various strategies for Down syndrome screening. Their decision model assumes that 100% of women underwent prenatal care at 10-14 weeks AOG, with NT having a detection rate of 75% at a false positive rate of 5%. Results showed that screening with NT would result in 7.6 fewer births with Down syndrome compared with no screening, and that the incremental cost-effectiveness ratio (ICER) was 22,000 pounds per prevented birth of a baby with Down syndrome. The performance of NT screening was second in cost-effectivity only to integrated testing (first trimester NT, PAPP-A + second trimester quadruple test) and was superior to the rest of the strategies (71).

4.6.4 Equity, Acceptability, and Feasibility

In a population-based case control study, it was found that as the number of poor socioeconomic factors (e.g. low maternal educational attainment, lowly paternal occupation, low family income) increases, the risk of conceiving a fetus with Down syndrome also increases (72,73). A similarly done population-based retrospective cohort study also concluded that lower household income, unemployment status, and living in poverty could

increase the risk of CHD (74). The average lifetime economic burden of Down syndrome is deemed substantial from a family and societal perspective amounting to USD 47,000 and USD 55,000, respectively (75). A study estimated the incurred incremental out-of-pocket medical cost of patients with Down syndrome from birth to 18 years old to be USD 18,248 which is greater than those of matched controls (76). Total healthcare cost is more than four times compared to a normal population with major costs being hospitalization and respite care with most of the total economic loss attributed to productivity losses (75,77).

A pilot study by Drysdale et. al. at St. Mary's Hospital in the UK in 2002 sought to evaluate the acceptability of routine early ultrasound at 12-14 weeks (including NT) among women presenting to a community midwife. In this study, 99% of women accepted the offer of ultrasound at 12-14 weeks age of gestation (AOG). Of these 984 women, 85% agreed to undergo Down syndrome screening by NT. Twenty-seven women were assessed to have high risk based on NT (3.2%). Of these, 66.7% (n = 18) opted to proceed with invasive confirmatory testing, which detected two cases of Down syndrome. Both cases then underwent elective termination. After the study, patients answered questionnaires regarding the acceptability of their experience. Majority of the women (83%) answered that they would accept a scan at their next pregnancy and found the scan to be a reassuring experience (78).

Several studies explored the psychological effect of Down syndrome screening through NT on participating mothers. In a cohort study by Muller et al. in 2006, the investigators assessed whether offering NT screening would affect the levels of anxiety and depression among 687 pregnant women seen at a hospital in The Netherlands. Results showed that offering screening did not affect anxiety or depression levels (regardless if offer was accepted or declined) as measured by the Hospital Anxiety and Depression Scale (HADS) (79). An RCT by Öhman et al. in 2004 involving 2,026 women assessed the effect of NT screening on the anxiety levels of mothers mid-pregnancy and 2 months after delivery. Compared to unscreened mothers, screened mothers did not exhibit increased levels of anxiety on Spielberger's State-Trait Anxiety Inventory (STAI) questionnaire. In both groups, anxiety declined over mid-pregnancy and 2 months post-delivery (80). In 2007, Chueh et al. performed a cohort study involving 352 women to compare pre-screening and post-screening levels of anxiety among those undergoing NT measurement and to explore the impact of a positive screen result. While anxiety increased immediately after a receiving positive result, this was not sustained to mid-pregnancy and the puerperium (81). Similarly, a cohort study by Öhman et al. in 2009 involving 620 women also found that though women who were deemed high risk after NT screening were slightly more worried at mid-pregnancy, worry levels declined to baseline at 2 months postpartum (82). Overall, two studies found that there was no increase in anxiety or worry with NT screening, while two others showed that there was a small increase in anxiety after a positive screen, but this effect was not sustained.

A study done in a district general hospital with multiethnic patients concluded that nuchal translucency screening can be effectively and equitably provided regardless of racial origin. Although African and Asian women consult significantly later during their pregnancy, they still presented early enough for nuchal translucency to be possible (83).

4.6.5 Recommendations from Other Groups

The recommendations from other guidelines are presented in Table 11 below.

Table 11. Summary of existing guideline recommendations (fetal aneuploidy)

Guideline	Recommendation	Strength of Recommendation n	Level of Evidence
American College of Obstetrics and Gynecology 2020	Prenatal genetic screening (serum screening with or without nuchal translucency [NT] ultrasound or cell-free DNA screening) and diagnostic testing (chorionic villus sampling [CVS] or amniocentesis) options should be discussed and offered to all pregnant women regardless of maternal age or risk of chromosomal abnormality.	None reported	Level A (Recommendations are based on good and consistent scientific evidence.)
American Academy of Family Physicians 2020	All pregnant women should be counseled and offered aneuploidy screening regardless of maternal age.	None reported	Level C (Consensus, disease-oriented evidence, usual practice, expert opinion, or case series)
	First-trimester nuchal translucency, NIPT, and first- or second trimester serum testing can be performed in twin pregnancies.	None reported	Level C (Consensus, disease-oriented evidence, usual practice, expert opinion, or case series)
Society of Obstetricians and Gynaecologists of Canada 2021	All women should be offered a routine complete 11-14 week prenatal sonographic examination (including screening for aneuploidy).	Strong	High
Society of Obstetricians and Gynaecologists of Canada 2019	Nuchal translucency screening should be offered as part of a prenatal genetic screening and counselling program by experienced operators with appropriate quality assurance processes in place. Any patient with a nuchal translucency greater than 3.5 should be offered referral to maternal-fetal medicine.	None reported	Level A (There is good evidence to recommend the clinical preventive action.)
Society of Obstetricians and Gynaecologists of Canada 2017	First trimester nuchal translucency...should not be offered as a screen without biochemical markers in singleton pregnancies.	None reported	Level E (There is good evidence to recommend against the clinical preventive action.)

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4.7 Screening using Second Trimester Ultrasound

RECOMMENDATION

We suggest routine second trimester ultrasound for all pregnant Filipino women to improve maternal and perinatal outcomes. (*WEAK recommendation, low level of evidence*)

Considerations

The Consensus Panel considered the following when formulating this recommendation:

- The Panel members believe that apart from large desirable effects (i.e., detection of 3 more fetal congenital anomalies per 1,000 pregnancies before 24 weeks AOG compared to no ultrasound, 4 more multiple pregnancies per 1,000 pregnancies by 24 to 26 weeks AOG compared to selective ultrasound, 15 fewer induction of labor for postterm pregnancy per 1,000 pregnancies) and trivial harm (i.e., feeling worried about their pregnancy) of the intervention compared to none, the routine second trimester ultrasound for all pregnant Filipino women is acceptable to key stakeholders and feasible to implement.
- In the absence of ultrasound, other approaches such as a) doing Leopold's maneuver, and b) checking for large for gestational age fundal height, and detection of two heart rates, are currently being done to detect multifetal pregnancy. Moreover, the portable Doppler's monitor, which is now widely available and mostly provided by local government units, is used to identify fetal heart tones.
- There are concerns about resource requirements, as district and provincial hospitals face deficiencies in terms of equipment and manpower in remote areas necessary for performing ultrasound.

4.7.1 Burden of disease

Epidemiology, Natural Course, Management, Economic impact, and Social impact of the Disease

Ultrasound as Routine Antenatal Care

Second trimester ultrasound is usually performed to evaluate pregnancy complications as well as fetal well-being. It is usually done to determine fetal age and number (if not yet done during the first trimester), detect intrauterine growth restriction, assess placental location, and identify placental or amniotic fluid abnormalities. Although this may be routine in other countries such as in the United States, there are no local clinical practice guidelines which recommend its routine use in antenatal care (POGS) (1). Moreover, exact accuracy of second trimester ultrasound in fetal aging remains unknown. This is particularly relevant in low to middle income countries as many seek antenatal care after 20 weeks AOG (2).

Antenatal Ultrasound in the Philippines

According to the latest available Philippine Health Statistics, there were 1,673,923 live births in the country during the year 2019. Majority of these live births were attended by

health professionals (95.3%) (3), which included physicians, midwives, and public health nurses, with only a minority (4.4%) being attended by traditional birth attendants. No local data exists on how many of these pregnant women had ultrasound as part of their antenatal care. The Department of Health released an administrative order (2019-0026) ensuring all primigravids and multigravids receive antenatal care from a specialist in a CeMONC (comprehensive emergency obstetric and newborn care) provider facility (level II or III hospital) but implementing guidelines do not include an ultrasound in routine antenatal care (DOH) (4).

4.7.2 Benefits, Harms and Diagnostic Performance of Screening Tests

Screening Cascade

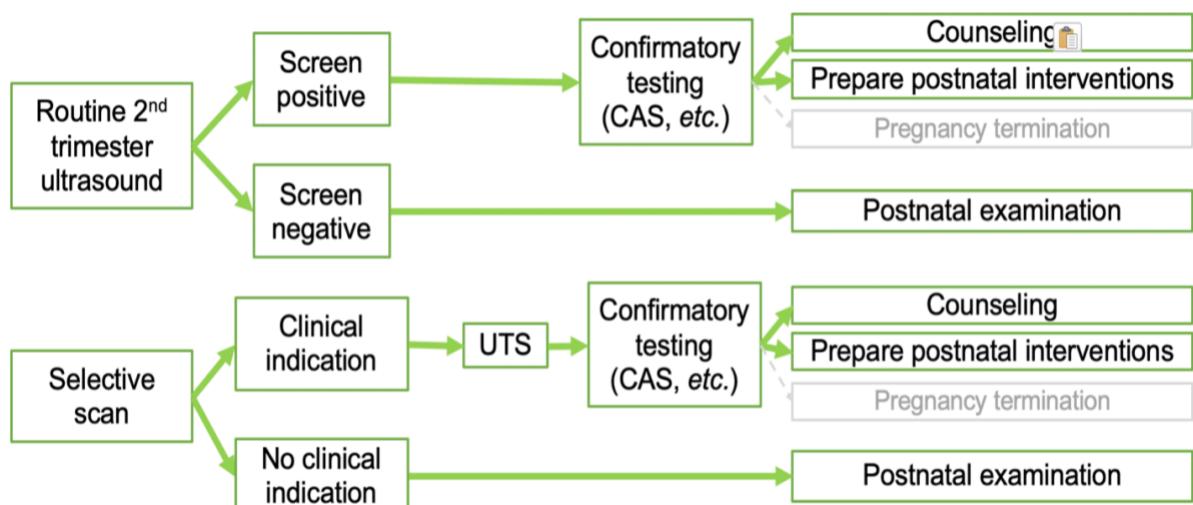


Figure 19. Screening cascade for fetal anomalies

If second trimester ultrasound detects fetal anomalies, a confirmatory test such as congenital anomaly scan (CAS) will be performed. If the confirmatory test was positive, the patient will be counseled and a multidisciplinary team will prepare the patient and the family for postnatal interventions. Pregnancy termination, for whatever reason, is unethical and illegal in the Philippines. If a routine ultrasound is not performed, a clinical indication for a scan should arise to trigger the cascade (e.g. abnormal fundal height on physical examination might lead a physician to request for a second trimester ultrasound as this may be a sign of polyhydramnios which might be due to esophageal atresia).

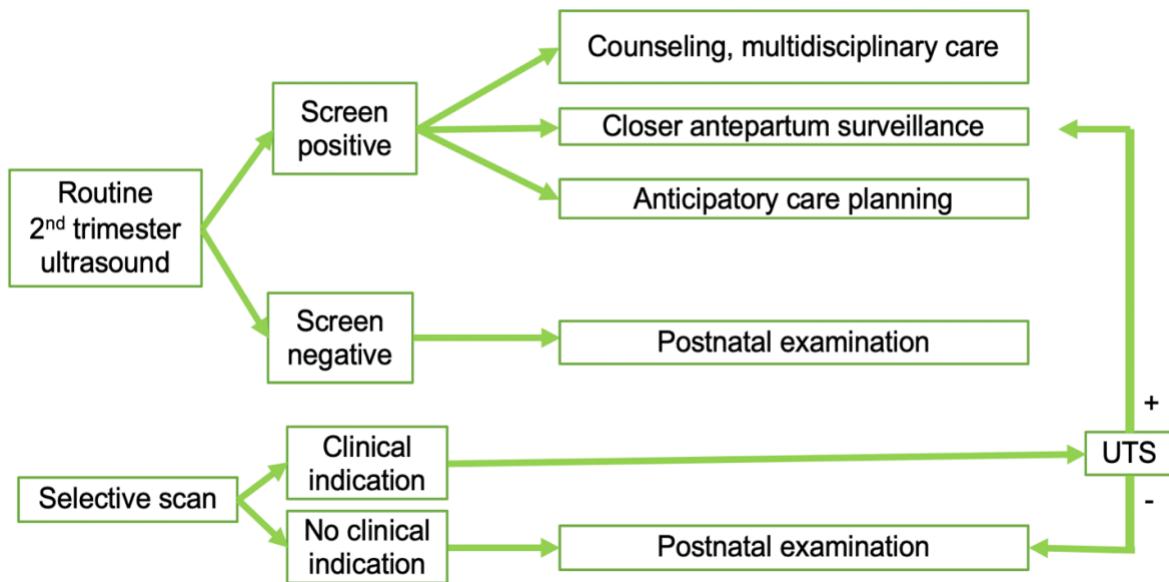


Figure 20. Screening cascade for multifetal pregnancy

Detection of multifetal pregnancy using second trimester ultrasound will lead to counseling and anticipatory care planning. The patient may be referred to subspecialist care as the multidisciplinary team (e.g. obstetrician-gynecologist, perinatologist, neonatologist) will help manage possible complications of multifetal pregnancy. This will lead to more clinic visits and possible more tests, as part of closer antepartum surveillance needed in high risk pregnancy. If a routine ultrasound is not performed, a clinical indication for a scan should arise to trigger the cascade (e.g. Leopold's maneuver or detection of two fetal heartbeats on auscultation might lead to suspicion of a multifetal pregnancy). (Figure 20)

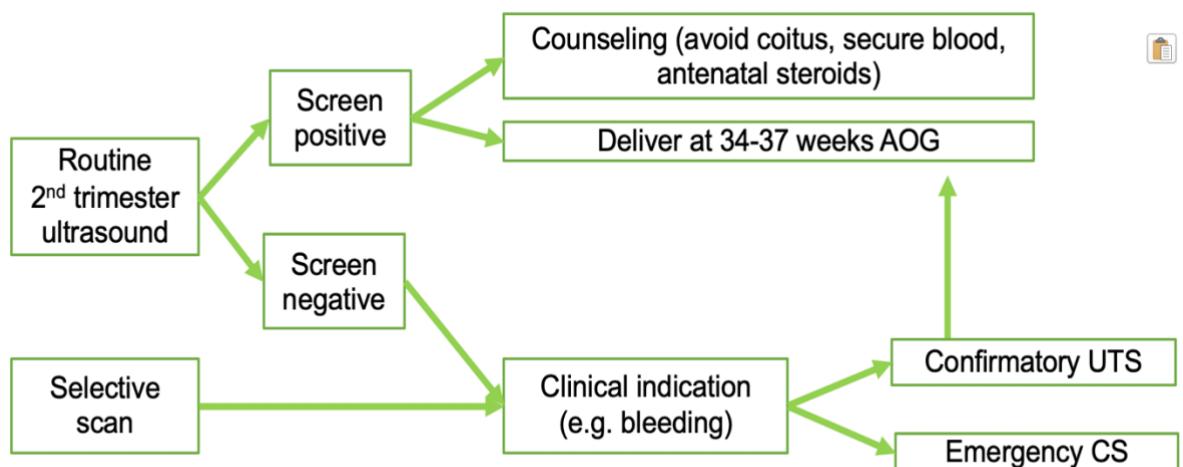


Figure 21. Screening cascade for placenta previa

If placenta previa is detected using second trimester ultrasound, the patient will be asked to avoid coitus during pregnancy, secure blood products for possible transfusion in case of severe bleeding, and the need for antenatal steroids to promote fetal lung maturity in case of premature labor. The patient might be advised to deliver at 34-37 weeks AOG. If

second trimester ultrasound is not routine, a clinical indication (e.g. bleeding) is needed to trigger the cascade. Major bleeding (especially with hemodynamic compromise) will lead to an emergency Cesarean section, with potential maternal and fetal complications. (Figure 21)

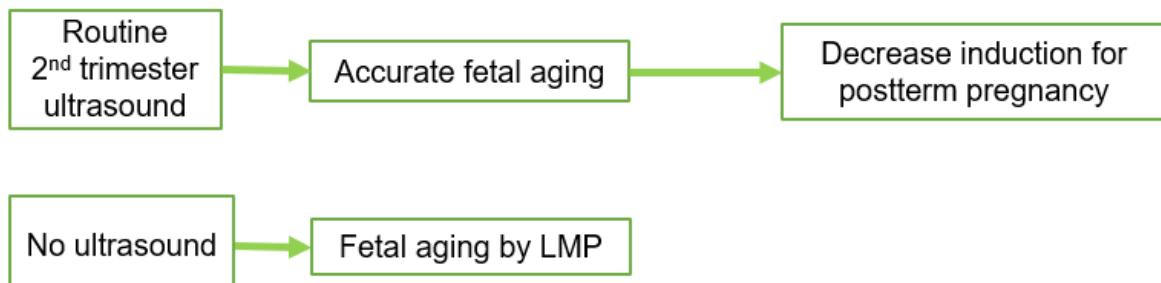


Figure 22. Screening cascade for induction of labor for postterm pregnancy

Accurate fetal aging using routine second trimester ultrasound might decrease the incidence of postterm pregnancy. In the absence of ultrasound, fetal aging is usually determined by the last menstrual period (LMP). This may be inaccurate to some due to incorrect recall, irregular menstrual cycles, and variable timing of ovulation during the menstrual cycle. (Figure 22)

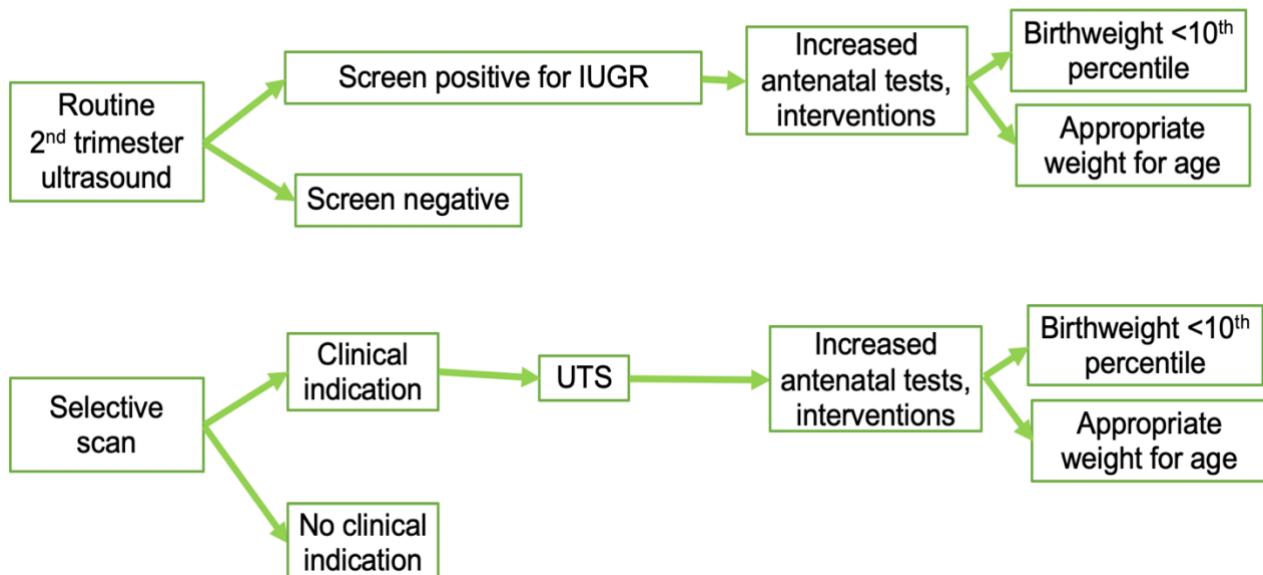


Figure 23. Screening cascade for growth restriction

Detection of intrauterine growth restriction (IUGR) using second trimester ultrasound will lead to increased antenatal tests and interventions. Neonates may then be born small-for-gestational age (i.e. birthweight <10th percentile) or appropriate for gestational age (i.e. birthweight between 10th to 90th percentile). (Figure 23)

Detection of Fetal Congenital Anomalies before 24 weeks AOG

Routine second trimester ultrasound was associated with increased detection of fetal anomalies (RR: 3.39, 95% CI: 1.76 to 6.54, $I^2 = 0$, $n = 17,713$) before 24 weeks age of gestation. The evidence has moderate certainty based on 3 RCTs, with study design limitations (lack of blinding and pre-registered protocols, and unclear allocation concealment, one had selection bias) (10–14).

Routine second trimester ultrasound detected 16.6% of malformations while selective ultrasound detected only 4.4% of malformations before 24 weeks AOG. Majority of malformations remained undetected by both routine and selective ultrasound at 24 weeks AOG (10–12). The study of van Dyk (2007) did not report if there were malformations missed by ultrasound in both groups (13,14). (Figure 24)

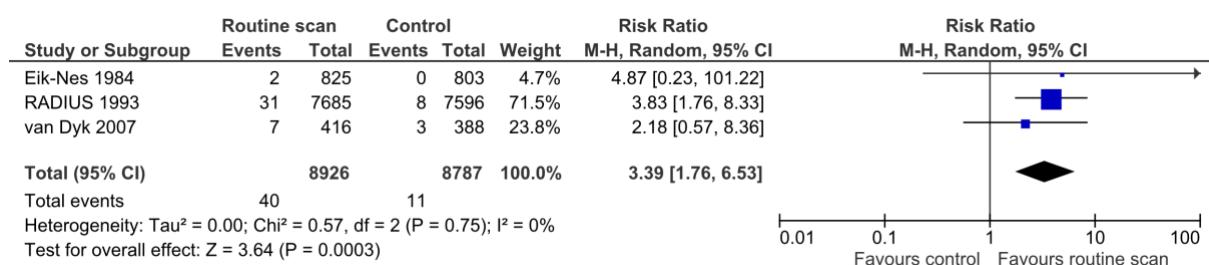


Figure 24. Forest plot on the use of routine second trimester ultrasound versus selective ultrasound in detection of fetal anomalies before 24 weeks AOG

Detection of multiple pregnancies by 24-26 weeks AOG

Routine second trimester ultrasound was associated with increased detection of multiple pregnancies by 24-26 weeks age of gestation (RR: 1.89, 95% CI: 1.17 to 3.04, $I^2 = 48\%$, $n = 31,343$). The evidence has moderate certainty based on 5 RCTs with study design limitations (lack of blinding and preregistered protocols, one has attrition bias) (10–12,15–17). There were only 2/144 (1.4%) multiple pregnancies missed by routine ultrasound – one of the women changed her place of residence and was not able to attend her routine screening ultrasound schedule while the reason for the other one was not reported. On the other hand, selective ultrasound missed 53/130 (40.7%) multiple pregnancies by 24-26 weeks AOG.

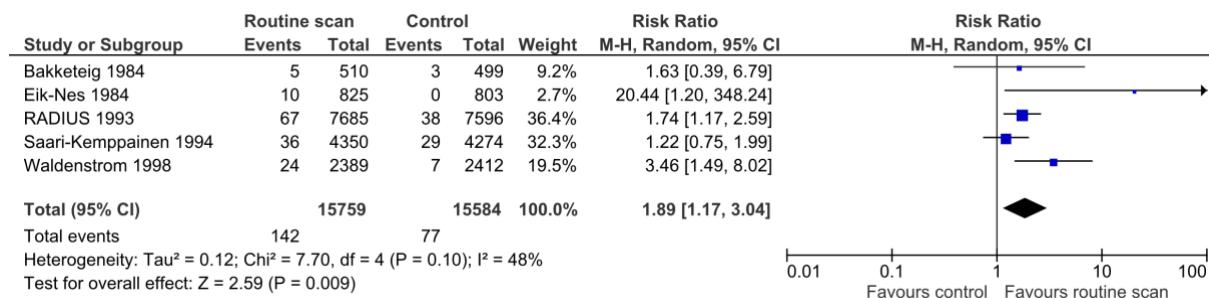


Figure 25. Forest plot on the use of routine second trimester ultrasound versus selective ultrasound in detection of multiple pregnancies by 24-26 weeks AOG

Complications of placenta previa

The effect of routine second trimester ultrasound in the rate of complications of placenta previa was inconclusive (RR 1.32, 95% CI 0.09-18.95, $I^2 = 31\%$, n = 2,637). The evidence has low certainty based on two RCTs with study design limitations (lack of blinding and pre-registered protocols, and unclear allocation concealment, one had attrition bias) and imprecision (low event rate with wide confidence interval) (10,11,15).

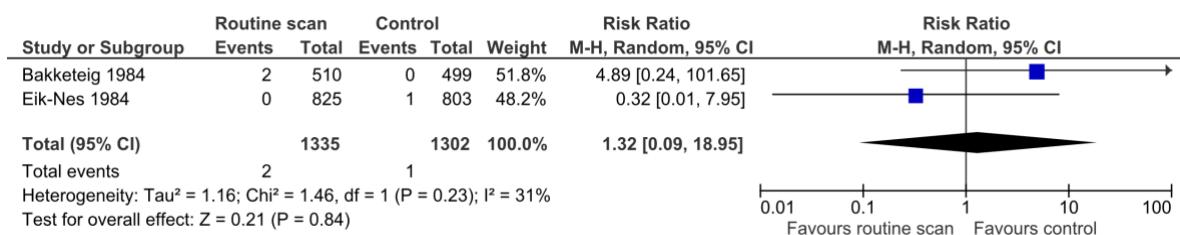


Figure 26. Forest plot on the use of routine second trimester ultrasound versus selective ultrasound in complications of placenta previa

The study of Bakkeig (1984) reported two pregnancies with placenta previa, both of which occurred in the routine screening group – one did not attend the screening ultrasound and was diagnosed after a sudden onset of hemorrhage while the other one was diagnosed with low-lying placenta at 29 weeks AOG and had hemorrhage and onset of labor at 32 weeks AOG. She delivered via Caesarean section a live baby weighing 1,745 grams. There were no cases of placenta previa in the selective ultrasound group and no cases of abruptio placenta in both groups.

The study of Eik-Nes (1984) reported three pregnancies with placenta previa – one occurred in the routine screening group and two in the selective ultrasound group. The woman in the routine screening group had an uneventful pregnancy and delivered at 34 weeks AOG. One woman in the selective ultrasound group had minor bleeding at 30 weeks AOG and delivered electively without complications. The second woman in the selective ultrasound group had bleeding at 33 weeks AOG and delivered via emergency Caesarean section. The baby was asphyxiated and hospitalized for 33 days at the neonatal ward and was later discharged without sequelae. There were 4 cases of low-lying placenta in the routine screening group but they were not previa by 32 weeks AOG.

Small for gestational age

One study reported the number of infants that were small for gestational age and the evidence was inconclusive (RR: 1.49, 95% CI: 0.93 to 2.38, n = 1,009) (15). The evidence has low certainty due to study design limitations (lack of blinding and pre-registered protocols, unclear allocation concealment, attrition bias) and imprecision (wide confidence interval crossing the line of no effect).

Induction of labor for postterm pregnancy

Routine second trimester ultrasound was associated with decreased induction of labor for postterm pregnancy (RR: 0.48, 95% CI: 0.32 to 0.73, $I^2 = 70\%$, n = 24,511). There were fewer inductions of labor for postterm pregnancy in the routine ultrasound group (1.6%) compared to the selective ultrasound group (2.8%), presumably due to more accurate dating. The decrease in induction of labor was hypothesized to be beneficial as it can decrease rates of Cesarean section. The evidence has low certainty based on 6 RCTs with study design limitations (lack of blinding and pre-registered protocols, and unclear allocation concealment, one has selection bias while another has attrition bias) and inconsistency (heterogeneity) (10–15,17–18).

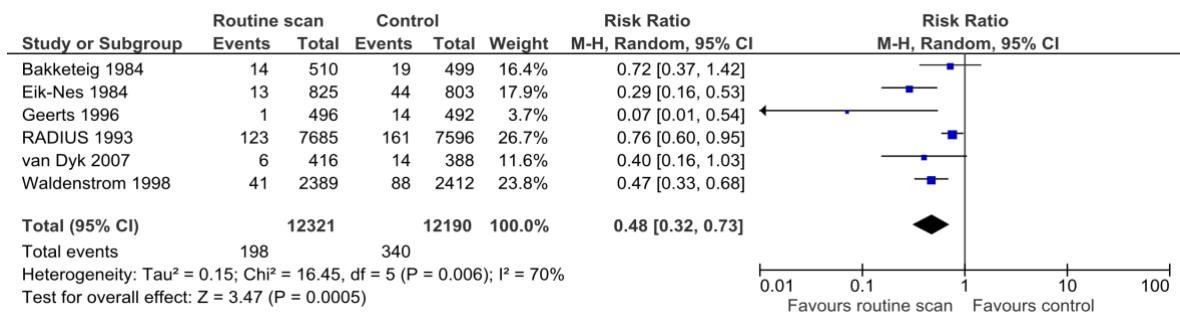


Figure 27, Forest plot on the use of routine second trimester ultrasound versus selective ultrasound in induction of labor for postterm pregnancy

Accuracy in fetal aging

Second trimester ultrasound (18-22 weeks AOG) underestimated the true gestational age by a mean of -0.1 ± 0.4 days ($p = 0.87$) for singletons, -0.6 ± 0.3 days ($p = 0.083$) for twins, and -0.6 ± 0.5 days ($p = 0.21$) for triplets, insignificantly(9). When compared to first trimester ultrasound estimates, second trimester estimates were more variable (*i.e.*, had a larger random error) so that the accuracy was better in the first trimester. This evidence has high certainty of evidence.

Overall Certainty of Evidence

The overall certainty of evidence is low. This was rated down primarily due to limitations in study design. Due to the nature of the intervention, it was impossible to blind pregnant participants and providers of care. Many of the trials were also conducted before it was customary for trials to be registered and protocols published. The study of Bakketeig (1984) had attrition bias as 10.6% of women in the screening group failed to attend the scheduled ultrasound. The study of van Dyk (2007) had serious selection bias. All women presenting on a single day were defined as a cluster. This could lead to bias as the next day of presentation could be affected by transport or community activities. Moreover, allocation concealment was done by blinded selection of cards from a box. Half of the cards were marked A and half were marked B. If an A is drawn, the cluster was assigned to the ultrasound group. Staff would then be aware of allocation at the point of randomization. Other reasons for rating down certainty of evidence include issues on imprecision (wide confidence interval) and inconsistency (heterogeneity) for some outcomes.

In the study of Kalish (2004) on the accuracy of ultrasound in fetal aging, it was unclear if the index test (screening ultrasound) was performed without knowledge of the reference standard (true gestational age as determined by date of fertilization via IVF + 14 days). No other potential sources of bias were found hence the overall assessment was low risk for bias.

4.7.3 Cost Implication

The cost of routine antenatal ultrasound in government facilities ranges from PhP 250 to 500 as of 2021 (19,20). Special tests such as biophysical profile scoring, congenital anomaly scanning, and placental doppler may each cost around PhP 500 on top of the usual routine first and second trimester ultrasound. For private institutions, clinics or diagnostic centers, regular ultrasound and special procedures may range from PhP 700 to 5,500 (21,22).

Table 12. Cost of ultrasound procedures in Dr. Jose Fabella Memorial Hospital as of 2021, September 28.

Procedure	Cost (PhP)
Transvaginal Sonography (1st trimester)	250.00
Transabdominal Sonography (2nd trimester)	250.00
Biophysical Profile Scoring	490.00
Congenital Anomaly Scanning	500.00
Placental Doppler	500.00
OB Doppler (Doppler Velocimetry)	500.00
First Trimester Ultrasound Screening Markers	500.00
OB 3D/4D	600.00
Fetal Echo	700.00

4.7.4 Equity, Acceptability, and Feasibility

One study by Kelly-Hedrick (2023) done in the US ($n = 289$) explored the views of pregnant women on receiving abnormal ultrasound findings, and the effect of these abnormal findings on decision-making and whether or not to terminate pregnancy (23). Pregnant patients above 18 years old who presented to Johns Hopkins Hospital for scheduled antenatal ultrasounds (any trimester) were recruited in the study. Participants were given a questionnaire containing close-ended and open-ended items regarding their desire to know abnormal results, if abortion is an option if results are not normal, and reasons behind their responses. Results showed that 95% of the participants wanted information on abnormal ultrasound results, but only half would consider abortion or terminating the pregnancy due to congenital anomalies. Some of the reasons for desiring abnormal finding disclosure included preparedness, valuing knowledge, and for informed decision-making. Cited perspectives on termination were mostly about weighing harms and benefits, maternal duties, and deeming termination as morally impermissible or permissible.

In addition, based on the 2015 circular of the Philippine Health Insurance Corporation (PHIC/PhilHealth) on the benefits for women about to give birth, the case rate for the antenatal package is worth PhP 1,500 (24). Requirements include updated contributions to the social health insurance, at least four prenatal check-ups with the last one during the third trimester, and proper documentation and referral for delivery. However, this amount shouldered by PhilHealth is not enough to cover for the expenses incurred by any patient seeking private consultation and imaging.

No cost-effectiveness or economic evaluation studies were found on doing routine, first trimester or second trimester ultrasound.

4.7.5 Recommendations from Other Groups

The recommendations from other professional groups are presented in Table 13 below.

Table 13. Summary of existing guideline recommendations (2nd Trimester Ultrasound)

Guideline	Recommendation	Strength of Recommendation	Level of Evidence
International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) Practice Guidelines (updated): performance of the routine mid-trimester fetal ultrasound scan (ISUOG 2022) (25)	<ul style="list-style-type: none"> ● All pregnant women should be offered a mid-trimester scan as part of routine pregnancy care ● A routine mid-trimester ultrasound scan can be performed between about 18 and 24 weeks of gestation, depending on technical considerations and local legislation ● A routine mid-trimester fetal ultrasound examination includes an evaluation of the following: <ul style="list-style-type: none"> ○ cardiac activity ○ fetal number (and chorionicity and amnioticity in cases of multiple pregnancy) ○ gestational age/fetal size ○ basic fetal anatomy ○ placental appearance and location ○ amniotic fluid volume 	N/A	N/A

National Institute for Health and Care Excellence (NICE) Antenatal Care (5) (NICE 2021)	<ul style="list-style-type: none"> Offer pregnant women an ultrasound scan to take place between 18+0 weeks and 20+6 weeks to: <ul style="list-style-type: none"> screen for fetal anomalies determine placental location 	N/A	N/A
The Society of Obstetricians and Gynaecologists of Canada (SOGC) Guideline No. 223: Content of a Complete Routine Second Trimester Obstetrical Ultrasound Examination and Report (26) (SOGC 2017)	<ul style="list-style-type: none"> Pregnant women should be offered a routine second trimester ultrasound between 18 and 22 weeks' gestation Second trimester ultrasound should screen for the number of fetuses, gestational age, and the location of the placenta Second trimester ultrasound should screen for fetal anomalies 	Level II-2 Level II-1 Level II-2	Grade B Grade A Grade B
The Society of Obstetricians and Gynaecologists of Canada (SOGC) No. 388: Determination of Gestational Age by Ultrasound (27) (SOGC 2019)	<ul style="list-style-type: none"> In the absence of better assessment of gestational age, routine ultrasound in the first or second trimester reduces inductions for postterm pregnancies Ideally, every pregnant woman should be offered a first-trimester dating ultrasound; however, if the availability of obstetrical ultrasound is limited, it is reasonable to use a second-trimester scan to assess gestational age 	Level I Level I	N/A N/A
American College of Obstetrician and Gynecologists (ACOG) Practice Bulletin #175: Ultrasound in Pregnancy (28) (ACOG 2016)	<ul style="list-style-type: none"> Ultrasonography can be beneficial in many situations in the second and third trimesters. Some of the indications are: <ul style="list-style-type: none"> To confirm the presence of an intrauterine pregnancy To evaluate a suspected ectopic pregnancy 	N/A	N/A

-
- To diagnose or evaluate multiple gestations
 - To confirm cardiac activity
 - To assess for certain fetal anomalies, such as anencephaly, in patients at high risk
 - To screen for fetal aneuploidy
-

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4.8 Screening for Risk for Pre-eclampsia

RECOMMENDATION

We suggest assessing the risk for preeclampsia in the first trimester in all pregnant women. (*WEAK recommendation, very low level of evidence*)

Considerations

The Consensus Panel considered the following when formulating this recommendation:

- The guideline question dealt with screening using any strategy (either maternal factors alone or multimarker screening).
- The paucity of direct trials that looked into the entire screening cascade for preeclampsia contributed to the very low level of evidence. The recommendation statement also takes into account the indirect evidence of the related treatment (i.e., low-dose aspirin from 5 RCTs) among women identified as being at risk for preeclampsia. Maternal risk factors alone ($n = 4$ RCTs) and multimarker screening comprising maternal risk factors, biomarkers, and uterine artery pulsatility index evaluated via ultrasound ($n = 1$ RCT) were used to identify these women at risk for the disorder. Despite the inconclusive effects on other critical and important outcomes, such as preterm labor, stillbirth, maternal bleeding, and neonatal hemorrhage, there was a reduction in perinatal death in the trials.
- Recommendations from ACOG and NICE can be used to guide healthcare providers, particularly those in primary care settings, on the maternal factors that identify those at risk and can be used as bases to provide prophylactic management or linked treatment (i.e., low-dose aspirin): any of the high-risk factors for pre-eclampsia, such as previous pregnancy with preeclampsia, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes mellitus, and chronic hypertension), and those with more than one of the moderate-risk factors (first pregnancy, maternal age of 35 years or older, a body mass index of more than 30, family history of preeclampsia, sociodemographic characteristics, and personal history factors).
- The subsequent question/recommendation for pre-eclampsia then specifies the screening test that should be performed.

4.8.1 Burden of disease

Epidemiology and Natural Course of the Disease

Preeclampsia is commonly defined as new-onset hypertension with proteinuria or end-organ dysfunction after 20 weeks age of gestation (AOG) (1). It is among the classification of hypertensive disorders of pregnancy which may also include gestational hypertension and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets).

According to global estimates, preeclampsia occurs in about 1 in 20 deliveries (2). Local prevalence is more uncertain, but 18.3% of pregnancies is complicated by hypertension

based on National Nutrition Survey figures (3). Eclampsia (16.0%) and gestational hypertension with significant proteinuria (14.7%) are the top causes of maternal death in the Philippines (4).

Management

Managing preeclampsia involves treating hypertension, preventing seizures and delivery in a timely manner (5). Severe features (e.g., SBP \geq 160 mmHg, DBP \geq 100 mmHg, visual disturbances) are associated with maternal morbidity and thus are indications for more urgent delivery (5).

Low-dose aspirin has been used in early pregnancy to prevent preeclampsia. The latest local guidance from POGS recommends giving aspirin before 16 weeks AOG in patients at high risk of developing hypertensive disorders in pregnancy (6).

There are two general approaches to stratify pregnant patients according to their risk for preeclampsia. NICE and ACOG recommend using maternal characteristics (e.g., hypertensive disease in a prior pregnancy, chronic kidney disease, diabetes) to select patients for aspirin prophylaxis (7). Meanwhile risk calculators such as that from the Fetal Medicine Foundation utilize a prediction model based on competing risks and Bayes' theorem (8). The latter involves a combination of maternal factors as well as biomarkers (i.e., placental growth factor (PIGF) and pregnancy-associated plasma protein A [PAPP-A]).

Economic and Social impact of the disease

One study from a private hospital found that management of early preeclampsia costs P119,687.02 to P149,687.02 (9). Meanwhile, for late preeclampsia urgent care and delivery amount to P103,587.02 to P133,587.02 (9).

4.8.2 Benefits, Harms and Diagnostic Performance of Screening Tests

Screening Cascade

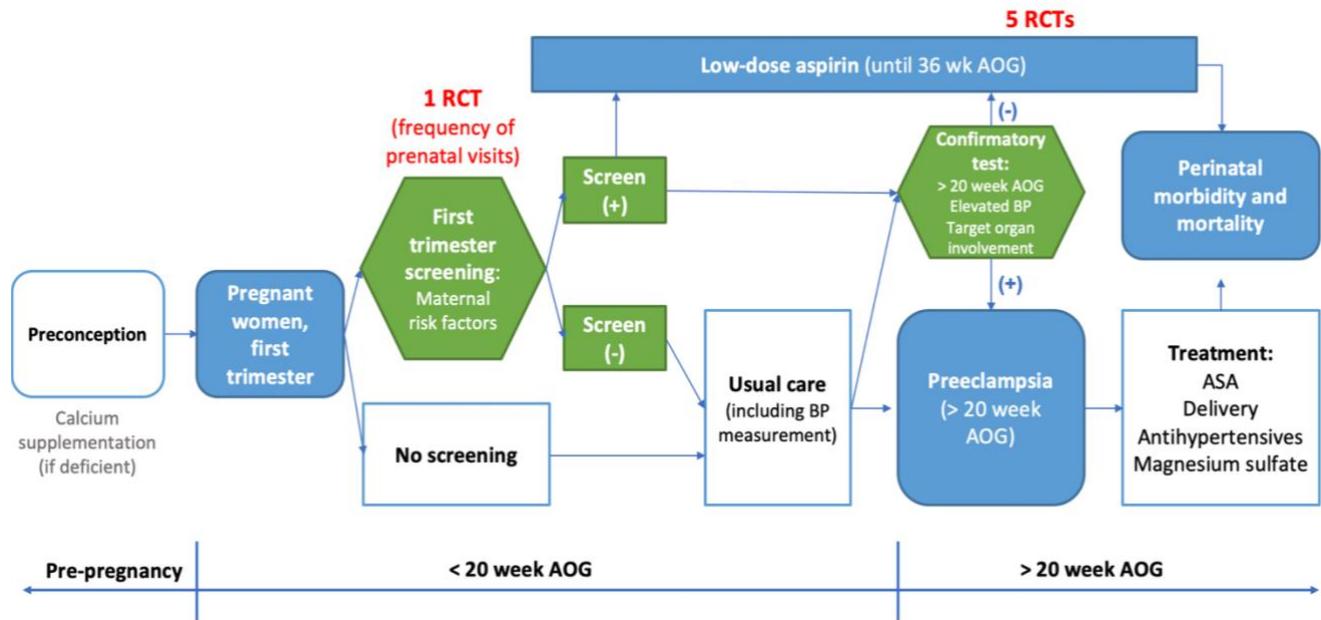


Figure 27. Screening cascade for preeclampsia.

The first trimester screening among pregnant women include any strategies to screen for pre-eclampsia. Pregnant women who test positive throughout the screening process will be prescribed low-dose aspirin and confirmatory test, whilst those who test negative will get standard care and also require additional confirmatory testing. Mothers who initially tested positive for high-risk preeclampsia and have been adhering to a regimen of low-dose aspirin, but then tested negative in the confirmatory test, are advised to continue taking low-dose aspirin until they reach 36 weeks of gestation. Mothers who were diagnosed with pre-eclampsia in the confirmatory test will receive therapy, which involves the use of low-dose aspirin until they reach 36 weeks of gestation.

Preterm labor

Fewer antenatal visits, and thus less frequent preeclampsia screening, did not significantly increase the risk of preterm labor < 37 weeks AOG (RR: 1.01, 95% CI: 0.86 to 1.18).

Stillbirth

The risk of stillbirth was not statistically significant between groups that had less and more frequent prenatal visits (RR: 1.00, 95% CI: 0.54 to 1.86).

Perinatal death

The risk of perinatal death was reduced by half with intake of low-dose aspirin < 16 weeks into the pregnancy (RR 0.47, 95% CI 0.25 to 0.88). Additionally, meta-regression found

a similar reduction in prenatal death even in pregnancies without preeclampsia (RR: 0.40, 95% CI: 0.19 to 0.78).

Other outcomes

No evidence was found for maternal death, eclampsia, HELPP syndrome and multiorgan dysfunction.

Overall Certainty of Evidence

Indirectness was downgraded because a trial investigated frequency of prenatal visits rather than a screening strategy (10), and indirect evidence was also used on aspirin prophylaxis (11). There was also downgrade for serious risk of bias due to unclear allocation concealment and lack of blinding, while wide confidence intervals resulted in imprecision for preterm labor and stillbirth outcomes. Hence, the overall certainty of evidence across the critical outcomes is very low.

4.8.3 Cost Implication

A local economic evaluation of first trimester preeclampsia screening and early treatment with aspirin determined net cost savings of Php 69,694.02 and Php 53,594.02 for early and late preeclampsia respectively (9). No local cost-effectiveness studies involving multimarker screening was available.

The suggested retail prices for Aspirin 80-mg and 100mg-tablets are Php 1.03-3.13 and Php 1.79-2.54 respectively. (DOH, 2021) In the cost-effectiveness study, the costs cited for the screening strategy are Php 9,405 for first-trimester ultrasound and Php 588 for aspirin (9).

4.8.4 Equity, Acceptability, and Feasibility

No research evidence was found on patient preferences on preeclampsia screening. Additionally, no social, equity and health systems impact assessments of preeclampsia screening were found.

4.8.5 Recommendations from Other Groups

Several guidelines recommend a minimum screening for preeclampsia with clinical risk markers (1, 12-15) usually at the first visit (12,13). NICE and USPSTF recommend measuring blood pressure at each visit, while NICE recommends offering urine dipstick at every appointment. Recent guidelines also recommend using a combination of clinical risk markers, blood pressure, uterine artery pulsatility index and PIGF if available (12,14,15). Recommendation statements from various groups are summarized in Table 14.

Locally, the latest available guidelines do not have a recommendation statement for particular preeclampsia screening strategies. POGS 2015 does recommend initiation aspirin before 16 weeks AOG in pregnant patients at high risk for developing hypertensive disorders.

Table 14. Summary of existing guideline recommendations (pre-eclampsia)

Guideline	Recommendation
International Society for the Study of Hypertension in Pregnancy (ISSHP) 2022 The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice	<ul style="list-style-type: none"> At minimum, women should be screened for clinical risk markers of pre-eclampsia risk at antenatal care booking (good practice point). If testing is available, after appropriate counselling, women should be screened at 11–14 weeks for preterm pre-eclampsia risk, using a combination of clinical risk factors, BP, uterine artery pulsatility index, and PIGF, as available, even if they have been already been identified as having clinical 'high-risk' factors ($\oplus\oplus\oplus O$/Strong).
Society of Obstetrician and Gynaecologists of Canada (SOGC) 2022 Guideline No. 426: Hypertensive Disorders of Pregnancy: Diagnosis, Prediction, Prevention, and Management	<ul style="list-style-type: none"> In early pregnancy, women should be screened, at a minimum, for clinical risk markers for preeclampsia (strong, moderate). If testing is available, women should be screened at 11–14 weeks gestation using a combination of clinical risk markers, uterine artery pulsatility index, and placental growth factor (PIGF) to individualize the risk of developing preeclampsia (strong, moderate). At the first antenatal (booking) appointment and again in the second trimester, assess the woman's risk factors for pre-eclampsia, and advise those at risk to take aspirin in line with the section on antiplatelet agents in the NICE guideline on hypertension in pregnancy. Measure and record the woman's blood pressure at every routine face-to-face antenatal appointment using a device validated for use in pregnancy, and following the recommendations on measuring blood pressure in the NICE guideline on hypertension in adults. Offer a urine dipstick test for proteinuria at every routine face-to-face antenatal appointment.
National Institute for Health and Care Excellence (NICE) / Royal College of Obstetrics & Gynaecologists (RCOG) 2021 Antenatal Care	<ul style="list-style-type: none"> Women with any of the high-risk factors for preeclampsia (previous pregnancy with preeclampsia, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes mellitus, and chronic hypertension) and those with more than one of the moderate-risk factors (first pregnancy, maternal age of 35 years or older, a body mass index of more than 30, family history of preeclampsia, sociodemographic characteristics, and personal history factors) should receive low-dose (81 mg/day) aspirin for preeclampsia prophylaxis, initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks of gestation) and continuing until delivery.
American College of Obstetrics and Gynecologists (ACOG) 2020 ACOG Practice Bulletin: Gestational Hypertension and Preeclampsia	

International Federation of Gynecology and Obstetrics (FIGO) 2019	<ul style="list-style-type: none"> Universal screening: All pregnant women should be screened for preterm PE during early pregnancy by the first-trimester combined test with maternal risk factors and biomarkers as a one-step procedure. The best combined test is one that includes maternal risk factors, measurements of mean arterial pressure (MAP), serum placental growth factor (PIGF), and uterine artery pulsatility index (UTPI). Where it is not possible to measure PIGF and/or UTPI, the baseline screening test should be a combination of maternal risk factors with MAP, and not maternal risk factors alone. Contingent screening: Where resources are limited, routine screening for preterm PE by maternal factors and MAP in all pregnancies and reserving measurements of PIGF and UTPI for a subgroup of the population (selected on the basis of the risk derived from screening by maternal factors and MAP) can be considered. Screen for preeclampsia with blood pressure measurements throughout pregnancy. (Grade B)
US Preventive Services Task Force (USPSTF) 2017	
Screening for Preeclampsia US Preventive Services Task Force Recommendation Statement	

Philippine Obstetrical and Gynecological Society (POGS) 2015	<ul style="list-style-type: none"> No recommendation statement on screening strategy (only narrative on evidence) Aspirin should be given to patients at high risk for development of hypertensive disorders of pregnancy. (Level I, high grade) Aspirin should be given starting < 16 weeks age of gestation. (Level I, high grade)
Clinical Practice Guidelines on Hypertension in Pregnancy (3 rd ed.)	

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4.9 Screening for Pre-eclampsia

RECOMMENDATION

We suggest using multimarker screening rather than maternal risk factors alone to assess the risk for pre-eclampsia in the first trimester in all pregnant women. (*WEAK recommendation, low level of evidence*)

Considerations

The Consensus Panel considered the following when formulating this recommendation:

- The evidence suggests that multimarker screening is more accurate than using maternal risk factors alone. Multimarker screening includes prediction models or risk calculators that take into account variables such as maternal factors, biomarkers (i.e., placental growth factor (PIGF) and pregnancy-associated plasma protein A [PAPP-A]), and/or uterine artery pulsatility index from an ultrasound.
- The consideration of feasibility concerns and resource constraints was prompted by the potentially high cost associated with multimarker screening. Nonetheless, for patients in low-resource settings, a contingent screen that includes maternal risk factors and arterial pressure without the uterine artery pulsatility index or serum biomarkers can be done. Risk calculators used in multimarker screening allow risk assessment even in the presence of incomplete data.

4.9.1 Burden of disease

Epidemiology and Natural Course of the Disease

Preeclampsia is commonly defined as new-onset hypertension with proteinuria or end-organ dysfunction after 20 weeks age of gestation (AOG) (1). It is among the classification of hypertensive disorders of pregnancy which may also include gestational hypertension and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets).

According to global estimates, preeclampsia occurs in about 1 in 20 deliveries (2). Local prevalence is more uncertain, but 18.3% of pregnancies is complicated by hypertension based on National Nutrition Survey figures (3). Eclampsia (16.0%) and gestational hypertension with significant proteinuria (14.7%) are the top causes of maternal death in the Philippines (4).

Management

Managing preeclampsia involves treating hypertension, preventing seizures, and delivering in a timely manner (5). Severe features (e.g., SBP \geq 160 mmHg, DBP \geq 100 mmHg, visual disturbances) are associated with maternal morbidity and thus are indications for more urgent delivery (5).

Low-dose aspirin has been used in early pregnancy to prevent preeclampsia. The latest local guidance from POGS recommends giving aspirin before 16 weeks AOG in patients at high risk of developing hypertensive disorders in pregnancy (6).

There are two general approaches to stratify pregnant patients according to their risk for preeclampsia. NICE and ACOG recommend using maternal characteristics (e.g., hypertensive disease in a prior pregnancy, chronic kidney disease, diabetes) to select patients for aspirin prophylaxis (7). Meanwhile risk calculators such as that from the Fetal Medicine Foundation, utilize a prediction model based on competing risks and Bayes' theorem (8). The latter involves a combination of maternal factors as well as biomarkers (i.e., placental growth factor (PIGF) and pregnancy-associated plasma protein A [PAPP-A]).

Economic and Social impact of the disease

One study from a private hospital found that management of early preeclampsia costs P119,687.02 to P149,687.02 (9). Meanwhile, for late preeclampsia urgent care and delivery amount to P103,587.02 to P133,587.02 (9).

4.9.2 Benefits, Harms and Diagnostic Performance of Screening Tests

Screening Cascade

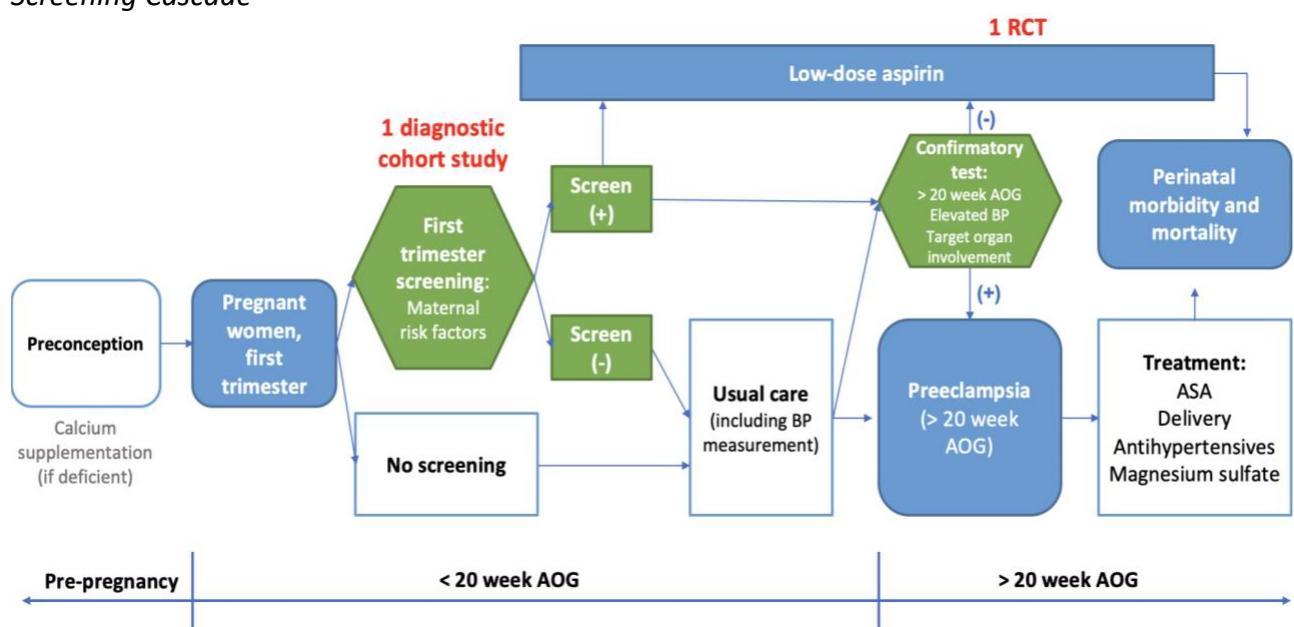


Figure 28. Screening cascade for preeclampsia

Early neonatal death

The use of serum PIGF was associated with reduced early neonatal death, on average, but the difference was not statistically significant (RR: 0.43, 95% CI: 0.11 to 1.64).

Eclampsia

The risk of eclampsia was similar between intervention and control groups (0% vs 0.2%, $p = 0.27$).

Preterm delivery

The addition of serum PIGF to routine care did not significantly reduce the risk of preterm delivery among pregnant women with suspected preeclampsia (RR: 0.92, 95% CI: 0.79 to 1.08).

HELLP syndrome

The risk of developing HELLP syndrome (hemolysis, elevated liver enzymes and low platelet) was not significantly different with PIGF screening (RR: 1.18, 95% CI: 0.17 to 8.38).

Maternal death

There was no significant difference in the risk of maternal mortality between groups (0.1% vs 0%, $p = 0.47$).

Diagnostic accuracy

Both mini-combined test and the NICE method had similar true negative rates (specificity 0.91 [95% CI: 0.90 to 0.91] vs 0.90 [95% CI: 0.90 to 0.91], respectively). However, the combination of PAPP-A, MAP and maternal factors was more sensitive for preeclampsia than maternal characteristics alone (0.43 [95% CI: 0.38 to 0.47] vs 0.30 [95% CI: 0.26 to 0.35], respectively). The odds of preeclampsia is increased by about four times with a positive multimarker screen and by about three times with a positive result by NICE method (positive likelihood ratio of 4.56 and 3.13, respectively).

Other outcomes

No evidence was found for maternal multiorgan dysfunction and stillbirth.

Overall Certainty of Evidence

The certainty of evidence was downgraded twice for very serious indirectness because 1) the trial involved women already suspected to have preeclampsia (> 20 weeks), 2) the screening test used serum PIGF solely, and 3) the management algorithm did not specify aspirin use (1). It was also downgraded for imprecision for most outcomes due to the wide confidence intervals. For diagnostic accuracy, which is not a critical outcome, it was downgraded once for indirectness (screening test used PAPP-A but not PIGF).

Overall, among critical outcomes, the certainty of evidence was very low.

4.9.3 Cost Implication

No local cost-effectiveness studies on multimarker screening for preeclampsia were found. The suggested retail prices for Aspirin 80-mg and 100mg-tablets are Php 1.03-3.13 and Php 1.79-2.54 respectively (3).

4.9.4 Equity, Acceptability, and Feasibility

No research evidence was found on patient preferences on preeclampsia screening. Also, no social, equity and health systems impact assessments of preeclampsia screening were found.

4.9.5 Recommendations from Other Groups

Most guidelines recommend screening for preeclampsia with a minimum of maternal risk factors (4-8). Some guidelines also recommend using a combination of clinical risk markers, blood pressure, uterine artery pulsatility index and PIgf if available (ISSHP 2022, SOGC 2022 and FIGO 2019) (4,6,8).

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4.10 Screening for Iron Deficiency Anemia

RECOMMENDATION

We suggest against screening for iron deficiency anemia using complete blood count among all asymptomatic pregnant Filipino women to improve maternal and perinatal outcomes. (WEAK recommendation, very low level of evidence)

Considerations

The Consensus Panel considered the following when formulating this recommendation:

- There is no direct evidence found that assessed screening for IDA using CBC in pregnancy to improve maternal and perinatal outcomes. There is only indirect evidence with moderate certainty on accuracy of CBC (particularly Hct < 35.5%) in detecting IDA among Filipino women and indirect evidence with very low certainty on (1) association of maternal anemia and adverse maternal and perinatal outcomes and (2) association of lower rates of low birthweight infants and daily maternal supplementation without the need for CBC screening.
- Based on WHO guidelines, CBC is not recommended for determining the need for iron supplementation. Instead, the prevalence of anemia in a certain population should already be considered as a determining factor for the dosage of iron supplementation in patients. In the country, anemia is at 25.5%, and for those in the 20-40% range, 30 mg of elemental iron in the first trimester and doubled in the second trimester should be given.
- Practice variation with regards to iron supplementation among OB-GYN/private practitioners and midwives was also considered. In the rural setting, midwives give iron supplements in the first visit of the patient. While for OB-GYN, iron supplement is not prescribed in the first visit, especially in the first trimester because, during this period, the iron demands are not that high and iron supplementation could aggravate nausea and vomiting. Only folic acid is then provided, and iron is started in the second trimester or when IDA is detected. There are no written guidelines, but this timing followed by OB-GYN is based on textbooks on prenatal care and POGS CPG on maternal nutrition stating that iron stores are still sufficient in the first trimester.

4.10.1 Burden of disease

Epidemiology, Natural Course, Management, Economic impact, and Social impact of the Disease

Anemia is known to be prevalent in pregnancy. In the Philippines the prevalence of anemia in pregnant women has steadily decreased from 42.3% in 2000 to 25.5% in 2019 (1). Of this estimate, an overwhelming majority had mild (14.2%) and moderate (10.3%) anemia. Among pregnant Filipino women, the prevalence of severe anemia is estimated to be 1%, translating to around 139,000 cases.

Among the pathologic causes of anemia in pregnancy, iron deficiency anemia (IDA) is widely accepted as the most frequently occurring condition (2). However, confirmation of IDA cases is limited because the gold standard for iron deficiency diagnosis remains to be the absence of stainable reticuloendothelial iron on bone marrow specimen. In clinical practice the surrogate markers of low serum ferritin or decreased transferrin saturation by iron are used (3).

Furthermore, associations between maternal IDA with adverse outcomes appear inconsistent, but maternal anemia may predispose to worse outcomes. The observational studies assessing the relationship between iron deficiency with or without anemia show inconsistent or no association for outcomes such as post-partum hemorrhage, low birth weight, small for gestational age at birth, and perinatal mortality. Moreover, a systematic review of 19 observational studies and 8 randomized controlled trials (RCTs) found unclear associations between low iron status in pregnancy and offspring behavior, cognition, and academic achievement (4). Assessing the true impact of IDA in pregnancy on maternal and perinatal outcomes may also be confounded by the evidence suggesting that maternal anemia is more common in socioeconomically disadvantaged populations (5,6), predisposing to worse outcomes.

Screening for maternal anemia is also widely practiced. Professional medical societies recommend screening for maternal anemia and treating iron deficiency (7–10) partly due to the increased iron demands during pregnancy (11). Iron is an essential element and cofactor in many physiologic processes including heme generation, cerebral nervous system development, and immune system maturity (3). Iron demands increase substantially in pregnancy to support fetoplacental development and maternal gestational adaptations that rationalizes supplementation (12).

Although supplementation in pregnancy is widely available, evidence for improved outcomes in the offspring is still unclear. While generally considered acceptable in pregnancy (13), oral iron supplementation using ferrous sulfate or ferrous fumarate has unassigned pregnancy risk category from the US Food and Drugs Administration and is considered exempt from assessment by the Australian Therapeutic Goods Administration (14).

A review of reviews found inconsistent effects of maternal antenatal and early childhood oral iron interventions on early and long-term childhood cognitive outcomes (15). The existing studies suggest no or minimal benefit with use of antenatal iron supplementation on infant and childhood outcomes and are riddled with methodological heterogeneity due to discrepancies in the anemia definitions used, differences in follow-up times, and overall study quality.

4.10.2 Benefits, Harms and Diagnostic Performance of Screening Tests

Screening Cascade

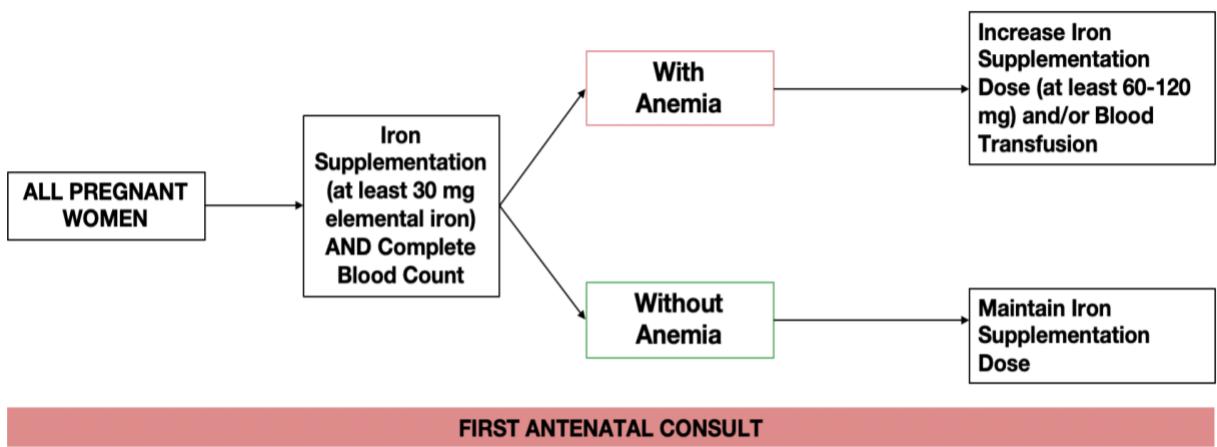


Figure 28. Screening cascade for IDA

In practice, at the first prenatal consult, all pregnant women are given supplementation of at least 30 mg of elemental iron in anticipation of the demands of pregnancy.

Complete blood count is performed to diagnose and quantify the level of anemia. Women with anemia undergo increased iron supplementation and/or blood transfusion, and are monitored to term; while women without anemia are advised to continue iron supplementation to term. (Figure 28)

Direct Evidence

No evidence was found that directly assessed screening for IDA using CBC in pregnancy to improve maternal and perinatal outcomes.

Indirect Evidence

Association between Maternal Anemia and Adverse Outcomes (Table 15)

Preterm labor and delivery

Based on the meta-analysis involving 26 studies (18–20,22,27,31,33,36,40–44,48,50–52,54,56,57,59–62,65,66) ($n = 4,925,319$), maternal anemia is significantly associated with 69% greater odds (OR: 1.69, 95% CI: 1.45 to 1.96) of preterm birth compared to absence of maternal anemia. There was significant heterogeneity which was attributed to differences in study design and methodologies. The certainty of evidence was deemed to be very low due to study design, indirectness, and inconsistency.

In the Cochrane review of 3 studies ($n = 4,449$), iron supplementation during pregnancy was associated with 4% lower risk of preterm birth, but the effect was not statistically significant (RR: 0.96, 95% CI: 0.81 to 1.14). There was minimal heterogeneity, and certainty of evidence was deemed to be low due to indirectness and imprecision.

Perinatal/neonatal mortality

For the meta-analysis of 23 studies (20–22,26,29–31,33–37,44,46,47,50,52,56,58,59,62–64) ($n = 4,043,426$), maternal anemia is significantly associated with 26% greater odds (OR: 1.26, 95% CI: 1.05 to 1.52) of perinatal or neonatal death compared to absence of maternal anemia. There was significant heterogeneity which was due to differences in study design and methodologies. The certainty of evidence was deemed to be very low because of the study design, indirectness, and inconsistency.

In one study in the Cochrane review ($n = 2,495$), maternal iron supplementation was associated with 19% lower risk of neonatal death, but it was not statistically significant (RR: 0.81, 95% CI: 0.56 to 1.19). The certainty of evidence was deemed to be low due to indirectness and imprecision.

Infant mortality

There was only one cross-sectional study (39) ($n = 301$) that assessed maternal anemia and risks for offspring mortality within the first year of life. The study was conducted between 1999 and 2001 in Tanzania, a malaria-endemic area with moderate to high risk for severe anemia and considerable resource limitations. The threshold for anemia was at <80 g/L measured at the earliest time during pregnancy. The said study found that maternal anemia was significantly associated with more than four times greater odds of infant death (OR: 4.18, 95% CI: 1.57 to 11.12). The certainty of evidence was deemed to be very low due to study design and indirectness.

Maternal mortality

In the meta-analysis of two retrospective cohort studies (32,52) ($n = 460,239$), maternal anemia is associated with 50% greater odds of maternal death compared to absence of maternal anemia (OR: 1.50, 95% CI 1.02 to 2.21). Gonzales, 2012 (32) was conducted in Peru at varying levels of altitude and measured maternal hemoglobin at the third trimester. Maternal anemia of <90 g/L was significantly associated with maternal mortality, with greater odds seen among those living at higher altitudes. Rukuni, 2016 (52) was conducted in the United Kingdom and measured maternal hemoglobin at the earliest antenatal visit. The certainty of evidence was deemed to be very low due to study design and indirectness.

ADHD in the offspring

A population-based retrospective cohort study conducted in Sweden (61) involving 532,232 offsprings matched to 299,768 mothers was done to assess associations between maternal anemia and a range of neurodevelopmental conditions, with the greatest proportion being attention-deficit/hyperactivity disorder (ADHD). Maternal anemia was defined as hemoglobin <110 g/L measured prior to 30 weeks age of gestation. Offspring between 6 and 29 years of age at the end of the follow-up were reviewed for occurrence of offspring ADHD and maternal anemia. Unadjusted analysis shows that maternal anemia is

associated with 4% greater odds (OR: 1.04, 95% CI: 1.001 to 1.09) of occurrence of ADHD in the offspring. Upon adjustment for socioeconomic, maternal, and pregnancy-related factors, maternal anemia during the first 30 weeks of gestation is associated with 37% greater odds (OR: 1.37, 95% CI: 1.14 to 1.64) of ADHD in the offspring. The certainty of evidence was deemed to be very low due to study design, indirectness, and inconsistency.

Low birthweight

In a meta-analysis of 22 studies [18,20,23–25,27,28,33,36,38,41,45,50–55,57,59,62,66] (n = 805,746), maternal anemia is significantly associated with 54% greater odds of low birthweight offspring (OR: 1.54, 95% CI: 1.32 to 1.81) compared to absence of maternal anemia. There was significant heterogeneity which was attributed to differences in study design and methodologies. The certainty of evidence was deemed to be very low due to study design, indirectness, and inconsistency.

Based on the Cochrane review of 3 studies (n = 3,770), iron supplementation during pregnancy was significantly associated with 18% lower risk of low birthweight (RR: 0.82, 95% CI: 0.72 to 0.94). There was no heterogeneity and certainty of evidence was deemed to be moderate due to indirectness.

Neonatal ICU admission

For the meta-analysis of 6 studies (24,33,50,52,56,57) (n = 1,108,346), maternal anemia was associated with 14% greater odds of NICU admission compared to absence of maternal anemia. However, this is not statistically significant (OR: 1.14, 95% CI: 0.96 to 1.37). There was significant heterogeneity as a result of differences in study design and methodologies. The certainty of evidence was deemed to be very low due to study design, indirectness, and imprecision.

Table 15. Associations between maternal anemia and adverse outcomes

Outcomes	No. of Studies	n	OR	95% CI	<i>I</i> ² Statistic
Preterm birth	26	4,925,319	1.69	1.45 to 1.96	99%
Perinatal or neonatal death	23	4,043,426	1.26	1.05 to 1.52	89%
Infant death	1	301	4.18	1.57 to 11.12	-
Maternal death	2	460,238	1.50	1.02 to 2.21	0%
ADHD in offspring	1	532,312	1.04	1.001 to 1.09	-
Low birthweight	22	805,746	1.54	1.32 to 1.81	90%
NICU admission	6	1,108,346	1.14	0.96 to 1.37	96%

Accuracy of CBC parameters

An accuracy study involving 170 Filipino women of reproductive age from Manila found that CBC parameters could satisfactorily discriminate iron deficiency anemia (73). Based on the QUADAS 2 tool, we deem the study to have unclear to low risk of bias. A

hematocrit cutoff value of 35.5% has an AUC of 0.96, with a 100% sensitivity and 93% specificity to detect iron deficiency anemia. Other CBC parameters such as mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were also found to have satisfactory performance. The certainty of evidence was moderate due to serious risk of bias.

Effectiveness of Oral Iron Supplementation on Outcomes

Based on a meta-analysis that included 44 RCTs ($n = 43,274$ women) comparing the effects of daily oral supplements containing iron versus no iron or placebo on maternal and perinatal outcomes, there was no significant difference in the outcomes of infants delivered by pregnant women who received oral iron supplementation compared to those who did not. On the other hand, the risk of maternal anemia (Hgb less than 110 g/L) at term was lower in women who received oral iron supplementation during pregnancy compared to those who did not regardless of anemia status at baseline (RR: 0.30, 95% CI: 0.19 to 0.46). There was no significant difference between groups for other maternal outcomes.

Table 16 shows the results of subgroup analysis for perinatal outcomes according to baseline level of anemia. This analysis included 4 RCTs with 4,632 women with unspecified or mixed anemia status, i.e. trials where no screening for anemia level was done at baseline. Infants born to women who received oral iron supplementation had a lower risk of low birthweight compared to those born to women who did not receive oral iron supplementation (RR: 0.82, 95% CI: 0.72 to 0.94). There was no significant difference between treatment groups for preterm birth or neonatal death. Certainty of evidence was very low due to serious risk of bias, indirectness, and imprecision.

Table 16. Effect of oral iron supplementation on outcomes

Outcomes	No. of RCTs	n	RR	95% CI	I^2 Statistic
Preterm birth	3	4,449	0.96	0.81 to 1.14	4%
Neonatal death	1	2,495	0.81	0.56 to 1.19	-
Low birthweight	3	3,770	0.82	0.72 to 0.94	0

Overall Certainty of Evidence

No direct evidence was found on the use of screening for IDA in pregnancy. The available indirect evidence on the accuracy of CBC and the effectiveness of daily maternal oral iron supplementation is of very low certainty due to serious risk of bias, indirectness, and inconsistency.

4.10.3 Cost Implication

Partly because of the already widespread and longstanding use of complete blood count (CBC) to screen for maternal anemia in clinical practice, there were no cost-effectiveness studies found on its universal application nor studies assessing patient values and preferences on its use. However, CBC as a routine examination is widely available and

accessible as part of the PhilHealth primary care benefit package (74). The blood examination may be associated with some short-term discomfort and anxiety, which can be minimized by the relatively short turn-around time of routine CBC tests. Moreover, oral iron supplementation is also widely accessible, available, and affordable all over the Philippines and may even be dispensed at the level of the barangay health centers.

4.10.4 Equity, Acceptability, and Feasibility

The available indirect evidence does not support screening for maternal iron deficiency anemia nor anemia in general using complete blood count. Regardless of levels of maternal hemoglobin, the Cochrane subgroup analysis of mothers with unknown or mixed baseline anemia status found that daily maternal iron supplementation is beneficial in reducing occurrence of low birthweight infant. Hence, the use of CBC may be justified to diagnose and quantify, but not to screen, maternal anemia. Both CBC and iron supplementation may be covered under the PhilHealth prenatal care package (75).

4.10.5 Recommendations from Other Groups

The recommendations from other guidelines are summarized in Table 17 below.

Table 17. Summary of existing guideline recommendations (IDA)

Guideline	Recommendation	Strength of Recommendation	Level of Evidence
UK National Screening Committee 2021 (16)	A national screening programme for maternal iron deficiency anemia using complete blood count should NOT be recommended	Strong	-
ACOG Practice Bulletin 2021 (7)	All pregnant women should be screened for anemia with a complete blood count in the first trimester and again at 24 0/7 – 28 6/7 weeks of gestation	Strong	Level C (Based on consensus and expert opinion)
British Society for Haematology 2019 (8)	Haemoglobin concentration should be routinely measured at booking and at around 28 weeks' gestation.	Strong	Level D
US Preventive Services Task Force 2015 (76)	The current evidence is insufficient to assess the balance of benefits and harms of screening for iron deficiency anemia in pregnant women to prevent maternal health and birth outcomes.	No recommendation	Insufficient

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4.11 Screening for Undernutrition

RECOMMENDATION

We suggest screening for undernutrition via measurement of mid-upper arm circumference in all pregnant Filipino (adolescent and adult) women to improve perinatal outcomes. (WEAK recommendation, very low level of evidence)

Considerations

The Consensus Panel considered the following when formulating this recommendation:

- BMI is still regarded to be the standard tool for evaluating nutritional status. However, compared to BMI, MUAC was considered due to its stability across ages of gestation and practicality in local settings, particularly in humanitarian situations where tools, such as weighing scales, may be limited.
- Moreover, MUAC has already been included in existing protocols for assessing nutritional status among infants and children; thus, using it among pregnant women is considered viable. Cutoff values and their interpretation (i.e., ≤ 23.5 to ≤ 25 cm to detect undernutrition) must be provided. These reference points serve as essential guidelines for primary care health workers, enabling them to effectively utilize this information for the benefit of the general adult population, including pregnant women.
- More importantly, the evidence shows that compared to BMI cutoffs as reference standard for underweight, MUAC can clearly discriminate between underweight and non-underweight general adult populations.
- MUAC should only be used to screen for undernutrition in the first trimester. In the second and third trimesters, weight monitoring is crucial among pregnant women to ensure healthy weight gain.
- There is a research gap on the suitable cut-off levels for Filipino pregnant adolescents and women.

4.11.1 Burden of disease

Epidemiology, Natural Course, Management, Economic impact, and Social impact of the Disease

Undernutrition is associated with significant morbidity and mortality for both mother and infant. Being classified as underweight based on the body mass index (BMI) is associated with increased risk for preterm birth (RR: 1.29, 95% CI: 1.15 to 1.46) and low birth weight (RR: 1.64, 95% CI: 1.38 to 1.94) (1). Underweight pregnant women are also at higher risk of obstetric anal sphincter injuries and increased hospitalization compared to women with normal weight (2). Maternal and child undernutrition may indicate other physical and socioeconomic deprivations that predispose the dyad to worse outcomes (3).

According to the 8th Expanded National Nutrition Survey, the prevalence of nutritionally-at-risk pregnant women in the Philippines in 2018 was 20.1% (4). The national prevalence has steadily decreased from 30.7% in 1998, the first time the definition of nutritionally-at-risk based on weight-for-height measurements was implemented. The key subgroups deemed to be of particularly higher prevalence of being nutritionally-at-risk include pregnant women below 20 years of age, widowed/separated adult pregnant women, women who had at least elementary level education, those who were not working, those living in rural areas, and those in the poorest economic quintile. These local findings support the evidence base on the interplay between socioeconomic conditions and nutrition.

Since the use of the weight-for-height assessment in detecting nutritional risk among pregnant women in the 1990s, various nutritional assessment tools have been developed to improve outcomes (5,6). Some of the tools rely solely on anthropometry while others include diagnostic testing. The BMI remains to be one of the most widely used screening tools, primarily for overnutrition, despite increasing recognition of its limitations in differentiating weight from muscle mass and visceral fat (7). A challenge common to most nutritional screening tools is the amount of resources required to implement them universally, as even the accurate anthropometric measurements using weighing scales have been associated with challenges and limitations especially in the community setting (8).

Screening for undernutrition early in pregnancy and even in pre-pregnancy allows the implementation of early interventions. The latest Lancet Review on effective interventions to address maternal and child malnutrition found increasing evidence supporting the use of antenatal multiple micronutrient supplementation to prevent low birthweight and small-for-gestational age newborns; the use of supplementary food in food-insecure settings; and the implementation of nutrition-sensitive interventions such as improved water, sanitation, and hygiene promotion, preconception care, and malaria prevention (9).

In clinical practice, nutritional assessment begins at the first antenatal consult. Maternal anthropometric measurements such as weight and height are conducted, and women are classified accordingly. Underweight individuals are further assessed for organic causes and undergo dietary counselling. Overweight and obese individuals are further screened for other metabolic diseases such as screening for gestational diabetes mellitus. Regardless of BMI category, pregnant women require repeated assessments to monitor for appropriate gestational weight gain throughout the succeeding antenatal consults (6).

The mid-upper arm circumference (MUAC) is an alternative anthropometric measure to BMI in screening for malnutrition. The World Health Organization has recommended the use of certain MUAC cut-offs to screen for acute malnutrition in children 6-60 months of age. It has since become a global standard for severe acute malnutrition in children and used to monitor nutritional interventions in children (10). Currently there is no guidance from the WHO on the use of MUAC in adults or in pregnant women.

4.11.2 Benefits, Harms and Diagnostic Performance of Screening Tests

Screening Cascade

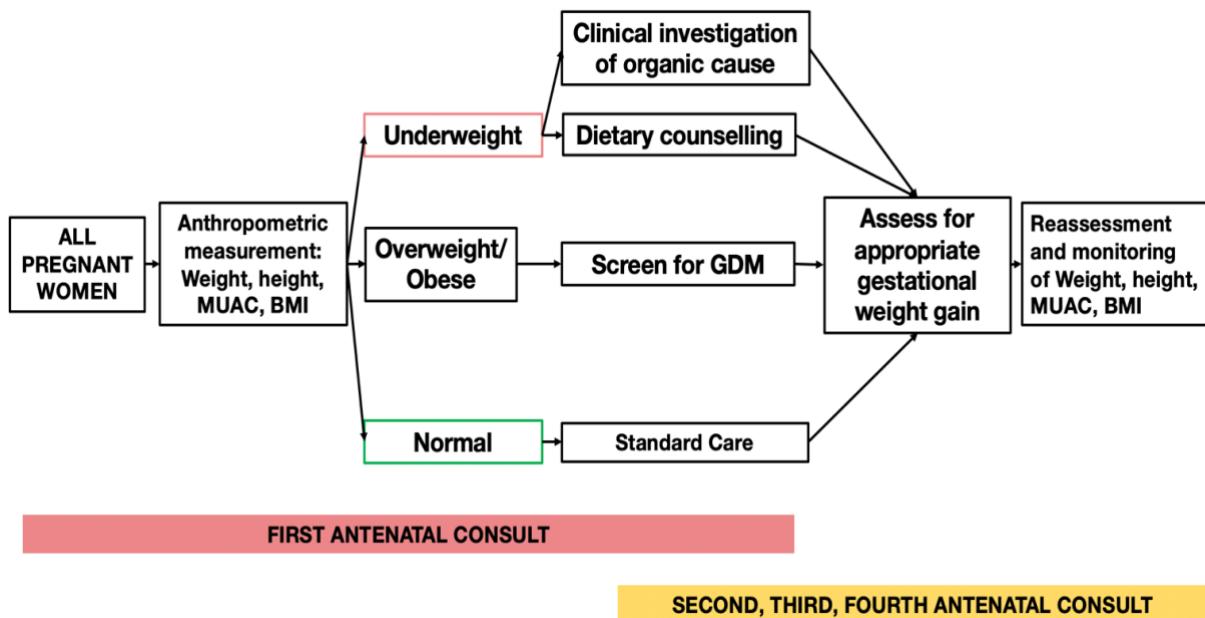


Figure 29. Screening cascade for undernutrition

The screening cascade for malnutrition in pregnant women is shown in Figure 29. Anthropometric measurement and classification are ideally done at the first antenatal consult. Pregnant women are classified if they are underweight, overweight/obese, or within normal. Interventions such as clinical investigation of organic causes, dietary counselling and intervention is then done for underweight pregnant women, wherein they are reassessed and monitored at subsequent antenatal visits. Overweight and obese pregnant women are screened for GDM and other metabolic disorders. For all weight categories, women are assessed for appropriate gestational weight gain throughout their pregnancy.

Direct and Indirect Evidence

No direct evidence was found on the use of MUAC as a screening tool among pregnant women to improve maternal and perinatal outcomes. Furthermore, no indirect evidence was seen on the diagnostic accuracy of MUAC among adults and among pregnant women, and on the association of low MUAC and adverse birth outcomes of interest.

Accuracy of MUAC

General adult population

An individual participant data meta-analysis analyzed data from 20 unique data sets ($n = 13,835$ non pregnant adults, 64.4% female, mean age 32.6 years) to determine appropriate MUAC cut-off values for accurate detection of low BMI ($<18.5 \text{ kg/m}^2$). The studies were drawn from Africa, South Asia, Southeast Asia, North America, and South America. The pooled area under the receiver operating curve (AUROC) was 0.91 (range: 0.61 to 0.98, with 13 of 20 values ≥ 0.90), which means that MUAC can clearly discriminate between underweight and non-

underweight populations (Figure 30). The study also estimated the sensitivity and the specificity of various cut-off values to identify underweight (Table 18). The review suggests screening cut-off values of ≤ 23.5 to ≤ 25 cm to detect underweight in the general adult population (11). Certainty of evidence was rated down once for indirectness.

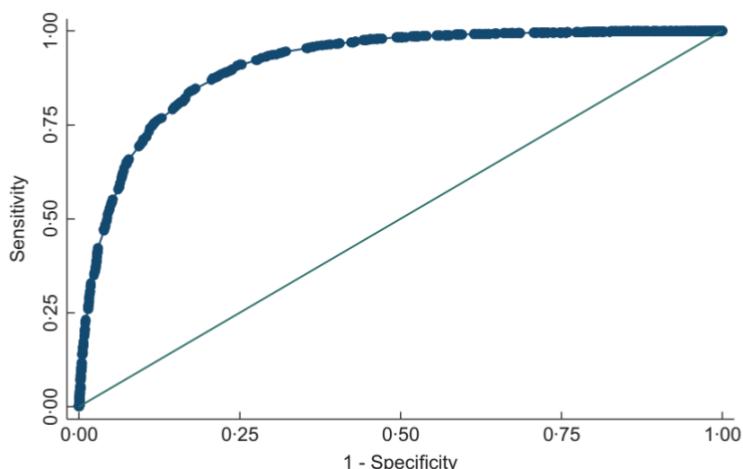


Figure 30. Receiver operating curve (ROC) for all studies combined.
Area under the ROC = 0.91 (11)

Table 18. Pooled sensitivity and specificity of different MUAC cut-offs

MUAC (cm)	No. of Studies	Sensitivity (95% CI)	Specificity (95% CI)	True Positive* (Det ecte d)	False Positive* (Incorrect Dx)	False Negative* (Missed Dx)
≤ 23.5	19	75 (61 to 85)	89 (79 to 94)	150 per 1,000 tested	88 per 1,000 tested	50 per 1,000 tested
≤ 24.0	19	84 (74 to 91)	83 (72 to 91)	168 per 1,000 tested	136 per 1,000 tested	32 per 1,000 tested
≤ 24.5	19	90 (82 to 95)	77 (64 to 87)	180 per 1,000 tested	184 per 1,000 tested	20 per 1,000 tested
≤ 25.0	19	93 (88 to 96)	73 (62 to 82)	186 per 1,000 tested	216 per 1,000 tested	14 per 1,000 tested

*False Positive/False Negative calculated at a prevalence of nutritionally-at risk of 20.1%.

Pregnant population

A cohort study was done in Brazil between 2015 to 2018, which evaluated the diagnostic accuracy of MUAC compared to BMI in 1,165 nulliparous women (13% adolescents) with singleton pregnancies recruited from maternity hospitals. The study assessed the performance of MUAC to detect underweight, overweight, and obese compared to BMI across 3 different ages of gestation: 19 to 21 weeks, 27 to 29 weeks, and 37 to 39 weeks. Based on the high levels of the area under the receiver operating characteristic curves, MUAC has excellent discrimination between underweight and non-underweight (AUC range: 0.84 to 0.88) and has outstanding discrimination between obese and non-obese (AUC range: 0.96 to

0.98) across different time periods from mid pregnancy to late pregnancy (Figure 31). Although the study suggested <25.75 cm as the optimal MUAC cut-off value to diagnose undernutrition, it also emphasized the need for a MUAC cut-off value that was approximate to the BMI reference value for the population of interest (12).

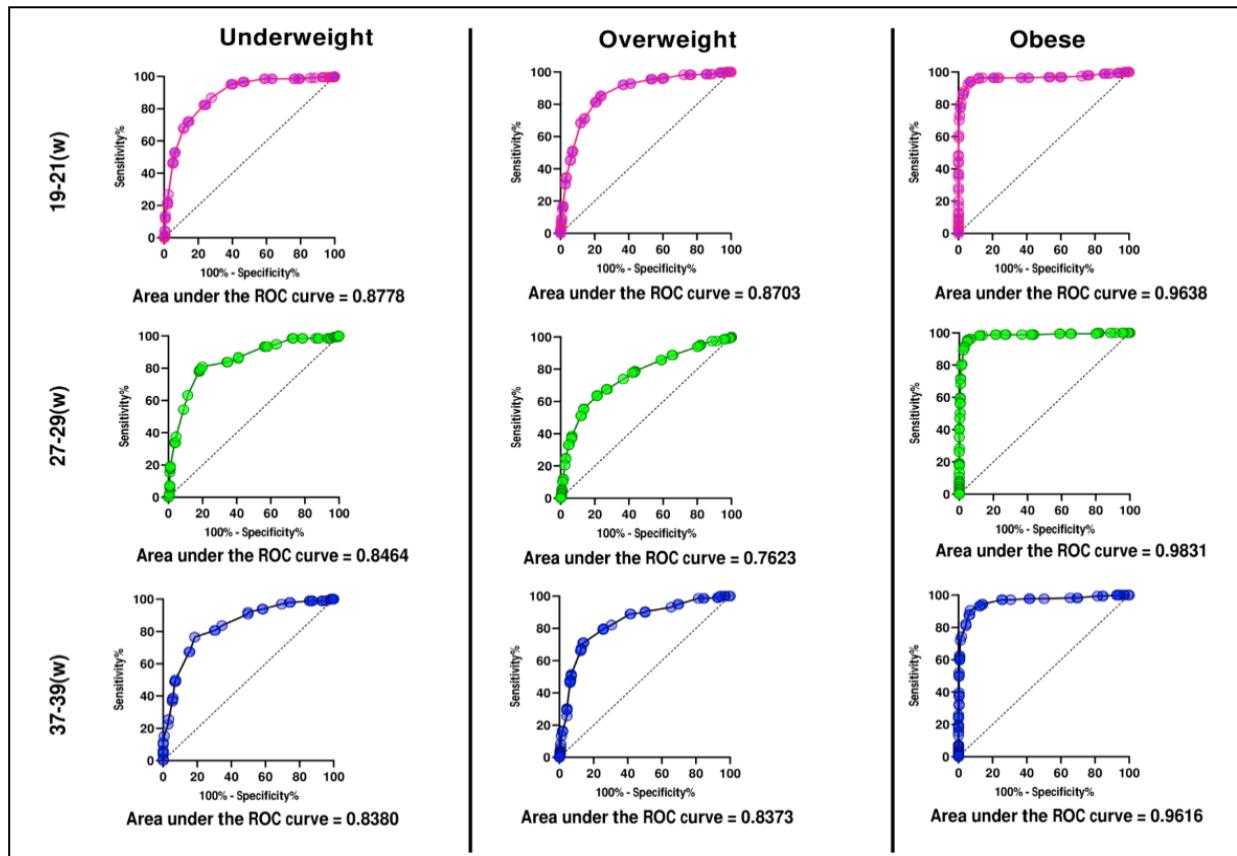


Figure 31. ROC curves for different MUAC cut-off values based on BMI categories and their respective AUROC at different ages of gestation. (12)

Association between low MUAC and adverse birth outcomes

Low birthweight

Based on 8 observational studies ($n = 4,135$), mothers with a low MUAC had increased odds (OR: 2.39, 95% CI: 1.76 to 3.26) for low birth weight infants, which would correspond to 152 more low birthweight infants per 1,000 live births in mothers with low MUAC (from 122 more to 182 more) (14-21). A cross-sectional study done in the Philippines was included (13), which evaluated the use of various MUAC cut offs in pregnant adolescents aged 10 to 18 ($n = 237$) and its association to low birth weight. The study determined a MUAC cut off of 24 cm to have a statistically significant association with low birth weight (unadjusted OR: 2.39, 95%CI: 1.38 to 4.13; adjusted OR: 1.93 (i.e., multivariable adjustment for height, gravidity, occupation, education, income, and smoking status), 95% CI: 1.07 to 3.49) in Filipino adolescents (13).

Preterm birth

There were six observational studies ($n = 33,990$) that determined preterm birth in mothers with a low MUAC. We found an increased odds (OR: 2.06, 95% CI: 1.48 to 2.86) of preterm birth in mothers with low MUAC, about 123 more preterm births per 1,000 live births in mothers with low MUAC (from 60 more to 194 more) (14, 21-25).

Adverse birth outcomes

Two observational studies were found ($n = 1,038$) that evaluated the use of MUAC to determine the risk for adverse birth outcomes, which was a composite of preterm birth and low birthweight. There was increased odds (OR: 3.47, 95% CI: 1.49 to 8.11) of adverse birth outcomes in mothers with a low MUAC. This is estimated to be 265 more adverse birth outcomes per 1,000 live births in mothers with low MUAC (from 72 more to 470 more). Based on indirect evidence, a low maternal MUAC was found to have increased adverse birth outcomes, a composite which includes the critical outcomes of low birthweight and preterm birth (26,27).

Overall Certainty of Evidence

Based on very low certainty of evidence, low maternal MUAC is associated with increased odds for the critical outcomes of low birth weight, preterm birth, and adverse birth outcomes. The certainty of evidence was downgraded due to indirectness, with differences in study design and MUAC cut-offs for underweight. No evidence was found on the critical outcomes of neonatal mortality and maternal mortality. Results of some included studies could not be pooled because of statistical adjustments made and unavailability of event rates (28-30). However, these studies similarly show that low maternal MUAC is associated with increased odds of low birth weight and preterm birth. Overall, the certainty of evidence was determined to be very low.

4.11.3 Cost Implication

The measurement of MUAC requires less resources and the simple method of measurement can be easily trained among community health care workers compared to determination of weight, height and BMI. The use of a specified MUAC cut off is advantageous as it requires no further computation. The use of MUAC to screen for malnutrition in pregnant women is potentially cost-saving, as it does not require special equipment and may easily be integrated in routine anthropometric work or programs in the community.

4.11.4 Equity, Acceptability, and Feasibility

No studies on patient values or preferences were found. It is anticipated that there are minimal to no concerns on the use of MUAC measurement as it is non-invasive and can be quickly performed.

The ease of use and minimal resources needed in the measurement of MUAC may potentially aid in identification of more pregnant women who are undernourished and require nutritional support and intervention.

4.11.5 Recommendations from Other Groups

No CPGs or reviews recommending the use of MUAC were found for screening of pregnant women. Systematic reviews of CPGs done in the Asia-Pacific region and in higher-resourced settings did not report recommendations for the use of MUAC in anthropometric measurement (7).

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5. Research Implications/Gaps

Even though prenatal disorders belong to the leading causes of neonatal mortality in the country, studies are still lacking as to its true burden and epidemiology in the population. For instance, the prevalence of GBS and thyroid disease among pregnant women are yet to be determined.

Moreover, the majority of evidence found, including those for cost-effectiveness, were done in high-income countries; hence, concerns on local applicability were raised by the Panel. Research on maternal and neonatal health particularly in the Philippines, as a lower middle-income country, should then be included or reinforced in the national health research agenda.

6. Dissemination, Implementation, and Monitoring

A full copy of this document will be sent to the Department of Health for transmittal and publication. The Disease Prevention and Control Bureau will transmit copies of this CPG to the Philippine Health Insurance Corporation (PHIC), and health maintenance organizations (HMOs) and non-governmental organizations involved in a periodic health examination. The recommendations and the evidence summaries will be posted in the PHEX web-based application, and in the medical societies involved in the Consensus Panel.

The DOH plans to develop a simplified version of this CPG and make it available in the format that will be ready for reproduction and dissemination to the patients in different health care settings. It will also be accessible for interested parties who might visit the DOH website, as well as those in the medical societies.

The SC and DOH will develop a program of implementation and monitoring to determine the adherence and best practices of relevant stakeholders in terms of screening for prenatal disorders. Surveys in different healthcare institutions and among healthcare workers may be given annually to monitor adherence to the recommendations and gather further information regarding applicability and impact of the guidelines. This can also be used for implementation research.

7. Applicability Issues

The technical working group searched electronic databases for published local or international economic evaluation studies, and the Philhealth website to determine existing coverage rates for the interventions of interest. The information gathered was presented to the consensus panel for its consideration. During the consensus panel meeting, the panelists shared their knowledge and experience regarding the resources required for the

implementation of the various interventions and its feasibility. The facilitators and barriers to application of this CPG, which include costs, resources, existing policies and patients' health-seeking behavior were mainly drawn from the input of the members of the consensus panel and discussed during the deliberations on the recommendations. The consensus panel considered the variation in availability and feasibility across different areas of the country during its deliberations on the guideline.

The PHEX Task Force accentuates some caveats of this CPG using equity and applicability lenses. Comprehensive history taking, physical examination, and monitoring are essential parts of evaluating risk factors and the probability of developing diseases. This CPG does not necessarily supersede the consumers' (i.e., health professionals, hospital administrators, employers, payors, patients) values, settings, and circumstances.

Although this CPG intends to influence the direction of health policies for the general population, it should not be the sole basis for recreating or abolishing practices that aim to improve the health conditions of many Filipinos, particularly those who are part of the workforce.

8. Updating of the Guidelines

The recommendations herein shall hold until such time that new evidence on screening, diagnosing or managing various risk factors and diseases emerges and contingencies dictate updating this Philippine Guidelines on Periodic Health Examination. This guideline will be updated after three (3) years.

9. References

Introduction

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10. Appendices

APPENDIX 10.1. PERIODIC HEALTH EXAMINATION TASK FORCE ON PRENATAL DISORDERS 2022-2023

Task Force Steering Committee

Chair:	Maria Julieta Corazon V. Germar, MD
Members:	Betha Fe M. Castillo, MD Sherri Ann L. Suplido, MD Ma. Susan B. Villaluz, MD Potre Mairasna P. Boransing, MD Mike Justin A. Galian, MD Endrick H. Sy, MD Maria Theresa G. Cacas, MD Helen B. De Peralta-Yambao, MD

Technical Working Group

Technical Coordinator:	Lia Aileen M. Palileo-Villanueva, MD
Evidence Review Experts:	John Jefferson Besa, MD Ella Mae Masamayor, MD Greco Mark Malijan, MD Cary Amiel Villanueva, MD Andrew Rufino Villafuerte, MD Johannes Paolo Cerrado, MD Marie Gene Cruz, MD Lea de Castro, MD Ma. Sergia Fatima Sucaldito, MD

Technical Facilitator:	Maria Asuncion A. Silvestre, MD
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Consensus Panelists:

Clarissa L. Velayo , MD, PhD <i>Philippine Society of Maternal Fetal Medicine</i>
Alfonso Syoei R. Yoshida, MD <i>Philippine Academy of Family Physicians</i>
Lester Sam A. Geroy,MD <i>Philippine Society of Public Health Physicians</i>
Kristine Therese R. Elises-Molon, MD <i>Philippine Obstetrical and Gynecological Society</i>
Elvie U. Estrada, MD <i>Integrated Midwives Association of the Philippines</i>
Daisy Evangeline C. Garcia, MD <i>Philippine Society of Newborn Medicine</i>
Ferdinand Sta. Ana, MD <i>Primary Care Providers-DTTB</i>
Karla Kristine S. Fernando, MD <i>Philippine Society of Endocrinology and Metabolism</i>
Lara Marie D. Bustamante, MD

Philippine Society of Ultrasound in Obstetrics and Gynecology
Ms. Jo-Ann L. Diosana
Management Collective of Action for Economic Reforms /Patient Advocate

DOH Representative: Ysa Gonzales-Andres, MD

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Ms. Hygeia Grace C. Agosto

External Reviewers: Patricia Ann A. Factor-Taruc, MD
Kareen N. Reforma, MD

Administrative Officer: Ms. Princess T. Sulit

APPENDIX 10.2. PERIODIC HEALTH EXAMINATION PHASE 3 CENTRAL COMMITTEE

Program Leader: Ian Theodore Cabaluna, MD, GDip, MSc (cand.)
Co-Program Leaders: Leonila Dans, MD, MSc
Marissa Alejandria, MD, MSc

Steering Committee Members: Antonio Dans, MD, MSc
Dante Morales, MD
Diana Lachica, MD
Aileen Espina, MD
Maria Vanessa Sulit, RN, MSc

COI Committee Members: Dante Morales, MD
Antonio Dans, MD, MSc
Maria Vanessa Sulit, RN, MSc
Angela Du, MD
Camilo Te, MD
Miriam Timonera, MD

Program Managers: Josephine Sanchez, RN
Assistant Program Manager: Lea Galia, MD

Administrative Staff: Pamela Tagle
Lailanie Tejuco
Michelle Recana

COI Administrative Officer: Ivy Cruz

APPENDIX 10.3. SUMMARY OF COI DECLARATIONS

Steering Committee

Name	Relevant Expertise/Affiliation	Summary of Declared Conflicts of Interest	Decisions and Management
Maria Julieta Corazon M. Victoriano-Germar, MD (TF Chair)	Obstetrics and Gynecology Gynecologic Oncology Research Epidemiology University of the Philippines Manila	<p>Non-financial COI:</p> <ul style="list-style-type: none"> ▪ Role on editorial boards and clinical societies, ▪ Lectures on ante natal care Prof 4 UPCM; ▪ Founding Member-Asia Oceania (Research Org on Genital Infections & Neoplasia); Publication Committee, 	B To declare Non-financial COI
Betha Fe Manaois - Castillo, MD	Obstetrics and Gynecology Ob Gyn Ultrasound Dagupan Doctors Villaflor Memorial Hospital		D COIC recommends the ff: To make sure that the majority of SC members are unconflicted vs the conflicted in the steering committee
Sherri Ann L. Suplido, MD	Obstetrics and Gynecology Maternal Fetal Medicine University of the Philippines Manila	<p>Financial COI:</p> <ul style="list-style-type: none"> ▪ Does ultrasound in the clinic 	
Potre Mairasna M. Pangarungan-Boransing, MD	Obstetrics and Gynecology Maternal Fetal Medicine Amai Pakpak Medical Center		
Ma. Susan B. Villaluz, MD	Obstetrics and Gynecology Maternal Fetal Medicine	<p>Financial COI:</p> <ul style="list-style-type: none"> ▪ Does ultrasound in the 	

	Cebu Maternity Hospital Mactan Doctors Hospital	hospital and OB-GYN ultrasound centers	
Helen de Peralta Yambao, MD	Obstetrics and Gynecology Gynecologic Oncology Cotobato Sanitarium and General Hospital Amado Diaz Provincial Hospital Maguindanao Provincial Hospital Aleosan District Hospital	None	A No COI
Mike Justin A. Ganan, MD	Family Medicine Public Health University of the Philippines Manila	None	
Endrik H. Sy, MD	Family Medicine Baguio General Hospital and Medical Center	None	
Maria Theresa G. Cacas, MD	Pediatrics Neonatology University of Perpetual Help Binan UERMMMC	None	

Technical Working Group

Name	Relevant Expertise/ Affiliation	Summary of Declared Conflicts of Interest	Decisions and Management
Lia Palileo Villanueva, MD (Technical Coordinator)	Clinical Epidemiology Internal Medicine University of the Philippines Manila	None	A No COI

John Jefferson Besa, MD	Critical appraisal, Systematic Review, GRADE Methodology Internal Medicine Culion Foundation, Inc.	None	
Ella Mae Masamayor, MD	Critical appraisal, Systematic Review, GRADE Methodology Internal Medicine University of the Philippines Manila Philippine General Hospital	None	
Greco Mark Malijan, MD	Critical appraisal, Systematic Review, GRADE Methodology, Quantitative Data Analysis Internal Medicine San Lazaro Hospital - Nagasaki University Collaborative Research Office	None	
Andrew Rufino Villafuerte, MD	Critical appraisal, Systematic Review, GRADE Methodology Internal Medicine San Beda University College of Medicine Molino Doctors Hospital South Imus Specialist Hospital Asian Hospital and Medical Center	None	
Johannes Paolo Cerrado, MD	Critical appraisal, Systematic Review, GRADE Methodology Internal Medicine	None	

	Nuffield Department of Medicine, University of Oxford		
Maria Gene Cruz, MD	Critical appraisal, Systematic Review, GRADE Methodology Internal Medicine San Beda University College of Medicine St. Luke's Medical Center Global City	None	
Lea Roselle De Castro, MD	Critical appraisal, Systematic Review, GRADE Methodology Internal Medicine	None	
Ma. Sergia Fatima Sucaldito, MD	Critical appraisal, Systematic Review, GRADE Methodology Internal Medicine St. Camillus Medical Center	None	
Cary Amiel Villanueva	Critical appraisal, Systematic Review, GRADE Methodology, Quantitative Data Analysis Internal Medicine Brokenshire College School of Medicine, Davao City	None	

Consensus Panel Members

Name	Affiliation	Summary of Declared Conflicts of Interest	Decisions and Management
Clarissa L. Velayo , MD, PhD	Obstetrics and Gynecology Maternal Fetal Medicine	Financial Conflict	C Cannot vote for questions 7 & 8

	Philippine Society of Maternal Fetal Medicine	Grant Application entitled: Philippine Initiative for National Antenatal Screening	
Alfonso Syoei R. Yoshida, MD	Family Medicine Philippine Academy of Family Physicians	None	No COI
Lester Sam A. Geroy,MD	Public Health Philippine Society of Public Health Physicians	None	No COI
Kristine Therese R. Elises-Molon, MD	Obstetrics and Gynecology Maternal Fetal Medicine Philippine Obstetrical and Gynecological Society	Indirect financial COI: did lectures for Unilab on progesterone for preterm births	Cannot vote on questions 1,2,3,5, 7 and 8
Elvie U. Estrada, MD	Midwifery Integrated Midwives Association of the Philippines	None	No COI
Daisy Evangeline C. Garcia, MD	Pediatrics Neonatology Philippine Society of Newborn Medicine	None	No COI
Karla Kristine S. Fernando, MD	Internal Medicine	Financial COI	C

	<p>Endocrinology Philippine College of Endocrinology, Diabetes, and Metabolism</p>	<ul style="list-style-type: none"> ▪ Has shares of stocks and she is actually also part of the Speaker's Bureau of several companies. Merck Sharp & Dohme (MSD), Sanofi-Aventis, AstraZeneca, LRI Therapharma, Novartis, Merck Becton, Dickinson & Co. (BD needles) 	Cannot vote on all questions
Lara Marie D. Bustamante, MD	<p>Obstetrics and Gynecology Ob Gyn Ultrasound Philippine Society of Ultrasound in Obstetrics and Gynecology</p>	<p>Financial COI</p> <ul style="list-style-type: none"> ▪ Ultrasound fellow 	<p>C</p> <p>Cannot vote for questions 7 & 8</p>
Ferdinand Sta. Ana, Jr. , MD	<p>Primary Care Primary Care Providers-DTTB</p>	<p>Non- Financial COI</p> <ul style="list-style-type: none"> ▪ involvement in Safe Motherhood Program 	<p>B</p> <p>To declare involvement in Safe Motherhood Program</p>
Jo-Ann L. Diosana, MD	Management Collective of Action for Economic Reforms	None	No COI

APPENDIX 10.4. SEARCH STRATEGY

Appendix Table 1. Search strategy for the guideline question on GDM using PubMed and Cochrane Library

SEPTEMBER 15, 2022

SEARCH	QUERY	RESULTS
#1	"Diabetes, Gestational"[Mesh]	16144
#2	"Glucose Tolerance Test"[Mesh]	36666
#3	#1 AND #2	2883
#4	#1 AND #2 Filters: Meta-Analysis	29
#5	#1 AND #2 Filters: Systematic Review	41
#6	#1 AND #2 Filters: Randomized Controlled Trial	140
#7	"Prenatal Diagnosis"[Mesh]	79794
#8	#3 AND #7	154
#9	#3 AND #7 Filters: Randomized Controlled Trial	7
#10	#3 AND #7 Filters: Observational Study	6
#11	#3 Filters: Observational Study	111
#12	"Pregnancy"[Mesh]	978229
#13	#2 AND #12	5080
#14	#2 AND #12 Filters: Meta-Analysis	32

Appendix Table 2. Search strategy for the guideline question on GBS

Search number	Query	Search Details	Results
1	("group b streptococcus"[Title/Abstract] OR "streptococcus agalactiae"[Title/Abstract] OR "streptococcus agalactiae"[MeSH Terms] OR "group b strep"[Title/Abstract]) OR ("streptococcus agalactiae"[Title/Abstract])	"group b streptococcus"[Title/Abstract] OR "streptococcus agalactiae"[Title/Abstract] OR "streptococcus agalactiae"[MeSH Terms] OR "group b strep"[Title/Abstract] OR "streptococcus agalactiae"[Title/Abstract]	11,641
2	((((mass screening[MeSH Terms]) OR (prenatal screening[MeSH Terms])) OR (antenatal screening[MeSH Terms])) OR (prenatal diagnoses[MeSH Terms])) OR (diagnostic screening programs[MeSH Terms])) OR (screen*[Title/Abstract])	"mass screening"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "diagnostic screening programs"[MeSH Terms] OR "screen*"[Title/Abstract]	1,056,417
3	((((antenatal[Title/Abstract]) OR (ante-natal[Title/Abstract])) OR (prenatal[Title/Abstract])) OR (pre-natal[Title/Abstract])) OR (prenatal care[MeSH Terms])	"antenatal"[Title/Abstract] OR "ante-natal"[Title/Abstract] OR "prenatal"[Title/Abstract] OR "pre-natal"[Title/Abstract] OR "prenatal care"[MeSH Terms]	166,256
4	"MEDLINE"[Text Word] OR "systematic review"[Text Word] OR "meta-analysis"[Publication Type] OR "intervention*"[Title]	"MEDLINE"[Text Word] OR "systematic review"[Text Word] OR "meta-analysis"[Publication Type] OR "intervention*"[Title]	598,575
5	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	1,481,443

6	Economics OR "Costs and Cost Analysis"[mh] OR Economics, Nursing[mh] OR Economics, Medical[mh] OR Economics, Pharmaceutical[mh] OR Economics, Hospital[mh] OR Economics, Dental[mh] OR "Fees and Charges"[mh] OR Budgets[mh] OR budget*[tiab] OR economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab] OR pharmaco-economic*[tiab] OR expenditure[tiab] OR expenditures[tiab] OR expense[tiab] OR expenses[tiab] OR financial[tiab] OR finance[tiab] OR finances[tiab] OR financed[tiab] OR value for money[tiab] OR monetary value*[tiab] OR models, economic[mh] OR economic model*[tiab] OR markov chains[mh] OR markov[tiab] OR monte carlo method[mh] OR monte carlo[tiab] OR Decision Theory[mh] OR decision tree*[tiab] OR decision analy*[tiab] OR decision model*[tiab]	"economical"[All Fields] OR "economics"[MeSH Terms] OR "economics"[All Fields] OR "economic"[All Fields] OR "economically"[All Fields] OR "economics"[MeSH Subheading] OR "economization"[All Fields] OR "economize"[All Fields] OR "economized"[All Fields] OR "economizes"[All Fields] OR "economizing"[All Fields] OR "Costs and Cost Analysis"[MeSH Terms] OR "economics, nursing"[MeSH Terms] OR "economics, medical"[MeSH Terms] OR "economics, pharmaceutical"[MeSH Terms] OR "economics, hospital"[MeSH Terms] OR "economics, dental"[MeSH Terms] OR "Fees and Charges"[MeSH Terms] OR "budgets"[MeSH Terms] OR "budget"[Title/Abstract] OR "economic"[Title/Abstract] OR "cost"[Title/Abstract] OR "costs"[Title/Abstract] OR "costly"[Title/Abstract] OR "costing"[Title/Abstract] OR "price"[Title/Abstract] OR "prices"[Title/Abstract] OR "pricing"[Title/Abstract] OR "pharmacoeconomic*[Title/Abstract] OR "pharmaco economic*[Title/Abstract] OR "expenditure"[Title/Abstract] OR "expenditures"[Title/Abstract] OR "expense"[Title/Abstract] OR "expenses"[Title/Abstract] OR "financial"[Title/Abstract] OR "finance"[Title/Abstract] OR "finances"[Title/Abstract] OR "financed"[Title/Abstract] OR "value for money"[Title/Abstract] OR "monetary value*[Title/Abstract] OR "models, economic"[MeSH Terms] OR "economic model*[Title/Abstract] OR "markov chains"[MeSH Terms] OR "markov"[Title/Abstract] OR "monte carlo method"[MeSH Terms] OR "monte carlo"[Title/Abstract] OR "decision theory"[MeSH Terms] OR "decision tree*[Title/Abstract] OR "decision analy*[Title/Abstract] OR "decision model*[Title/Abstract]	1,868,912
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7	#1 AND #2	("group b streptococcus"[Title/Abstract] OR "streptococcus agalactiae"[Title/Abstract] OR "streptococcus agalactiae"[MeSH Terms] OR "group b strep"[Title/Abstract] OR "streptococcus agalactiae"[Title/Abstract]) AND ("mass screening"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "diagnostic screening programs"[MeSH Terms] OR "screen*"[Title/Abstract])	1,399
8	#1 AND #2 AND #3	("group b streptococcus"[Title/Abstract] OR "streptococcus agalactiae"[Title/Abstract] OR "streptococcus agalactiae"[MeSH Terms] OR "group b strep"[Title/Abstract] OR "streptococcus agalactiae"[Title/Abstract]) AND ("mass screening"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "diagnostic screening programs"[MeSH Terms] OR "screen*"[Title/Abstract]) AND ("antenatal"[Title/Abstract] OR "ante-natal"[Title/Abstract] OR "prenatal"[Title/Abstract] OR "pre-natal"[Title/Abstract] OR "prenatal care"[MeSH Terms])	375
9	#1 AND #2 AND #3 AND #4	("group b streptococcus"[Title/Abstract] OR "streptococcus agalactiae"[Title/Abstract] OR "streptococcus agalactiae"[MeSH Terms] OR "group b strep"[Title/Abstract] OR "streptococcus agalactiae"[Title/Abstract]) AND ("mass screening"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "diagnostic screening programs"[MeSH Terms] OR "screen*"[Title/Abstract]) AND ("antenatal"[Title/Abstract] OR "ante-natal"[Title/Abstract] OR "prenatal"[Title/Abstract] OR "pre-natal"[Title/Abstract] OR "prenatal care"[MeSH Terms]) AND ("MEDLINE"[Text Word] OR "systematic review"[Text Word] OR "meta-analysis"[Publication Type] OR "intervention*"[Title])	10

10 #1 AND #2 AND #3 AND #5

("group b streptococcus"[Title/Abstract] OR "streptococcus agalactiae"[Title/Abstract] OR
"streptococcus agalactiae"[MeSH Terms] OR "group b strep"[Title/Abstract] OR
"streptococcus agalactiae"[Title/Abstract]) AND ("mass screening"[MeSH Terms] OR
"prenatal diagnosis"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "prenatal
diagnosis"[MeSH Terms] OR "diagnostic screening programs"[MeSH Terms] OR
"screen*"[Title/Abstract] AND ("antenatal"[Title/Abstract] OR "ante-natal"[Title/Abstract] OR
"prenatal"[Title/Abstract] OR "pre-natal"[Title/Abstract] OR "prenatal care"[MeSH Terms])
AND (("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication
Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as
topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH
Terms] NOT "humans"[MeSH Terms]))

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11 #1 AND #2 AND #3 AND #6

("group b streptococcus"[Title/Abstract] OR "streptococcus agalactiae"[Title/Abstract] OR "streptococcus agalactiae"[MeSH Terms] OR "group b strep"[Title/Abstract] OR "streptococcus agalactiae"[Title/Abstract]) AND ("mass screening"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "prenatal diagnosis"[MeSH Terms] OR "diagnostic screening programs"[MeSH Terms] OR "screen*"[Title/Abstract] AND ("antenatal"[Title/Abstract] OR "ante-natal"[Title/Abstract] OR "prenatal"[Title/Abstract] OR "pre-natal"[Title/Abstract] OR "prenatal care"[MeSH Terms]) AND ("economical"[All Fields] OR "economics"[MeSH Terms] OR "economics"[All Fields] OR "economic"[All Fields] OR "economically"[All Fields] OR "economics"[MeSH Subheading] OR "economization"[All Fields] OR "economize"[All Fields] OR "economized"[All Fields] OR "economizes"[All Fields] OR "economizing"[All Fields] OR "Costs and Cost Analysis"[MeSH Terms] OR "economics, nursing"[MeSH Terms] OR "economics, medical"[MeSH Terms] OR "economics, pharmaceutical"[MeSH Terms] OR "economics, hospital"[MeSH Terms] OR "economics, dental"[MeSH Terms] OR "Fees and Charges"[MeSH Terms] OR "budgets"[MeSH Terms] OR "budget*"[Title/Abstract] OR "economic*"[Title/Abstract] OR "cost"[Title/Abstract] OR "costs"[Title/Abstract] OR "costly"[Title/Abstract] OR "costing"[Title/Abstract] OR "price"[Title/Abstract] OR "prices"[Title/Abstract] OR "pricing"[Title/Abstract] OR "pharmacoeconomic*"[Title/Abstract] OR "pharmaco economic*"[Title/Abstract] OR "expenditure"[Title/Abstract] OR "expenditures"[Title/Abstract] OR "expense"[Title/Abstract] OR "expenses"[Title/Abstract] OR "financial"[Title/Abstract] OR "finance"[Title/Abstract] OR "finances"[Title/Abstract] OR "financed"[Title/Abstract] OR "value for money"[Title/Abstract] OR "monetary value*"[Title/Abstract] OR "models, economic"[MeSH Terms] OR "economic model*"[Title/Abstract] OR "markov chains"[MeSH Terms] OR "markov"[Title/Abstract] OR "monte carlo method"[MeSH Terms] OR "monte carlo"[Title/Abstract] OR "decision theory"[MeSH Terms] OR "decision tree*"[Title/Abstract] OR "decision analy*"[Title/Abstract] OR "decision model*"[Title/Abstract])

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Appendix Table 3. Search strategy for the guideline question on prenatal first and second trimester ultrasound (Date of last PubMed search: August 29, 2022)

Query	Results	Time
((("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND (((prenatal OR pregnan*) AND ((first trimester OR second trimester) AND ("Ultrasonography, Prenatal"[Mesh] OR ultrasound))) AND (((("Congenital Abnormalities"[Mesh]) OR ("Fetal Growth Retardation"[Mesh])) OR ("Multiple Birth Offspring"[Mesh]))) OR (fetal aging OR cardiac activity OR congenital anomaly)) OR (intrauterine pregnancy OR ectopic pregnancy)))	20	13:06:07
Filters: from 2020/8 - 2022/8/29		
((("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND (((prenatal OR pregnan*) AND ((first trimester OR second trimester) AND ("Ultrasonography, Prenatal"[Mesh] OR ultrasound))) AND (((("Congenital Abnormalities"[Mesh]) OR ("Fetal Growth Retardation"[Mesh])) OR ("Multiple Birth Offspring"[Mesh]))) OR (fetal aging OR cardiac activity OR congenital anomaly)) OR (intrauterine pregnancy OR ectopic pregnancy)))	202	13:05:47
("MEDLINE"[Text Word] OR "systematic review"[Text Word] OR "meta-analysis"[Publication Type] OR "intervention*[Title]) AND (((prenatal OR pregnan*) AND ((first trimester OR second trimester) AND ("Ultrasonography, Prenatal"[Mesh] OR ultrasound))) AND (((("Congenital Abnormalities"[Mesh]) OR ("Fetal Growth Retardation"[Mesh])) OR ("Multiple Birth Offspring"[Mesh]))) OR (fetal aging OR cardiac activity OR congenital anomaly)) OR (intrauterine pregnancy OR ectopic pregnancy)))	23	13:01:52
("MEDLINE"[Text Word] OR "systematic review"[Text Word] OR "meta-analysis"[Publication Type] OR "intervention*[Title]) AND (((prenatal OR pregnan*) AND ((first trimester OR second trimester) AND ("Ultrasonography, Prenatal"[Mesh] OR ultrasound))) AND (((("Congenital Abnormalities"[Mesh]) OR ("Fetal Growth Retardation"[Mesh])) OR ("Multiple Birth Offspring"[Mesh]))) OR (fetal aging OR cardiac activity OR congenital anomaly)) OR (intrauterine pregnancy OR ectopic pregnancy)))	175	13:00:39
((prenatal OR pregnan*) AND ((first trimester OR second trimester) AND ("Ultrasonography, Prenatal"[Mesh] OR ultrasound))) AND (((("Congenital Abnormalities"[Mesh]) OR ("Fetal Growth Retardation"[Mesh])) OR ("Multiple Birth Offspring"[Mesh]))) OR (fetal aging OR cardiac activity OR congenital anomaly)) OR (intrauterine pregnancy OR ectopic pregnancy)))	7,453	12:59:08

((("Congenital Abnormalities"[Mesh]) OR ("Fetal Growth Retardation"[Mesh])) OR ("Multiple Birth Offspring"[Mesh])) OR (fetal aging OR cardiac activity OR congenital anomaly)) OR (intrauterine pregnancy OR ectopic pregnancy)	1,118,317	12:58:58
(prenatal OR pregnan*) AND ((first trimester OR second trimester) AND ("Ultrasonography, Prenatal"[Mesh] OR ultrasound))	15,384	12:57:42
(first trimester OR second trimester) AND ("Ultrasonography, Prenatal"[Mesh] OR ultrasound)	15,552	12:57:15
"Congenital Abnormalities"[Mesh]	640,526	12:55:13
"Fetal Growth Retardation"[Mesh]	18,112	12:54:04
"Multiple Birth Offspring"[Mesh]	29,736	12:52:08
fetal aging OR cardiac activity OR congenital anomaly	1,026,666	12:50:01

Appendix Table 4. Search strategy for the guideline question on prenatal first and second trimester ultrasound using other databases

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE OF SEARCH	RESULTS	
			Yield	Hits
Cochrane Library	#1 antenatal ultrasound	Aug. 29, 2022	584	0
	#2 first trimester		4472	
	#3 second trimester		3178	
	#4 2 OR 3		6161	
	#5 1 AND 4		149	
United States Preventive Services Task Forces (USPSTF)	"ultrasound" Filters: Status: All	Aug. 17, 2022	19	0

	Sex/Gender/Pregnancy Status: Pregnant Persons			
	Type of Preventive Service: Screening			
National Institute for Health and Care Excellence (NICE)	"pregnancy" "antenatal"	Aug. 17, 2022	14 5	0 1
Canadian Task Force on Preventive Health Care (CTFPH)	"pregnancy"	Aug. 17, 2022	2	0
World Health Organization (WHO)	Health topic: "pregnancy"	Aug. 17, 2022	33	1
International Society on Ultrasound for Obstetrics and Gynecology (ISUOG)	Practice Guidelines	Aug. 17, 2022	16	3
Society of Obstetricians and Gynaecologists of Canada (SOGC)	"ultrasound" "prenatal" "antenatal" "guidelines" "pregnancy"	Aug. 17, 2022	207	3

Appendix Table 5. Search strategy for the guideline question on screening for fetal aneuploidy using nuchal translucency

5.1. PubMed Search for CPGs

Terms	Results
3 #1 AND #2	33
2 (((("guideline" [pt]) OR "practice guideline" [pt]) OR "Consensus"[mesh]) OR "Consensus Development Conference, NIH" [Publication Type]) OR "Consensus Development Conference" [Publication Type]) OR (consensuses[ti] OR consensus[ti] OR "position statement"[ti] OR "position statements"[ti] OR "practice parameter"[ti] OR "practice parameters"[ti] OR "appropriate use criteria" [ti] OR "appropriateness criteria" [ti] OR "guidance statement"[ti] OR "guidance statements"[ti] OR guideline[ti] or guidelines[ti] OR bulletin[ti])	154,522
1 (nuchal translucency) OR (nuchal translucency measurement[MeSH Terms]) OR (nuchal translucency screening[MeSH Terms])	2,847

5.2. PubMed Search for Systematic Reviews

	Terms	Results
3	#1 AND #2	56
2	("MEDLINE"[Text Word] OR "systematic review"[Text Word] OR "meta-analysis"[Publication Type] OR "intervention**[Title])	575,397
1	(nuchal translucency) OR (nuchal translucency measurement[MeSH Terms]) OR (nuchal translucency screening[MeSH Terms])	2,847

5.3. PubMed Search for New Studies for Down syndrome (2011 onwards)

	Terms	Results
1 1	((("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal)) AND ("nuchal translucency" AND "ultrasound")) AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*)) AND ("Down syndrome" OR "Trisomy" OR "Aneuploidy" OR "Mosaicism") Filter: Humans, from 2011-2022	301
1 0	((("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal)) AND ("nuchal translucency" AND "ultrasound")) AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*)) AND ("Down syndrome" OR "Trisomy" OR "Aneuploidy" OR "Mosaicism") Filter: Humans	778
9	((("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal)) AND ("nuchal translucency" AND "ultrasound")) AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*)) AND ("Down syndrome" OR "Trisomy" OR "Aneuploidy" OR "Mosaicism")	814

8	"Down syndrome" OR "Trisomy" OR "Aneuploidy" OR "Mosaicism"	77,353
7	"ultrasound") AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*)	1,461
6	Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*	13,067,743
5	("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound")	1,496
4	"nuchal translucency" AND "ultrasound"	1,503
3	("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal)	1,037,367
2	Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal	1,036,943
1	"prenatal diagnosis"	57,741

5.4. PubMed Search for New Studies for Edwards syndrome

Terms	Results
9 (((("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal)) AND ("nuchal translucency" AND "ultrasound")) AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*)) AND ("Edwards syndrome" OR "Trisomy 18")	134
8 "Edwards syndrome" OR "Trisomy 18"	2,878
7 (((("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal)) AND ("nuchal translucency" AND "ultrasound")) AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*)	1,461
6 Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*	13,067,743
5 ("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound")	1,496
4 "nuchal translucency" AND "ultrasound"	1,503
3 ("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal)	1,037,367
2 Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal	1,036,943
1 "prenatal diagnosis"	57,741

5.5. PubMed Search for New Studies for Patau syndrome

Terms	Results
9 (((("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal)) AND ("nuchal translucency" AND "ultrasound")) AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*)) AND ("Patau syndrome" OR "Trisomy 13")	86
8 "Patau syndrome" OR "Trisomy 13"	1,988
7 (((("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal)) AND ("nuchal translucency" AND "ultrasound")) AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*)	1,461

6 Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*	13,067,743
5 ("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound")	1,496
4 "nuchal translucency" AND "ultrasound"	1,503
3 ("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal)	1,037,367
2 Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal	1,036,943
1 "prenatal diagnosis"	57,741

5.6. PubMed Search for New Studies for major congenital heart disease

Terms	Results
7 (((prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal)) AND ("nuchal translucency" AND "ultrasound")) AND ((congenital AND ("heart" OR "cardiac")) AND ("disease" OR "defect"))	99
6 (congenital AND ("heart" OR "cardiac")) AND ("disease" OR "defect")	61,923
5 ("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound")	1,496
4 "nuchal translucency" AND "ultrasound"	1,503
3 ("prenatal diagnosis") OR (Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal)	1,037,367
2 Antenatal OR prenatal OR trimester OR pregnan OR fetus OR fetal	1,036,943
1 "prenatal diagnosis"	57,741

5.7. Proquest Search for CPGs

Terms	Results
4 (#1 AND #2) Filter: Humans, 2017-2022	76
3 #1 AND #2	854
2 guideline* or guidance or statement or consensus or bulletin	5,515,540
1 "nuchal translucency" OR "nuchal translucency scan" OR "nuchal translucency ultrasound" OR "nuchal translucency screening"	9,531

5.8. Proquest Search for Systematic Reviews

Terms	Results
4 (#1 AND #2) Filter: Humans	131
3 #1 AND #2	509

2	"systematic review" OR "meta-analysis"	1,901,789
1	"nuchal translucency" OR "nuchal translucency scan" OR "nuchal translucency ultrasound" OR "nuchal translucency screening"	9,531

5.9. Proquest Search for New Studies for Down syndrome (2011 onwards)

Terms	Results
5 (((("prenatal diagnosis" or "antenatal diagnosis" OR Antenatal OR prenatal OR trimester OR pregnan* OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound")) AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "area under the curve" OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*) AND ("Down syndrome" OR "Trisomy" OR "Aneuploidy" OR "Mosaicism")) Filter: Humans, 2011-2022	742
4 (((("prenatal diagnosis" or "antenatal diagnosis" OR Antenatal OR prenatal OR trimester OR pregnan* OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound")) AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "area under the curve" OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*) AND ("Down syndrome" OR "Trisomy" OR "Aneuploidy" OR "Mosaicism")	2127
3 (((("prenatal diagnosis" or "antenatal diagnosis" OR Antenatal OR prenatal OR trimester OR pregnan* OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound")) AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "area under the curve" OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*)	5275
2 ("prenatal diagnosis" or "antenatal diagnosis" OR Antenatal OR prenatal OR trimester OR pregnan* OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound")	5275
1 (((("prenatal diagnosis" or "antenatal diagnosis") OR (Antenatal or "prenatal") OR (prenatal or "antenatal") OR trimester OR pregnan* OR fetus OR fetal)	3759847

5.10. Proquest Search for New Studies for Edwards syndrome

Terms	Results
4 (((("prenatal diagnosis" or "antenatal diagnosis" OR Antenatal OR prenatal OR trimester OR pregnan* OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound")) AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "area under the curve" OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*) AND ("Edwards syndrome" OR "Trisomy 18")	360
3 (((("prenatal diagnosis" or "antenatal diagnosis" OR Antenatal OR prenatal OR trimester OR pregnan* OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound")) AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "area under the curve" OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*)	5275
2 ("prenatal diagnosis" or "antenatal diagnosis" OR Antenatal OR prenatal OR trimester OR pregnan* OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound")	5275
1 (((("prenatal diagnosis" or "antenatal diagnosis") OR (Antenatal or "prenatal") OR (prenatal or "antenatal") OR trimester OR pregnan* OR fetus OR fetal)	3759847

5.11. Proquest Search for New Studies for Patau syndrome

Terms	Results
4 ("prenatal diagnosis" or "antenatal diagnosis" OR Antenatal OR prenatal OR trimester OR pregnan* OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound") AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "area under the curve" OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*) AND ("Patau syndrome" OR "Trisomy 13")	230
3 ("prenatal diagnosis" or "antenatal diagnosis" OR Antenatal OR prenatal OR trimester OR pregnan* OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound") AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "area under the curve" OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*)	5275
2 ("prenatal diagnosis" or "antenatal diagnosis" OR Antenatal OR prenatal OR trimester OR pregnan* OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound")	5275
1 ("prenatal diagnosis" or "antenatal diagnosis") OR (Antenatal or "prenatal") OR (prenatal or "antenatal") OR trimester OR pregnan* OR fetus OR fetal)	3759847

5.12. Proquest Search for New Studies for major congenital heart disease

Terms	Results
5 (((("prenatal diagnosis" or "antenatal diagnosis" OR Antenatal OR prenatal OR trimester OR pregnan* OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound") AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "area under the curve" OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*)) AND ((congenital AND ("heart" OR "cardiac")) AND ("disease" OR "defect")))	738
4 (congenital AND ("heart" OR "cardiac")) AND ("disease" OR "defect")	367118
3 ("prenatal diagnosis" or "antenatal diagnosis" OR Antenatal OR prenatal OR trimester OR pregnan* OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound") AND (Screen* OR Detect* OR Accura* OR Predict* OR ROC OR "ROC curve" OR AUC OR "area under the curve" OR "False positive" OR "false negative" OR "Likelihood ratio" OR Sensitiv* OR Specific* OR Diagnos*)	5275
2 ("prenatal diagnosis" or "antenatal diagnosis" OR Antenatal OR prenatal OR trimester OR pregnan* OR fetus OR fetal) AND ("nuchal translucency" AND "ultrasound")	5275
1 ("prenatal diagnosis" or "antenatal diagnosis") OR (Antenatal or "prenatal") OR (prenatal or "antenatal") OR trimester OR pregnan* OR fetus OR fetal)	3759847

5.13. Cochrane Search

Terms	Results
1 "nuchal translucency"	51

Appendix Table 6. Search strategy for the guideline question on screening for anemia

6.1. Search for direct evidence

"consensus development conference, nih"[Publication Type] OR
"Consensus Development Conference"[Publication Type] OR
("consensuses"[Title] OR "Consensus"[Title] OR "position
statement"[Title] OR "position statements"[Title] OR "practice
parameter"[Title] OR "practice parameters"[Title] OR "appropriate use
criteria"[Title] OR "appropriateness criteria"[Title] OR "guidance
statement"[Title] OR "guidance statements"[Title] OR "guideline"[Title]
OR "guidelines"[Title] OR "bulletin"[Title]) OR ("MEDLINE"[Text Word]
OR "systematic review"[Text Word] OR "meta-analysis"[Publication
Type] OR "intervention*"[Title]) OR ((("randomized controlled
trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR
"randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical
trials as topic"[MeSH
Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT
("animals"[MeSH Terms] NOT "humans"[MeSH Terms])))

15	#9 AND #12	(("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("complete"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "complete blood count"[All Fields] OR ("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("full"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "full blood count"[All Fields]) OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobin s'[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields]) OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields]) OR ("haematocrit"[All Fields] OR "hematocrit"[MeSH Terms] OR "hematocrit"[All Fields] OR "hematocrite"[All Fields] OR "haematocrits"[All Fields] OR "hematocrite"[All Fields]) OR ("haematocrit"[All Fields] OR "hematocrit"[MeSH Terms] OR "hematocrit"[All Fields] OR "haematoctrite"[All Fields] OR "haematocrits"[All Fields] OR "hematocrits"[All Fields] OR "hematocrite"[All Fields]) OR "hematocrite"[All Fields] OR "Erythrocyte Indices"[MeSH Terms]) AND ("pregnan*[All Fields] OR ("prenatal"[All Fields] OR "prenatally"[All Fields] OR "prenatal*[All Fields] OR "pre-natal*[All Fields] OR ("antenatal*[All Fields] OR "antenatally*[All Fields] OR "ante-natal*[All Fields] OR "Prenatal Care"[MeSH Terms]) AND ("screen*[All Fields] OR ("Prenatal Diagnosis"[MeSH Terms] OR "Noninvasive Prenatal Testing"[MeSH Terms])) AND ("anaemia"[All Fields] OR "Anemia"[MeSH Terms] OR "Anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields] OR ("anaemia"[All Fields] OR "Anemia"[MeSH Terms] OR "Anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields]) OR ((("iron"[MeSH Terms] OR "iron"[All Fields]) AND "deficien*[All Fields]) OR "Anemia"[MeSH Terms]) AND ((("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])))	84	7:19:56

14	#9 AND #11		(("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("complete"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "complete blood count"[All Fields] OR ("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("full"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "full blood count"[All Fields]) OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "haemoglobins"[All Fields] OR "haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields]) OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields]) OR ("haematocrit"[All Fields] OR "hematocrit"[MeSH Terms] OR "hematocrit"[All Fields] OR "haematocrite"[All Fields] OR "haematocrits"[All Fields] OR "hematocrite"[All Fields]) OR ("haematocrit"[All Fields] OR "hematocrit"[MeSH Terms] OR "hematocrit"[All Fields] OR "haematocrite"[All Fields] OR "haematocrits"[All Fields] OR "hematocrite"[All Fields]) OR ("Erythrocyte Indices"[MeSH Terms]) AND ("pregnan*"[All Fields] OR ("prenatal"[All Fields] OR	41	7:18:56

				"prenatally"[All Fields] OR "prenatals"[All Fields] OR "pre-natal"[All Fields] OR ("antenatal"[All Fields] OR "antenatally"[All Fields]) OR "ante-natal"[All Fields] OR "Prenatal Care"[MeSH Terms]) AND ("screen*[All Fields] OR ("Prenatal Diagnosis"[MeSH Terms] OR "Noninvasive Prenatal Testing"[MeSH Terms])) AND ("anaemia"[All Fields] OR "Anemia"[MeSH Terms] OR "Anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields] OR ("anaemia"[All Fields] OR "Anemia"[MeSH Terms] OR "Anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields]) OR ((iron"[MeSH Terms] OR "iron"[All Fields]) AND "deficien*[All Fields] OR "Anemia"[MeSH Terms]) AND ("MEDLINE"[Text Word] OR "systematic review"[Text Word] OR "meta-analysis"[Publication Type] OR "intervention*[Title])		
13	#9 AND #10			("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("complete"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "complete blood count"[All Fields] OR ("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("full"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "full blood count"[All Fields]) OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "hemoglobins"[All Fields] OR "haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields] OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields] OR ("haematocrit"[All Fields] OR "hematocrit"[MeSH Terms] OR "hematocrits"[All Fields] OR "hematocrits"[All Fields] OR "hematocrite"[All Fields] OR ("haematocrit"[All Fields] OR "hematocrits"[All Fields] OR "hematocrite"[MeSH Terms] OR "hematocrits"[All Fields] OR "hematocrite"[All Fields] OR "haematocrits"[All Fields] OR "hematocrits"[All Fields] OR "hematocrite"[All Fields] OR "Erythrocyte Indices"[MeSH Terms] AND ("pregnan*[All Fields] OR ("prenatal"[All Fields] OR "prenatally"[All Fields] OR "prenatals"[All Fields] OR "pre-natal"[All Fields] OR ("antenatal"[All Fields] OR "antenatally"[All Fields]) OR "ante-natal"[All Fields] OR "Prenatal Care"[MeSH Terms]) AND ("screen*[All Fields] OR ("Prenatal Diagnosis"[MeSH Terms] OR "Noninvasive Prenatal Testing"[MeSH Terms])) AND ("anaemia"[All Fields] OR "Anemia"[MeSH Terms] OR "Anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields] OR ("anaemia"[All Fields] OR "Anemia"[MeSH Terms] OR "Anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields]) OR ((iron"[MeSH Terms] OR "iron"[All Fields]) AND "deficien*[All Fields] OR "Anemia"[MeSH Terms]) AND ("guideline"[Publication Type] OR "practice guideline"[Publication Type] OR "Consensus"[MeSH Terms] OR "consensus development conference, nih"[Publication Type] OR "Consensus Development Conference"[Publication Type] OR ("consensuses"[Title] OR "Consensus"[Title] OR "position statement"[Title] OR "position statements"[Title] OR "practice parameter"[Title] OR "practice parameters"[Title] OR "appropriate use criteria"[Title] OR	14	7:17:44

			"appropriateness criteria"[Title] OR "guidance statement"[Title] OR "guidance statements"[Title] OR "guideline"[Title] OR "guidelines"[Title] OR "bulletin"[Title]))		
12	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	(("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "clinical trials as topic"[MeSH Terms] OR "randomly"[Title/Abstract] OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))	1,484,888	7:17:33	

11	"MEDLINE"[Text Word] OR "systematic review"[Text Word] OR "meta-analysis"[Publication Type] OR "intervention*"[Title]	"MEDLINE"[Text Word] OR "systematic review"[Text Word] OR "meta-analysis"[Publication Type] OR "intervention*"[Title]	601,916	7:17:24
10	(("guideline" [pt]) OR "practice guideline" [pt]) OR "Consensus"[mesh] OR "Consensus Development Conference, NIH" [Publication Type] OR "Consensus Development Conference" [Publication Type] OR (consensuses[ti] OR consensus[ti] OR "position statement"[ti] OR "position statements"[ti] OR "practice parameter"[ti] OR "practice parameters"[ti] OR "appropriate use criteria" [ti] OR "appropriateness criteria" [ti] OR "guidance statement"[ti] OR "guidance statements"[ti] OR guideline[ti] or guidelines[ti] OR bulletin[ti])	"guideline"[Publication Type] OR "practice guideline"[Publication Type] OR "Consensus"[MeSH Terms] OR "consensus development conference, nih"[Publication Type] OR "Consensus Development Conference"[Publication Type] OR "consensuses"[Title] OR "Consensus"[Title] OR "position statement"[Title] OR "position statements"[Title] OR "practice parameter"[Title] OR "practice parameters"[Title] OR "appropriate use criteria"[Title] OR "appropriateness criteria"[Title] OR "guidance statement"[Title] OR "guidance statements"[Title] OR "guideline"[Title] OR "guidelines"[Title] OR "bulletin"[Title]	157,960	7:17:11
9	(#1 OR #2) AND (#3 OR #4) AND (#5 OR #6) AND (#7 OR #8)	("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("complete"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "complete blood count"[All Fields] OR ("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("full"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "full blood count"[All Fields]) OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields]) OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields]) OR ("haematocrit"[All Fields] OR "hematocrit"[MeSH Terms] OR "hematocrit"[All Fields] OR "haematocrite"[All Fields] OR "haematocrits"[All Fields] OR "hematocrits"[All Fields] OR "hematocrit"[MeSH Terms] OR "hematocrit"[All Fields] OR "haematocrite"[All Fields] OR "haematocrits"[All Fields] OR "hematocrits"[All Fields] OR "hematocrite"[All Fields] OR "Erythrocyte Indices"[MeSH Terms]) AND ("pregnan*"[All Fields] OR ("prenatal"[All Fields] OR "prenatally"[All Fields] OR "prenatals"[All Fields]) OR "pre-natal"[All Fields] OR ("antenatal"[All Fields] OR "antenatally"[All Fields]) OR "ante-natal"[All Fields] OR "Prenatal Care"[MeSH Terms]) AND ("screen"[All Fields] OR ("Prenatal Diagnosis"[MeSH Terms] OR "Noninvasive Prenatal Testing"[MeSH Terms])) AND ("anaemia"[All Fields] OR "Anemia"[MeSH Terms] OR "Anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields] OR ("anaemia"[All Fields] OR "Anemia"[MeSH Terms] OR "Anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields] OR ("iron"[MeSH Terms] OR "iron"[All Fields]) AND "deficien*"[All Fields]) OR "Anemia"[MeSH Terms])	1,704	7:15:07
8	"Anemia"[Mesh]	"Anemia"[MeSH Terms]	174,423	7:14:41

7	((anemia) OR (anaemia)) OR (iron deficien*)	"anaemia"[All Fields] OR "anemia"[MeSH Terms] OR "anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields] OR ("anaemia"[All Fields] OR "anemia"[MeSH Terms] OR "anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields]) OR ("iron"[MeSH Terms] OR "iron"[All Fields]) AND "deficien*" [All Fields])	268,439	7:14:30
6	"Prenatal Diagnosis"[Mesh] OR "Noninvasive Prenatal Testing"[Mesh]	"Prenatal Diagnosis"[MeSH Terms] OR "Noninvasive Prenatal Testing"[MeSH Terms]	80,765	7:14:18

5	screen*			"screen*"[All Fields]	1,040,655	7:14:0 6
4	"Prenatal Care"[Mesh]			"Prenatal Care"[MeSH Terms]	32,133	7:13:5 3
3	((pregnan*) OR (prenatal) OR (pre-natal) OR (antenatal)) OR (ante-natal)			"pregnan*"[All Fields] OR "prenatal"[All Fields] OR "prenatally"[All Fields] OR "prenatals"[All Fields] OR "pre-natal"[All Fields] OR "antenatal"[All Fields] OR "antenatally"[All Fields] OR "ante- natal"[All Fields]	1,165,833	7:13:3 8
2	"Erythrocyte Indices"[Mesh]			"Erythrocyte Indices"[MeSH Terms]	6,216	7:13:2 6
1	(((((complete blood count) OR (full blood count)) OR (hemoglobin)) OR (haemoglobin)) OR (hematocrit)) OR (haematocrit))			"blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("complete"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "complete blood count"[All Fields] OR ("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("full"[All Fields] AND "blood"[All Fields] AND "count"[All Fields])) OR "full blood count"[All Fields] OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields]) OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields]) OR ("haematocrit"[All Fields] OR "hematocrit"[MeSH Terms] OR "hematocrit"[All Fields] OR "haematocrite"[All Fields] OR "haematocrits"[All Fields] OR "hematocrits"[All Fields] OR "hematocrits"[All Fields] OR "hematocrite"[All Fields] OR "haematocrit"[All Fields] OR "hematocrits"[All Fields] OR "hematocrite"[All Fields] OR "haematocrits"[All Fields] OR "hematocrits"[All Fields] OR "hematocrite"[All Fields] OR "haematocrits"[All Fields] OR "hematocrits"[All Fields] OR "hematocrite"[All Fields])	458,529	7:13:1 0

6.2. Search for indirect evidence

Search number	Query	Sort By	Filters	Search Details	Results	Time
9	(#1 OR #2) AND (#3 OR #4) AND (#5 OR #6) AND #7	from 2019 -	2023	((pregnan*"[All Fields] OR ("prenatal"[All Fields] OR "prenatally"[All Fields] OR "prenatals"[All Fields]) OR "pre-natal"[All Fields] OR ("antenatal"[All Fields] OR "antenatally"[All Fields])) OR "ante-natal"[All Fields] OR "Prenatal Care"[MeSH Terms]) AND ("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields])	640	23:05:0 3

		<p>OR ("full"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "full blood count"[All Fields] OR ("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("complete"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "complete blood count"[All Fields] OR ("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR "cbc"[All Fields]) OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields] OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR </p>	
		<p>"haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields] OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR </p>	

8	(#1 OR #2) AND (#3 OR #4) AND (#5 OR #6) AND #7	("pregnan**[All Fields] OR ("prenatal"[All Fields] OR "prenatally"[All Fields] OR "prenatals"[All Fields]) OR "pre-natal"[All Fields] OR ("antenatal"[All Fields] OR "antenatally"[All Fields]) OR "ante- natal"[All Fields] OR "Prenatal Care"[MeSH Terms]) AND ("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("full"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "full blood count"[All Fields] OR ("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("complete"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "complete blood count"[All Fields] OR ("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR "cbc"[All Fields]) OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields] OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "haemoglobins"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields] OR "Erythrocyte Indices"[MeSH Terms]) AND (((("maternally"[All Fields] OR "maternities"[All Fields] OR "maternity"[All Fields] OR "mothers"[MeSH Terms] OR "mothers"[All Fields] OR "maternal"[All Fields] AND ("anaemia"[All Fields] OR "Anemia"[MeSH Terms] OR "Anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields])) OR (((("maternally"[All Fields] OR "maternities"[All Fields] OR "maternity"[All Fields] OR "mothers"[MeSH Terms] OR "mothers"[All Fields] OR "maternal"[All Fields] AND ("anaemia"[All Fields] OR "Anemia"[MeSH Terms] OR "Anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields])) OR "Anemia"[MeSH Terms]) AND (((("adverse"[All Fields] OR "adversely"[All Fields] OR "adverses"[All Fields]) AND ("outcome"[All Fields] OR "outcomes"[All Fields])) OR ("pregnancy complications"[MeSH Terms] OR ("pregnancy"[All Fields] AND "complications"[All Fields]) OR "pregnancy complications"[All Fields] OR ("adverse"[All Fields] AND "birth"[All Fields] AND "outcomes"[All Fields]) OR "adverse birth outcomes"[All Fields] OR ("maternal health"[MeSH Terms] OR ("maternal"[All Fields] AND "health"[All Fields]) OR "maternal"	3,791	23:04:50
7	((adverse outcomes) OR (adverse birth outcomes)) OR (maternal health)) OR (perinatal outcomes)	health"[All Fields] OR ("perinatal"[All Fields] OR "perinatally"[All Fields] OR "perinatals"[All Fields]) AND ("outcome"[All Fields] OR "outcomes"[All Fields])))))	1,267,702	23:04:27

			Fields))))		
6	"Anemia"[Mesh]	Most Recent	"Anemia"[MeSH Terms]	174,464	23:03:57
5	(maternal anemia) OR (maternal anaemia)		((("maternally"[All Fields] OR "maternities"[All Fields] OR "maternity"[All Fields] OR "mothers"[MeSH Terms] OR "mothers"[All Fields] OR "maternal"[All Fields]) AND ("anaemia"[All Fields] OR "anemia"[MeSH Terms] OR "anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields])) OR ((("maternally"[All Fields] OR "maternities"[All Fields] OR "maternity"[All Fields] OR "mothers"[MeSH Terms] OR "mothers"[All Fields] OR "maternal"[All Fields]) AND ("anaemia"[All Fields] OR "anemia"[MeSH Terms] OR "anemia"[All Fields] OR "anaemias"[All Fields] OR "anemias"[All Fields])))	10,386	23:03:28
4	"Erythrocyte Indices"[Mesh]	Most Recent	"Erythrocyte Indices"[MeSH Terms]	6,220	23:02:24
3	(((full blood count) OR (complete blood count)) OR (CBC)) OR (hemoglobin) OR (haemoglobin)		"blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("full"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "full blood count"[All Fields] OR ("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR ("complete"[All Fields] AND "blood"[All Fields] AND "count"[All Fields]) OR "complete blood count"[All Fields]) OR ("blood cell count"[MeSH Terms] OR ("blood"[All Fields] AND "cell"[All Fields] AND "count"[All Fields]) OR "blood cell count"[All Fields] OR "cbc"[All Fields]) OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields] OR "hemoglobins"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields] OR ("haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields] OR "hemoglobin s"[All Fields] OR "hemoglobine"[All Fields] OR "hemoglobinization"[All Fields] OR "hemoglobinized"[All Fields]))	429,110	22:59:46
2	"Prenatal Care"[Mesh]	Most Recent	"Prenatal Care"[MeSH Terms]	32,141	22:59:16
1	(((pregnan*) OR (prenatal)) OR (pre-natal)) OR (antenatal)) OR (ante-natal)		"pregnan*"[All Fields] OR "prenatal"[All Fields] OR "prenatally"[All Fields] OR "prenatals"[All Fields] OR "pre-natal"[All Fields] OR "antenatal"[All Fields] OR "antenatally"[All Fields] OR "ante-natal"[All Fields]	1,166,448	22:58:37

Appendix Table 7. Search strategy for the guideline question on screening for malnutrition using MUAC

Search number	Query	Search Details	Results
1	(mid-upper arm circumference[Title/Abstract]) OR (mid upper arm circumference[Title/Abstract])	"mid upper arm circumference"[Title/Abstract]"	1,574
2	((pregnan*[Title/Abstract]) OR (prenatal screen*[Title/Abstract])) OR (pre-natal screen*[Title/Abstract])) OR (antenatal screen*[Title/Abstract])) OR (ante-natal screen*[Title/Abstract])	"pregnan*[Title/Abstract] OR "prenatal screen*[Title/Abstract] OR "pre natal screen*[Title/Abstract] OR "antenatal screen*[Title/Abstract] OR "ante natal screen*[Title/Abstract]	603,309
3	"Prenatal Diagnosis"[Mesh] OR "Noninvasive Prenatal Testing"[Mesh]	"Prenatal Diagnosis"[MeSH Terms] OR "Noninvasive Prenatal Testing"[MeSH Terms]	80,672
4	#1 AND (#2 OR #3)	("mid upper arm circumference"[Title/Abstract] OR "mid upper arm circumference"[Title/Abstract]) AND ("pregnan*[Title/Abstract] OR "prenatal screen*[Title/Abstract] OR "pre natal screen*[Title/Abstract] OR "antenatal screen*[Title/Abstract] OR "ante natal screen*[Title/Abstract] OR ("Prenatal Diagnosis"[MeSH Terms] OR "Noninvasive Prenatal Testing"[MeSH Terms]))	255

AGREE REPORTING CHECKLIST (SELF EVALUATION)

Fillable forms may be downloaded here: <http://www.agreetrust.org/resource-centre/agree-reporting-checklist/>

This checklist is intended to guide the reporting of clinical practice guidelines.

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES <i>Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.</i>	<input checked="" type="checkbox"/> Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) <input checked="" type="checkbox"/> Expected benefit(s) or outcome(s) <input checked="" type="checkbox"/> Target(s) (e.g., patient population, society)	p. 15 (Sections 2.1-2.4)
2. QUESTIONS <i>Report the health question(s) covered by the guideline, particularly for the key recommendations.</i>	<input checked="" type="checkbox"/> Target population <input checked="" type="checkbox"/> Intervention(s) or exposure(s) <input checked="" type="checkbox"/> Comparisons (if appropriate) <input checked="" type="checkbox"/> Outcome(s) <input checked="" type="checkbox"/> Health care setting or context	pp. 10-12 (Executive Summary, Table 1)
3. POPULATION <i>Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.</i>	<input checked="" type="checkbox"/> Target population, sex and age <input checked="" type="checkbox"/> Clinical condition (if relevant) <input checked="" type="checkbox"/> Severity/stage of disease (if relevant) <input checked="" type="checkbox"/> Comorbidities (if relevant) <input type="checkbox"/> Excluded populations (if relevant)	pp. 10-12 (Executive Summary) p. 15 (Section 2.3)
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP <i>Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.</i>	<input checked="" type="checkbox"/> Name of participant <input type="checkbox"/> Discipline/content expertise (e.g., neurosurgeon, methodologist) <input checked="" type="checkbox"/> Institution (e.g., St. Peter's hospital) <input type="checkbox"/> Geographical location (e.g., Seattle, WA) <input checked="" type="checkbox"/> A description of the member's role in the guideline development group	p. 152 (Appendix, Task Force)
5. TARGET POPULATION PREFERENCES AND VIEWS <i>Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.</i>	<input checked="" type="checkbox"/> Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) <input checked="" type="checkbox"/> Methods by which preferences and views were sought (e.g., evidence from	p. 15-18 (Methodology); pp. 22-125 (Recommendation and Evidence Summaries)

	<p>literature, surveys, focus groups)</p> <p><input type="checkbox"/> Outcomes/information gathered on patient/public information</p> <p><input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations</p>	
6. TARGET USERS <i>Report the target (or intended) users of the guideline.</i>	<p><input checked="" type="checkbox"/> The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators)</p> <p><input checked="" type="checkbox"/> How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)</p>	p. 15 (Sections 2.1-2.4); pp. 10-12 (Executive Summary)
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS <i>Report details of the strategy used to search for evidence.</i>	<p><input checked="" type="checkbox"/> Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL)</p> <p><input checked="" type="checkbox"/> Time periods searched (e.g., January 1, 2004 to March 31, 2008)</p> <p><input checked="" type="checkbox"/> Search terms used (e.g., text words, indexing terms, subheadings)</p> <p><input checked="" type="checkbox"/> Full search strategy included (e.g., possibly located in appendix)</p>	pp. 155-177 (Appendix 10.4. Search Strategy)
8. EVIDENCE SELECTION CRITERIA <i>Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.</i>	<p><input checked="" type="checkbox"/> Target population (patient, public, etc.) characteristics</p> <p><input checked="" type="checkbox"/> Study design</p> <p><input checked="" type="checkbox"/> Comparisons (if relevant)</p> <p><input checked="" type="checkbox"/> Outcomes</p> <p><input checked="" type="checkbox"/> Language (if relevant)</p> <p><input type="checkbox"/> Context (if relevant)</p>	p. 15-18 (Methodology); pp. 22-125 (Recommendation and Evidence Summaries)
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE <i>Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.</i>	<p><input checked="" type="checkbox"/> Study design(s) included in body of evidence</p> <p><input checked="" type="checkbox"/> Study methodology limitations (sampling, blinding, allocation concealment, analytical methods)</p> <p><input checked="" type="checkbox"/> Appropriateness/relevance of primary and secondary outcomes considered</p> <p><input checked="" type="checkbox"/> Consistency of results across studies</p> <p><input checked="" type="checkbox"/> Direction of results across studies</p> <p><input checked="" type="checkbox"/> Magnitude of benefit versus magnitude of harm</p> <p><input checked="" type="checkbox"/> Applicability to practice context</p>	pp. 22-125 (Recommendation and Evidence Summaries)

<p>10. FORMULATION OF RECOMMENDATIONS</p> <p><i>Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.</i></p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) <input checked="" type="checkbox"/> Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) <input checked="" type="checkbox"/> How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote) 	<p>p. 15-18 (Methodology); pp. 22-125 (Recommendation and Evidence Summaries)</p>
<p>11. CONSIDERATION OF BENEFITS AND HARMS</p> <p><i>Report the health benefits, side effects, and risks that were considered when formulating the recommendations.</i></p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Supporting data and report of benefits <input checked="" type="checkbox"/> Supporting data and report of harms/side effects/risks <input checked="" type="checkbox"/> Reporting of the balance/trade-off between benefits and harms/side effects/risks <input checked="" type="checkbox"/> Recommendations reflect considerations of both benefits and harms/side effects/risks 	<p>p. 15-18 (Methodology); pp. 22-125 (Recommendation and Evidence Summaries)</p>
<p>12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE</p> <p><i>Describe the explicit link between the recommendations and the evidence on which they are based.</i></p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> How the guideline development group linked and used the evidence to inform recommendations <input checked="" type="checkbox"/> Link between each recommendation and key evidence (text description and/or reference list) <input checked="" type="checkbox"/> Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline 	<p>p. 15-18 (Methodology); pp. 22-125 (Recommendation and Evidence Summaries)</p>
<p>13. EXTERNAL REVIEW</p> <p><i>Report the methodology used to conduct the external review.</i></p>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) <input checked="" type="checkbox"/> Methods taken to undertake the external review (e.g., rating scale, open-ended questions) <input checked="" type="checkbox"/> Description of the external reviewers (e.g., number, type of reviewers, affiliations) <input checked="" type="checkbox"/> Outcomes/information gathered from the external review (e.g., summary of key findings) <input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development 	<p>p. 19 (External Review)</p>

	process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	
14. UPDATING PROCEDURE <i>Describe the procedure for updating the guideline.</i>	<input checked="" type="checkbox"/> A statement that the guideline will be updated <input checked="" type="checkbox"/> Explicit time interval or explicit criteria to guide decisions about when an update will occur <input type="checkbox"/> Methodology for the updating procedure	p. 127 (Chapter 8. Updating of the Guidelines)
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS <i>Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.</i>	<input checked="" type="checkbox"/> A statement of the recommended action <input checked="" type="checkbox"/> Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) <input checked="" type="checkbox"/> Relevant population (e.g., patients, public) <input checked="" type="checkbox"/> Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) <input checked="" type="checkbox"/> If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	pp. 22-125 (Recommendation and Evidence Summaries)
16. MANAGEMENT OPTIONS <i>Describe the different options for managing the condition or health issue.</i>	<input checked="" type="checkbox"/> Description of management options <input checked="" type="checkbox"/> Population or clinical situation most appropriate to each option	pp. 22-125 (Recommendation and Evidence Summaries)
17. IDENTIFIABLE KEY RECOMMENDATIONS <i>Present the key recommendations so that they are easy to identify.</i>	<input checked="" type="checkbox"/> Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms <input checked="" type="checkbox"/> Specific recommendations grouped together in one section	pp. 10-12 (Executive Summary), pp. 22-125 (Recommendation and Evidence Summaries)
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION <i>Describe the facilitators and barriers to the guideline's application.</i>	<input checked="" type="checkbox"/> Types of facilitators and barriers that were considered <input checked="" type="checkbox"/> Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation)	pp.126-127 (Chapter 7. Applicability Issues)

	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) <input checked="" type="checkbox"/> How the information influenced the guideline development process and/or formation of the recommendations 	
19. IMPLEMENTATION ADVICE/TOOLS <i>Provide advice and/or tools on how the recommendations can be applied in practice.</i>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Additional materials to support the implementation of the guideline in practice. For example: <ul style="list-style-type: none"> ○ Guideline summary documents ○ Links to check lists, algorithms ○ Links to how-to manuals ○ Solutions linked to barrier analysis (see Item 18) ○ Tools to capitalize on guideline facilitators (see Item 18) ○ Outcome of pilot test and lessons learned 	p. 126 (Chapter 7. Dissemination, Implementation, and Monitoring)
20. RESOURCE IMPLICATIONS <i>Describe any potential resource implications of applying the recommendations.</i>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) <input checked="" type="checkbox"/> Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) <input checked="" type="checkbox"/> Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) <input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations 	p. 15 (Methodology); pp. 22-125 (Recommendation and Evidence Summaries)
21. MONITORING/ AUDITING CRITERIA <i>Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.</i>	<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Criteria to assess guideline implementation or adherence to recommendations <input checked="" type="checkbox"/> Criteria for assessing impact of implementing the recommendations <input checked="" type="checkbox"/> Advice on the frequency and interval of measurement <input checked="" type="checkbox"/> Operational definitions of how the criteria 	p. 126 (Chapter 7. Dissemination, Implementation, and Monitoring)

	should be measured	
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY <i>Report the funding body's influence on the content of the guideline.</i>	<input checked="" type="checkbox"/> The name of the funding body or source of funding (or explicit statement of no funding) <input checked="" type="checkbox"/> A statement that the funding body did not influence the content of the guideline	pp. 19-21 (Section 3.6. Editorial Independence)
23. COMPETING INTERESTS <i>Provide an explicit statement that all group members have declared whether they have any competing interests.</i>	<input checked="" type="checkbox"/> Types of competing interests considered <input checked="" type="checkbox"/> Methods by which potential competing interests were sought <input checked="" type="checkbox"/> A description of the competing interests <input checked="" type="checkbox"/> How the competing interests influenced the guideline process and development of recommendations	pp. 19-21 (Section 3.6. Editorial Independence)