Evidence Based Global Health Manual for Preterm Birth Risk Assessment

Dilly OC Anumba
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Editors

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University of Sheffield. This work was supported by the National Institute for Health and Care Research (NIHR) Global Health Research Programme ([GHR 17/63/26])

ISBN 978-3-031-04461-8 ISBN 978-3-031-04462-5 (eBook)
https://doi.org/10.1007/978-3-031-04462-5

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

I am delighted to commend this concise book to healthcare workers in Women's and Children's Health globally. The book provides evidenced practical guidance for systematic assessment of pregnancy risk for preterm birth during antenatal care, towards the provision of personalised care to prevent premature birth and other adverse pregnancy outcomes, consistent with the targets of the UN's Sustainable Development Goals (SDG, 3). It is written for maternal and newborn healthcare providers (doctors, nurses, community health workers) and provides desktop evidence-based information to facilitate antenatal risk assessment and the signposting of pregnant persons to care advice, referrals, supplements and treatments.

It is estimated that about 15 million babies are born prematurely annually, of who nearly a million die from preterm birth-related consequences. Premature birth is also the leading cause of under-5 deaths in many parts of the world, especially in low-resource settings. In the last two decades, modest improvements in child survival following preterm birth have been recorded, attributable to improved essential newborn care components.

An area where progress has lagged is the identification of risk factors for preterm birth for prevention by coordinated, multifactorial, intervention approaches. Whilst individually these interventions may contribute only modestly to preventing preterm birth, integrated approaches embedded into ANC can ensure synergistic reduction of the burden of preterm birth. This manual contains handy information about preterm birth screening in ANC and signposts the reader to published graded evidence, as well as relevant frameworks and guidance recommended by the World Health Organization (WHO) and other agencies. The information provided here is applicable to a global audience, but with special emphasis on low- and middle-income country (LMIC) settings where such resource is most needed.

In developing this manual, we synthesised global literature on preterm birth interventions and guidance, and conducted stakeholder-based prioritisation workshops in Bangladesh, South Africa, and Nigeria under the auspices of the National Institute for Health Research (NIHR) Global Health Research (GHR) Group for the

Preterm Birth Prevention and Management of Preterm Birth in LMICs (PRIME), between 2018 and 2020. These exercises enabled us to identify context-relevant knowledge gaps which are addressed herein.

Sheffield, UK Dilly OC Anumba

Acknowledgements

We acknowledge and thank the UK's NIHR GHR programme for funding the PRIME Research Group whose researchers undertook the evidence reviews that inform this book. The views expressed in this manual are those of the authors and do not reflect the position of the NIHR. We are also grateful to the multitude of stakeholders including women and their families who contributed to prioritising this piece. The evidence has global application and potential for use in multiple LMIC settings.

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Global Antenatal Care Coverage and Content

Dilly OC Anumba and Shamanthi M. Jayasooriya

1 Background Information

Common global risk factors for neonatal deaths include preterm births, birth complications, and infections such as tetanus, sepsis, and pneumonia, all of which disproportionately affect low- and middle-income countries (LMICs). These risk factors can be minimised or prevented through the delivery of high-quality antenatal care (ANC) [1]. ANC encompasses health promotion, education, disease screening, diagnoses, treatments, and interventions to ensure a good pregnancy outcome. Optimum ANC requires promptly initiated sustained care between the mother and usually a health-care professional, culminating in a safe birth experience and a good outcome for both mother and her baby.

The World Health Organisation (WHO) recommendation for effective ANC services, specific- to low-income countries, is four or more ANC visits [2], requiring each of the first two ANC visits to take place in the first two pregnancy trimesters and the last two visits to happen in the last trimester. Generic guidance for ANC is well documented by the WHO [3], as well as other published literature. These various guidelines seek to improve ANC globally in all settings, thereby mitigating adverse pregnancy outcomes, especially neonatal deaths from preterm birth, birth complications, and infections.

Despite the availability of guidance regarding the frequency and content of ANC, there has remained a paucity of literature addressing the gap in knowledge of

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D. O. Anumba, S. M. Jayasooriya (eds.), *Evidence Based Global Health Manual for Preterm Birth Risk Assessment*,
https://doi.org/10.1007/978-3-031-04462-5_1

prenatal risk factors for preterm birth, especially in LMICs and how to apply that knowledge to improve care aimed at prevention. Health-care professionals providing ANC should be aware of the well-evidenced risk factors as well as principles of care that mitigate against preterm birth that should form part of routine antenatal care. In view of this need, we provide in this chapter a brief summary of global ANC coverage and standards, thereby setting the scene for the subsequent chapters in this manual aimed at outlining guidance for early antenatal risk assessment of preterm birth globally, but with emphasis on practice in LMICs where the burden of preterm birth is often disproportionately high.

2 WHO Recommendations/Standards

The historical, basic, four-visit-focused global ANC model was replaced by the current WHO model in 2016 [3]. The latter recommends that interventions are delivered through a minimum of eight antenatal contacts. While continuing to monitor the number of visits or contacts pregnant women have, the 2016 WHO guidance also emphasises the importance of the quality and content of care received. In order to implement the WHO antenatal care model, a monitoring framework has been developed which includes the following three aspects of ANC: the organisation of health systems, the content of care, and the women's experience of care [4].

Programmatic assessment of the effectiveness of health systems to provide good quality ANC relies on the development of suitable content of care indicators. The WHO has therefore recommended a universally relevant list of nine core global and national indicators of ANC, to be measured and monitored by all countries [1]. These nine core indicators are shown in Table 1.

3 Global Variation in Skill of ANC Providers

Central to the provision of ANC is its delivery by skilled health-care professionals [3]. The benefits of ANC for the mother and child have been shown repeatedly to be higher when ANC is administered by trained health-care professionals, practice which also influences the standard of delivery and postnatal care [5]. There are also context-specific variations in access to, and availability of, technical equipment (such as ultrasound scans for dating and monitoring pregnancies) and biomedical engineering support for maintenance of hospital equipment.

Table 1 Global indicators of antenatal care standards

	Global indicators of antenatal care
1.	Percentage of pregnant women with first antenatal contact in the first trimester (before 12 weeks of gestation)
2.	Percentage of pregnant women who received iron and folic acid supplements for 90+ days
3.	Percentage of pregnant women screened for syphilis during antenatal care
4.	Percentage of pregnant women with at least four antenatal contacts Percentage of pregnant women with a minimum of eight antenatal contacts
5.	Percentage of pregnant women who were told about pregnancy danger signs during antenatal care
6.	Percentage of pregnant women with at least one blood pressure measurements during antenatal care. Percentage of pregnant women with at least one blood pressure measure in the third trimester during antenatal care
7.	Percentage of pregnant women whose baby's heartbeat was listened to at least once during antenatal care
8.	Percentage of pregnant women with an ultrasound scan before 24 weeks
9.	Experience of care (e.g. waiting time and support received during antenatal care contacts)

4 Global Situation of Implementation of ANC Monitoring Frameworks

Despite these published frameworks, there remains marked global variations in antenatal care coverage and standards. A full discussion of these global variations is outside the scope of this book. However, it is acknowledged that these variations are largely due to inequities regarding coverage, as well as standards and quality of ANC.

5 Global Inequity in Antenatal Care Coverage

Antenatal care coverage in LMCIs is currently described by limited data sets from population-based surveys such as Demographic and Health Surveys (DHS). The lowest levels of ANC, based on data reporting a minimum of four visits, are observed in sub-Saharan Africa and South Asia [6]. The proportion of women receiving at least four antenatal care visits varies greatly, ranging from 13% in countries in sub-Saharan Africa to over 90% in other countries in Latin America, the Caribbean, and European regions (UNICEF data). Although improvement has been recorded in the global coverage of early (starting at <12 weeks' gestation) antenatal care in the last two decades, the poorest women in LMICs often still do not have access to high-quality antenatal care [7].

6 Global Variations in the Content of Antenatal Care

It has also been acknowledged through several studies that even among women with patterns of care that complied with global recommendations, the content of care was poor, emphasising the need for efficient and effective action to improve care quality. One report surveyed 10 LMICs as illustrative examples and reported that receipt of the six routine components of ANC (measurement of blood pressure, urine sample, blood sample, tetanus protection, iron supplementation and receipt of information on potential pregnancy complications) varied widely [8]. Furthermore, it showed that even among the subset of women starting ANC in the first trimester and receiving over four visits, the percentage receiving all six routinely measured ANC components was low, ranging between 10% and 50%.

7 Antenatal Care Coverage and Preterm Birth

Given that global attainment of ANC quality indices is highly variable, with LMICs demonstrating lower attainment than high-income countries (HICs), it is highly likely that a similar picture exists when the focus is mitigating risk of PTB. Indicators of high-quality ANC may serve as suitable proxies for assessing ANC standards to mitigate PTB. Early ANC in the first trimester enables prompt risk assessment for preterm birth, earlier screening for infections which may be associated with PTB (such as urinary tract infections, HIV, malaria), prompt initiation of routine micronutrient supplements (including iron and folic acid), and, importantly, accurate pregnancy dating. Chapter "Pregnancy Dating Guidance" of this manual describes in-depth pregnancy dating guidance taking into account capacity limitations in LMICs. In addition, early establishment of baseline blood pressure will improve the initiation of preventative treatment where needed, the diagnosis of gestational hypertension, as well as on-going management of hypertension improving pregnancy outcomes by reducing the need for physician-indicated (iatrogenic) prematurity.

In subsequent chapters, this guidance summarizes the evidence for effective ANC screening and intervention for PTB. Many of these align with high-quality ANC, and their application has the potential to improve maternal and child health.

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Antenatal Risk Assessment for Preterm Birth: Summary Guidance for Healthcare Providers

Bronwen Gillespie and Caroline Mitchell

1 Background Information

About 80% of preterm births (PTB) occur in low- and middle-income countries (LMIC), and the highest rates are seen in sub-Saharan Africa and South-East Asia. This guidance aims to help identify women likely to experience PTB in LMIC settings to help reduce the risk of PTB and improve birth outcomes.

This chapter includes a summary of the following five key areas of guidance relevant to pregnancy care for PTB:

- Demographics and Patient History (Sect. 2.1, 3.1).
- Pregnancy Dating (Sect. 2.2, 3.2).
- Infection (Sect. 2.3, 3.3).
- Nutrition (Sect. 2.4, 3.4).
- Alcohol, Tobacco and Other Substance Use (Sect. 2.5, 3.5).

For discussion of the in-depth evidence on each of these key areas, please see Chapters "Prenatal Risk Assessment for Preterm Birth in Low-Resource Settings: Demographics and Obstetric History" to "Evaluating Alcohol, Tobacco and Other Substance Use in Pregnant Women".

The pregnancy booking (registration) visit affords the healthcare professional an opportunity to assess a pregnant woman's risk of PTB, among other potential adverse pregnancy outcomes. Although many of the following areas may be

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D. O. Anumba, S. M. Jayasooriya (eds.), *Evidence Based Global Health Manual for Preterm Birth Risk Assessment*,
https://doi.org/10.1007/978-3-031-04462-5_2

routinely enquired about during antenatal booking and registration in most contexts, the information is seldom used to identify the risk of PTB.

2 Evidence Statements

2.1 Demographics/Patient History

There is evidence of increased risk of PTB when mothers are either very young or very old, of black ethnicity or have a low maternal body mass index (BMI) (see Sect. 2.4).

PTB is multifactorial, sometimes related to health and lifestyle factors (such as nutrition (see Sect. 2.4) and smoking (see Sect. 2.5). Social circumstances must be taken into account, not only as a PTB risk but also in terms of helping to ensure appropriate access to care.

Domestic abuse is an evidence-based risk factor of PTB. Women with a previous history of spontaneous PTB or mid-trimester miscarriage, particularly when this occurs before 32 weeks, are also at high risk of PTB.

Other PTB risk factors which identify women that should ideally receive further risk assessment and specialist care include women who have had a previous caesarean section at full cervical dilatation and women with congenital uterine abnormalities.

2.2 Pregnancy Dating

Accurate pregnancy dating enables a diagnosis of preterm labour and birth to be made. This can ensure timely provision of obstetric interventions in appropriate healthcare settings for the management of complications of pregnancy and birth such as foetal growth abnormalities.

Pregnancy dating can be challenging. Women may not remember their last menstrual period, and menstrual cycle lengths may vary because of lactation following a recent previous baby (Chapter “Pregnancy Dating Guidance”).

Clinical palpation may not be accurate because of excess maternal weight, foetal growth restriction, uterine fibroids or foetal malpresentation often associated with high parity. Late presentation to pregnancy booking makes estimation of pregnancy duration more difficult.

Accuracy of pregnancy dating varies depending on the duration of the pregnancy at the time of presentation.

2.3 Infection Screening (See Chapter "Prenatal Risk Assessment for Preterm Birth in Low-Resource Settings: Infection")

Some maternal infections are associated with an increased risk of PTB; infections are estimated to contribute to between 40% and 50% of all PTB. High rates of maternal bacterial and viral infections are reported in LMIC settings compared to high-income settings.

Early diagnosis and treatment of HIV has been shown to reduce mother-to-child vertical transmission and horizontal transmission to unaffected sexual partners.

2.4 Nutrition

Both high and low BMI, as well as nutrient deficiencies, can have implications for PTB risk, as well as for pregnancy outcomes in general. Access to a well-balanced diet can represent a challenge for pregnant women in LMICs.

Iron and folic acid (and calcium in specific contexts) are necessary supplements for pregnancy in general, as well as having potential benefits for reducing the risk of PTB (iron and calcium).

Low-certainty evidence links some other nutrient deficiencies, such as zinc, to PTB outcomes, but the value of routine supplementation over and above a healthy diet is questioned. However, specific LMIC contexts where dietary zinc is low may benefit from supplementation.

2.5 Alcohol, Tobacco and Other Substance Use

Substance use disorder during pregnancy is a critical public health concern. The most widely used substances globally in pregnancy include tobacco, alcohol, cannabis, opioids and cocaine, but other illicit substances may also be consumed.

Use of alcohol, smoking, and other psychoactive substances during pregnancy leads to an increased risk of health problems for mother and child such as spontaneous abortion, PTB (see Chapter "Evaluating Alcohol, Tobacco and Other Substance Use in Pregnant Women"), stillbirth, low birth weight and birth defects. Concurrent use of these substances (i.e. using more than one) along with other psychosocial factors further increases the risk of adverse outcomes in all settings.

Despite gaps in current knowledge, the potential benefits of the recommended actions (see Sect. 3.5) outweigh the harms (see Chapter "Evaluating Alcohol, Tobacco and Other Substance Use in Pregnant Women").

3 Risk Assessment and Recommended Interventions

To enable formal evaluation and assessment of a woman's risk of PTB and to signpost the woman to appropriate care, the healthcare worker assessing the pregnant woman at booking and subsequently should systematically assess the following:

3.1 Risk Assessment: Demographics/Patient History

Risk of PTB is higher for pregnant women older than 40 and for adolescents. Maternal BMI (< 19Kg/m^2 is a risk factor for PTB) should be derived from maternal weight and height (see Sect. 3.4 below).

Recommended intervention: Document maternal age, weight and height.

Previous history of PTB or mid-trimester miscarriage is important as the earlier the pregnancy stage (gestation) of the previous PTB, the higher the risk of recurrence: women whose prior pregnancy ended between 16 and 20 weeks have a risk of having another PTB even higher than those for whom previous PTB occurred after 20 weeks of pregnancy. Short pregnancy interval (less than 6 months), previous cervical surgery, and intrapartum caesarean section at full cervical dilatation, which can damage the fibres of the cervix in the region of the cervical internal os, can increase the risk of PTB.

Recommended intervention: Document past obstetric history. Those deemed to be at high risk of PTB should be provided general advice as well as referred, where possible, to a specialist able to undertake further evaluation and management of risk. Specialised care, where resources permit and evidence of effectiveness exists, may include serial cervical scanning, cervical cerclage or progesterone supplementation.

3.2 Pregnancy Dating

Accurate pregnancy dating should be established. In early pregnancy, a reliable last menstrual period (LMP) can be confirmed by the foetal crown-rump length (CRL) if ultrasound is readily accessible. In the case of a difference of more than 1 week between estimated dates by LMP and CRL, the expected date of delivery indicated by the ultrasound CRL is more reliable. After the first trimester, foetal biometry using a formula (an algorithm that assesses BPD/HC/FL) may be employed if ultrasound is readily available. If ultrasound is not available and LMP is unknown, clinical assessment of the uterine fundal height (the symphysiofundal height) can be employed pending confirmation by ultrasound. Foetal biometric estimation of gestational age after 20–24 weeks is further improved if the transcerebellar distance can be employed either singly or with femur length assessment to estimate the

duration of a clinically advanced pregnancy >20 weeks' gestation. When pregnancy duration has been estimated by the best and earliest possible modality, this should not be changed by foetal size estimates at later gestation.

Recommended intervention: Document pregnancy dating at clinic visits. See Chapter "Pregnancy Dating Guidance" for more information, including a flow diagram to guide the dating of the pregnancy process.

Enquiring about social circumstances can help ensure access to personalised care. In particular, information on domestic abuse should be sensitively and tactfully sought to offer psychosocial support and safeguarding as available per local protocols.

Recommended interventions: Document social history. Patients with vulnerable social circumstances and other markers (e.g. low BMI, domestic abuse) related to lack of maternal wellbeing may lead to both pregnancy risks and also signal challenges in access to care. Women should be referred to local support services available (psychosocial support, social services) as well as be highlighted for ongoing special support by an identified caregiver.

3.3 Risk Assessment: Infection

Healthcare workers should determine the context-specific risk of infections linked to PTB, to inform testing and management as follows:

Urinary Tract Infections (UTI): UTIs and progression to pyelonephritis are risk factors for PTB.

Recommended intervention: A midstream urine specimen (MSU) should be collected from all women at the antenatal booking clinic. Point of care dipstick testing should be undertaken, and if there is evidence of infection from history or from the dipstick test, treatment should be instituted per clinical protocols, preferably also informed with sensitivities from MSU where laboratory culture is available.

Bacterial Vaginosis (BV)

Recommended intervention: Routine screening is NOT recommended for asymptomatic BV. For symptomatic BV, pregnant women should be asked about any changes to odour or consistency of vaginal discharge and/or vaginal itching.

Syphilis, HIV and Hepatitis B

Recommended intervention: Routine blood testing should be offered to all women at the booking clinic for syphilis, HIV and hepatitis B and treatment offered as per local protocols.

Malaria

Recommended intervention: In contexts where malaria infection occurs, a blood sample for malarial parasite investigation should be sent at booking and intermittent presumptive therapy offered as per local protocols.

3.4 Risk Assessment and Recommended Intervention: Nutrition

Maternal BMI should be calculated at the booking and subsequent appointments.

Recommended intervention (context-specific): If BMI is <19 kg/m2 or nutrition deficiencies detected in undernourished populations:

- Balanced energy and protein dietary supplementation are recommended for pregnant women (shown to reduce the risk of stillbirths and SGA but may also improve PTB risk).
- Zinc supplementation for low dietary levels may reduce the risk of PTB; however, further research is required.

Knowledge of and access to a well-balanced diet should be assessed during pregnancy.

Recommended intervention: Nutrition education (access to a well-balanced diet is advised above and beyond specific micronutrient supplementation) and exercise advice is recommended for healthy pregnancy outcomes in general.

Screening for iron deficiency anaemia should be done early in pregnancy and at 28 weeks.

Recommended intervention if no deficiency: Standard care consisting of iron (daily oral iron with 30 mg to 60 mg of elemental iron) and folic acid (daily folic acid supplementation with 400 μg (0.4 mg)) to improve general pregnancy outcomes, not specifically for PTB.

If anaemia prevalence in pregnant women is <20%, an alternative regimen of intermittent oral iron and folic acid with 120 mg of elemental iron and 2800 g (2.8 mg) of folic acid once weekly can be offered.

Recommended intervention if deficiency detected: If a woman is diagnosed with anaemia during pregnancy, her daily elemental iron should be increased to 120 mg until her haemoglobin concentration rises to normal (110 g/L or higher).

In a context where calcium deficiency may exist, patients with low dietary levels of calcium should be identified (risk of pre-eclampsia).

Recommended intervention: Daily calcium supplementation (1.5–2.0 g oral elemental calcium) for populations with low dietary calcium intake (to reduce the risk of pre-eclampsia). NOTE: Iron and calcium supplements should preferably be administered several hours apart to minimise interactions that reduce their absorption.

In populations at risk of vitamin D deficiency: patients with potentially low levels should be detected, due to risk for pregnancy outcomes in general. In the UK, for example, this includes women with darker skin (such as those of African, African–Caribbean or South Asian family origin) or women who have limited exposure to sunlight, who may usually be covered or housebound.

Recommended intervention: Vitamin D supplementation may be recommended for populations at risk of deficiency to improve general pregnancy outcomes, but routine supplementation is not proven to reduce the risk of PTB.

3.5 Risk Assessment: Alcohol, Tobacco and Other Substance Use

Sensitive and non-judgemental approaches to enquiry about alcohol, smoking (and exposure to second-hand smoke) and other substance use (past and present) are recommended.

Recommended intervention: Document substance use disorder. The presence of family members during maternal health checks may act as a barrier to full disclosure. Effort should be made to address fears of confidentiality. Screening and referral to local services (psychosocial interventions, detoxification and pharmacological treatment) were available.

Smoking and Second-Hand Exposure to Smoke

Recommended intervention: Advice on protection from second-hand smoke in pregnancy (homes and public places). Brief intervention and more intensive psychosocial interventions per local protocols. Pharmacological interventions (Nicotine Replacement Therapy (NRT)) according to local protocols.

Suggested Readings (More References in Chapters 3–7).

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Prenatal Risk Assessment for Preterm Birth in Low-Resource Settings: Demographics and Obstetric History

Dilly OC Anumba and Shamanthi M. Jayasooriya

1 Background

The pregnancy booking (registration) visit affords health-care professionals an opportunity to assess a pregnant woman's risk of PTB among other potential adverse pregnancy outcomes. PTB is multifactorial, with the highest rates seen in sub-Saharan Africa and Asia. This guidance facilitates early identification of women likely to experience PTB in LMICs. The following risk factors for PTB should ideally be explored at booking to enable pregnancy risk stratification and inform future care planning.

2 Evidence Statement

Interventions known to mitigate PTB should be offered at pregnancy booking following a risk assessment. There is evidence of increased risk of PTB with extremes of maternal age and black ethnicity (exclusively US data). Identified domestic abuse should trigger a referral for psychosocial support and safeguarding where services are available.

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D. O. Anumba, S. M. Jayasooriya (eds.), *Evidence Based Global Health Manual for Preterm Birth Risk Assessment*,
https://doi.org/10.1007/978-3-031-04462-5_3

Women with a previous history of spontaneous preterm birth or mid-trimester miscarriage, particularly when this occurs before 32 weeks, should be referred to specialist PTB services or a health-care professional with additional expertise in managing PTB where available. Surveillance at such specialist services should include, where resources permit, serial surveillance by cervical ultrasound and foetal fibronectin estimation. If there is capacity, individualised support that may include cervical cerclage or progesterone prophylaxis may be offered.

Other risk factors for which women should be referred for specialist preterm birth risk assessment and care include women who have had a caesarean section at full cervical dilatation and women with congenital uterine abnormalities.

3 Synopsis of best Evidenced Obstetric and Demographic Risk Factors for Preterm Birth

These, together with the interventions known to mitigate the risk of PTB, are also shown in Table 1.

3.1 Maternal Demographics

(i) *Maternal Age.*

Risk of preterm birth determined by maternal age follows a "U"-shaped distribution. Women over 40 yrs. (OR 1.20, 95% CI 1.06, 1.36) [2] and adolescents, 13–19 yrs., have an increased risk of very preterm (<32 w, aOR 2.12, 95% CI 1.06 to 4.25) and extremely preterm (<28 w, aOR 5.06, 95% CI 1.23 to 20.78) delivery [3], as do first (OR = 1.21, [95% CI: 1.01–1.45]) and second (OR = 1.93, [95% CI: 1.38–2.69]) time mothers aged 14–17 yrs. when compared with 20–29 yrs. [4]. A meta-analysis of 14 cohort studies conducted exclusively in LMICs found that nulliparous women below 18 years of age had the highest risk of PTB of all age/parity (OR: 1.52, 95% CI: 1.40–1.66) [26].

(ii) *Domestic Abuse.*

Rates of PTB are higher (OR 1.91, 95% CI 1.60–2.29) as is low birth weight, LBW (OR 2.11, 95% CI 1.68–2.65) [9].

(iii) *Race.*

Black women in the USA have a fourfold increased risk of PTB (16–18%) compared to White women (5–9%) [5–8]. However, the reason for this is unclear, and its implications for risk assessment in LMICs with predominant black populations are unclear.

Table 1 Summary of interventions for evidenced risk factors of preterm birth

Evidenced risk factor for preterm birth	**Evidence of risk**	**Recommended action for evidenced risk factors for preterm birth**
Generic increased risk		**Generic interventions of possible or clear benefit** [1]
Maternal age • 40 yrs. • <19 yrs.	Low certainty evidence [2] Low to moderate certainty evidence [3, 4]	• Largely none, generic support through pregnancy. • Smoking cessation advice—Substance use Chapter "Evaluating Alcohol, Tobacco and Other Substance Use in Pregnant Women". • Ca, Fe and folic acid supplementation—Nutrition Chapter "Nutritional Status and the Risk of Preterm Birth". • Refer for psychosocial support—Substance use Chapter "Evaluating Alcohol, Tobacco and Other Substance Use in Pregnant Women". • Nutrition advice and supplementation—Nutrition Chapter "Nutritional Status and the Risk of Preterm Birth".
Black race	Moderate certainty evidence [5–8]	
Domestic abuse	Moderate certainty evidence [9]	
Smoking	Low certainty evidence [10, 11]	
Multiple pregnancy	High certainty evidence [5, 8]	
Intermediate or high risk		**Surveillance and intervention pathways (unclear benefit)**
Previous preterm birth or mid-trimester loss (16 to 34 weeks)	Moderate to high certainty of evidence [12–14]	**Surveillance** • Further risk assessment based on history +/− examination as appropriate in secondary care with identification of women needing referral to tertiary. • Offer transvaginal cervix scanning as a secondary screening test to more accurately quantify risk at least twice (usually 2–4 weekly) between 16 and 24 weeks. • Additional use of quantitative foetal fibronectin in asymptomatic women may be considered where centres have this expertise. **Intervention** • Referral to secondary/tertiary preterm prevention (PP) or high-risk pregnancy service at 12–16 weeks. • Cervical cerclage. • Progesterone as deemed appropriate. • Cervical pessary.
Previous preterm prelabour rupture of membranes <34 weeks	Moderate to high certainty of evidence [15]	
Known uterine variant (such as unicornuate, bicornuate uterus, or uterine septum)	Moderate evidence [16]	
Intrauterine adhesions (Asherman's syndrome)	Low certainty of evidence [17]	
History of trachelectomy (for cervical cancer)	Low to moderate certainty of evidence [18, 19]	
Previous delivery by caesarean section at full dilatation	Low certainty of evidence [20]	
History of cervical excision - LLETZ where >10 mm depth removed, or > 1 LLETZ, cone biopsy	Low certainty of evidence [21–23]	
Interpregnancy interval < 6 months	Low certainty of evidence [24, 25]	

LETTZ large loop excision of the transformation zone

3.2 Obstetric and Gynaecological History

(i) *History of PTB.*

Previous PTB is a strong risk factor for repeat PTB (recurrence risk is 15–50% depending on the gestation at previous delivery and birth order [12, 13]). The earlier the gestation at previous PTB or mid-trimester miscarriage, the higher the chance of recurrence [27]. None of the studies in the main systematic review included data from an LMIC setting.

- Twin pregnancy PTB has an absolute risk of recurrence of 57.0% (95% CI 51.9–61.9%) vs 25% (95% CI 24.3–26.5%) after a previous term singleton.
- Singleton PTB has an absolute recurrence risk of 10% (95% CI 8.2–12.3%) vs 1.3% (95% CI 0.8–2.2) after a previous term twin.

(ii) Singleton PTB after a PTB singleton has an absolute recurrence risk of 20% (95% CI 19.9–20.6) [14].*Preterm Prelabour Rupture of Membranes (PPROM).*

(iii) Previous PPROM is associated with increased rates of PPROM (OR 20.6; 95% CI, 4.7–90.2) and PTB (OR 3.6; 95% CI, 2.1–6.4) [28].*Previous Stillbirth.*

(iv) A prior stillbirth is associated with a fourfold increased risk of PTB (OR, 4.2; 95% CI, 1.8–9.9) in the index pregnancy [15], attributable in part to ischaemic placental disease.*Cervical Trauma*: Caesarean section delivery at full cervical dilatation is associated with an increased risk of PTB in the subsequent pregnancy (RR 3.06, 95% CI 1.22–7.71) [20].*Cervical Surgery.*

- Previous history of cervical surgery increases the risk of PTB.
- Previous cold knife conisation (<37 weeks; RR 2.59, 95% CI 1.80–3.72 [14%] vs [5%]).
- Large loop excision of the transformation zone (LLETZ) (RR 1.70, 1.24–2.35, [11%] vs [7%]) [21–23].
- Trachelectomy: preterm birth rates of 30–60% [18, 19].

(v) Interpregnancy interval < 6 months is associated with a twofold increased risk of PTB [24, 25].*Known Uterine Variants and Intrauterine Synechiae (Asherman's Syndrome).*

(vi) Known uterine variants are associated with two- to fivefold increased risk [16], while Asherman's syndrome increases the risk of prematurity delivery two- to threefold to 29.4% (95% CI: 17.0, 35.3%) [17].*Multiple Pregnancy.*

Multiple pregnancy contributes to 2–3% of pregnancies but accounts for 15–20% of all PTBs [5]. Risk of PTB in twins after previous singleton PTB (56.9 versus 20.9%; OR 5.0; 95% CI 3.8–6.6) [8].

3.3 Factors Not Yet Shown to be Associated with Increased Risk of PTB in LMIC Settings

- The influence of social determinants on risk of PTB is complex to determine and evaluate but is probably critical to outcomes. Low maternal education has been associated with PTB in a meta-analysis of 12 cohorts, all from European settings [29].
- Socioeconomic disadvantage has also been associated with PTB: a systematic review and meta-analysis demonstrated a significant increase in risk of PTB in those living in the most deprived neighbourhood quintiles compared to the least deprived quintile, OD: 1.23 (95% CI: 1.18–1.28) [30]. All studies were from high-income settings (the UK, Canada, the Netherlands, the USA, Spain, Sweden, and Australia).
- There are currently no data from LMICs, likely due to the lack of routine record-keeping and major complexities around assessing differing contexts. Assessment of education level and socioeconomic status across a heterogeneous range of contexts is challenging, and while of relevance for individual patient care, this cannot currently be utilised to predict risk of PTB.

4 Practical Clinical Risk Assessment Instructions for PTB

- Although evaluation of the past obstetric history is routinely carried out during antenatal booking and registration in most contexts, information obtained is seldom employed to undertake a formal risk assessment for PTB. We therefore highlight below routine data collected to enable formal evaluation and categorisation of a women's risk of PTB in to low or high.

The health-care worker who conducts the booking assessment should systematically review the demographics of the woman to determine risk factors for PTB. Enquiry should address the following:

- Maternal age: Risk is higher for pregnant women older than 40 and adolescents.
- Past obstetric history for previous experience of PTB or mid-trimester miscarriage. The earlier the pregnancy stage (gestation) of the previous PTB, the higher the risk of recurrence: women whose prior pregnancy ended between 16 and 20 weeks have a risk of recurrent PTB that equals or exceeds the recurrence risk for women whose prior PTB occurred after 20 weeks.

- Short interpregnancy interval (< 6 months), previous cervical surgery, and intrapartum caesarean section at full cervical dilatation, which can damage the fibres of the cervix in the region of the cervical internal os.
- A history of domestic abuse should be sensitively and tactfully sought.
- Behavioural risk factors such as cigarette smoking and other substance misuse should be elicited.

These enquiries should ultimately lead to categorisation of risk of preterm birth and the signposting of the woman to appropriate care.

5 Interventions for Evidenced Risk Factors for PTB

These are outlined in Table 1.

6 Summary of Generic Health Systems ANC Interventions to Reduce PTB (Likely to Mitigate PTB Risk from Demographic and Obstetric Factors)

These are shown in Table 2.

7 Research and Clinical Practice Recommendation

Most of the evidence describing demographic and clinical historical risk factors for PTB is from high-income settings (HICs). Although some of these may apply to an LMIC setting, there is clear need for further research regarding the risk factors for PTB in LMIC settings where the contribution of factors such as infection and

Table 2 Benefits statements of generic health systems ANC interventions to reduce PTB

Moderate (clear) benefit [1]**.**
• Continuity of care vs other models of care for all women.
• Screening for lower genital tract infections <37wks without signs of labour, bleeding, Or infection
• Zn supplementation (see nutrition Chapter "Nutritional Status and the Risk of Preterm Birth").
• Cerclage for singleton pregnancy + high risk of PTB.
Low (possible) benefit [1]
• Group ANC for all pregnant women.
• Antibiotics for pregnant women with asymptomatic bacteriuria.
• Pharmacological interventions for smoking cessation.
• Vitamin D alone for women without pre-existing conditions, e.g. diabetes.

nutrient deficiencies may play a more crucial role. There is also a paucity of low-cost interventions and risk mitigation interventions accessible to health-care providers in LMIC settings. However, improved antenatal risk assessment can promote advice regarding lifestyle modifications such as smoking cessation, nutrient supplementation, and judicious use of indicated cervical cerclage, all of which could reduce the risk of spontaneous premature birth as well as of indicated preterm birth from conditions such as pre-eclampsia and placental insufficiency causing small for gestational age. Given the variable skills and competencies of providers of antenatal care (ANC) and birth in LMIC settings, further research is required to define care models and advocate for practitioners that may reduce incidence or severity of preterm birth in LMIC settings.

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Pregnancy Dating Guidance

Dilly OC Anumba

1 Background

An essential component of antenatal care is pregnancy dating, allowing for an accurate estimation of the duration of pregnancy. It is important for identifying the optimum timing of obstetric interventions such as location of birth, delivery mode, and management of foetal growth abnormalities. Accurate pregnancy dating improves the classification of preterm birth (PTB) and enables global PTB rates to be comparable. In low- and middle-income countries (LMICs), where the burden of PTB and intrauterine growth restriction is highest [1, 2], pregnancy dating is a challenge: women are often unable to recollect their last menstrual period, and menstrual cycle lengths vary due to short birth intervals and lactation [3, 4]. Clinical palpation to estimate uterine size is often inaccurate and influenced by foetal growth restriction, uterine fibroids, foetal malpresentation (associated with high parity), and maternal obesity. Late presentation for pregnancy registration is common in LMICs making pregnancy dating a challenge.

This guidance details the optimum approach to pregnancy dating utilising the best resources currently available in different contexts and taking into account late presentation.

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D. O. Anumba, S. M. Jayasooriya (eds.), *Evidence Based Global Health Manual for Preterm Birth Risk Assessment*,
https://doi.org/10.1007/978-3-031-04462-5_4

2 Evidence Statement

Accurate pregnancy dating is important to enable accurate diagnosis of preterm labour and delivery. It varies with the duration of the pregnancy at presentation.

In early pregnancy, a reliable last menstrual period (LMP) should be employed and confirmed by the foetal crown-rump length (CRL) if ultrasound is readily accessible. A discrepancy of more than 1 week between both modalities should trigger a switch in the confirmed pregnancy duration and expected date of delivery to the ultrasound CRL as this is more reliable.

After the first trimester, foetal biometry using a formula (algorithm that assesses BPD/HC/FL) may be employed if ultrasound is readily available. If ultrasound is not immediately accessible, clinical assessment of the uterine fundal height should be used pending confirmation by ultrasound where possible. Foetal biometric estimation of gestational age at 20–24 weeks' is further improved if the transcerebellar distance can be employed either singly or with femur length assessment to estimate the duration. Where ultrasound is unavailable, then the symphysiofundal height should be used.

3 Synopsis of Best-Evidenced Pregnancy Dating Methods

3.1 Last Menstrual Period

This is the most widely used method to estimate pregnancy duration. If known with certainty, it offers a good estimation of the baby's due date and accurate pregnancy dating. However, it may overestimate pregnancy duration by more than 3 days in high-income settings (HICS) [5] and longer in LMICs [6]. It is dependent on the regularity of the menstrual cycle and subjective recall of the first day of the last period.

(*Moderate to high certainty of evidence)*

3.2 First Trimester Ultrasound

Measurement of the foetal crown-rump length (CRL) is considered to be the gold-standard method for estimating gestational age (up to 14 weeks' gestation) [5, 7]. Unfortunately, in LMICs, ultrasound early in gestation is often not universally available, and there is the tendency for pregnant women to present late for antenatal care. These issues limit the application of CRL measurement in these settings.

(Moderate to high certainty of evidence)

3.3 Ultrasound Standard Foetal Biometric Measurements at 14 to 20 Weeks' Gestation

Standard biometric measurements (biparietal diameter, head circumference, abdominal circumference, and femur length) provide an accurate estimation of gestational age (to within ±1–2 weeks of the crown-rump length (CRL) measurement of gestational age) [8].

(Moderate to high certainty of evidence)

3.4 Ultrasound Standard Foetal Biometric Measurements after 20 Weeks' of Gestation

Standard biometry does not perform as well as it does at less than 20 weeks' gestation, with accuracy of only ± ≥ 3 weeks of the CRL measurement [7], especially in LMICs where 19·3% of infants are born small for gestational age [2]. Measurement of the cerebellum alone or combined with femur length [9] provides more accurate estimation of gestational age compared with standard biometry measurements [10].

(Moderate to high certainty of evidence)

3.5 Symphysiofundal Height Estimation

In late pregnancy after 20 weeks, this provides gestational age estimation comparable with the last menstrual period and may be employed against a validated normogram when women present late and menstrual dates are not reliable and access to ultrasound is limited [11].

(Low certainty of evidence)

Figure 1 outlines the pragmatic steps that facilitate estimating pregnancy duration as accurately as possible in low as well as high resource settings, based on careful evaluation of the last menstrual period history, the availability and utilisation of ultrasound, as well as the best ultrasound parameters that should be employed. In limited resource settings where late booking is rife, it highlights the use of clinical estimation of the symphysiofundal height to augment available information about pregnancy duration.

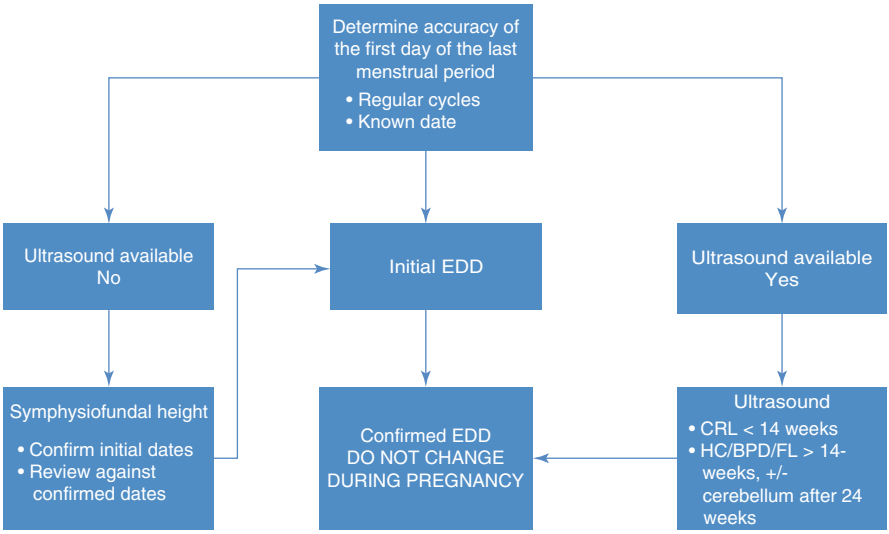

Fig. 1 Flow diagram to guide pregnancy dating. *EDD* Estimated date of delivery; *CRL* Crown-rump length, *HC* Head circumference, *BPD* Biparietal diameter; *FL* Femur length

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Prenatal Risk Assessment for Preterm Birth in Low-Resource Settings: Infection

Kerry M. Parris and Shamanthi M. Jayasooriya

1 Background

Infection is a major risk factor for PTB, accounting for 40–50% of all deliveries before 37 completed weeks of gestation. The most common route of infection is via the genital tract and subsequent microbial ascension and invasion of the amniotic cavity (25–40% of the total number of PTBs) [1–4]. Routine ANC provides an opportunity for health-care professionals to assess a pregnant woman's risk of PTB and other adverse pregnancy outcomes. High rates of maternal bacterial and viral infections are reported in LMICs, and it is in these settings where most PTBs occur (approximately 81%) [5].

2 Evidence Statement

Infection in pregnancy is associated with an increased risk of PTB. Current guidelines recommend routine testing and treatment for human immunodeficiency virus (HIV), hepatitis B virus, malaria (context dependent), and syphilis. The aim of this testing is to improve health outcomes of mothers and their babies and/or to prevent mother-to-child transmission.

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https://doi.org/10.1007/978-3-031-04462-5_5

The increased risk of PTB from other infections such as asymptomatic bacteriuria (ASB) should prompt testing a clean-catch midstream urine by microscopy, culture, and sensitivity, where available, and providing antibiotic treatment as appropriate. Pregnant women should be offered testing for lower genital tract infections in high-risk populations or cases of suspected disease, with or without symptoms, as evidence has shown that such treatment decreases PTB risk.

3 Synopsis of Best Evidenced Infectious Risk Factors for Preterm Birth

For a summary of the evidence of infectious risk factors for preterm birth, please see Table 1, in Sect. 5.

3.1 Human Immunodeficiency Virus

HIV is more prevalent in LMIC than HIC settings. HIV has been shown to increase the risk of spontaneous PTB 2.1-fold when compared to HIV-negative controls (17% vs. 8%; OR 2.27; 95% CI:1.2–4.3). Furthermore, a 3.2-fold increased risk for PTB was reported in HIV-positive women, and this was strongly associated with the use of highly active antiretroviral therapy (HAART) in the second trimester, OR 6.2 (95% CI:1.4–26.2) [6].

3.2 Malaria

Malaria infection is a risk factor for PTB. A systematic review and meta-analysis of 58 studies with 134,801 participants across 21 East African countries reported increased risks of PTB (aOR of 3.08 (95% CI:1.2–4.3) and also when malaria is a co-infection with HIV (aOR 2.59; 95% CI:1.84–3.66) [8]. Intermittent preventive treatment of malaria in pregnancy (IPTp) is an integral part of antenatal care in areas with moderate to high malaria transmission, alongside use of long-lasting insecticidal nets (LLINs), prompt diagnosis, and effective treatment of malaria infections.

Table 1 Evidenced infection-associated risk factors for PTB and effectiveness of interventions

Evidenced risk factor for preterm birth	Evidence of risk	Recommended action for risk factor for preterm birth	Evidence of effectiveness of action
HIV	Moderate certainty evidence. HIV increases PTB risk 2.1-fold compared to HIV-negative controls (17% vs. 8%; OR 2.27; 95% CI:1.2–4.3) [6]	Routine HIV testing in pregnancy ART initiated in all pregnant women diagnosed with HIV at any CD4 level and continued lifelong [7]	Association shown with increased risk in women with HIV, but low certainty evidence
Malaria	Low certainty evidence Data limited to East Africa [8]. Malaria increases risk of PTB, aOR 3.08 (95% CI:2.32–4.10) [8]	Follow current WHO guidance for IPTp [7]	High quality evidence, specifically for PTB, is lacking
Syphilis	Low certainty evidence Data limited to East Africa [8] Syphilis increases risk of PTB (OR 2.09; 95% CI:1.09–4.00) [9]		No current evidence available specifically relating to PTB
UTI	Low certainty evidence [8] Studies report odds ratios (OR) of 1.8 (95% CI:1.4–2.1) [10], 1.8 (95% CI:1.3–2.4) [11] and 5.05 (95% CI:1.16–21.8) [12, 13]	Routine midstream urine culture (limited by availability of laboratory services) Seven-day antibiotic regimen for positive urine culture to prevent PTB [7]	No current evidence available
ASB	Low certainty evidence ASB associated with PTB; aOR 1.6; 95% CI:1.5–1.7) [14].	Routine screening not recommended [7, 15]. Seven-day antibiotic regimen for positive urine culture to prevent PTB [7].	Low certainty evidence suggests that antibiotics for ASB may reduce preterm birth (RR: 0.27, 95% CI: 0.11–0.62) [16]
STIs	Low to moderate certainty evidence. Sexually transmitted infections (STI) of the lower genital tract increase risk of PTB • *Trichomonas vaginalis* parasite OR of 1.3 (95% CI:1.1–1.4) [17]. • *Chlamydia trachomatis bacteria.* ORs of 2.2 (95% CI:1.03–4.78) <37 weeks delivery [18, 19]. Limited evidence of connection between *N. gonorrhoeae* and PTB	Treating *C. trachomatis* is beneficial in reducing PTB [4] (may be limited by access to testing) Syndromic approach to STI treatment where laboratory facilities are limited can reduce unnecessary treatment [20]	Moderate evidence, Cochrane database of systematic reviews shows treatment of *T. vaginalis* with metronidazole increases risk of PTB (RR 1.78; 95%CI:1.19 to 2.66) [21]

(continued)

Table 1 (continued)

Evidenced risk factor for preterm birth	Evidence of risk	Recommended action for risk factor for preterm birth	Evidence of effectiveness of action
BV	Low certainty evidence, data limited to East Africa [8]. Data limited to East Africa, aOR 16.4 (95% CI: 4.3–62.7) [22]	None [23]	No current evidence available
CMV	Low certainty evidence, data limited to HIC. Cytomegalovirus (CMV), OR 1.6 (95% CI:1.14–2.27) [24]	None	No current evidence available
HSV	Low certainty evidence, data limited to HIC. Any herpesvirus, OR 1.51 (95% CI:1.08–2.10) [24]	None	No current evidence available
Influenza A	Moderate certainty evidence Data limited to HIC. Influenza A (H1N1), OR 2.21 (95% CI:1.47–3.33) [25]	Influenza vaccination (known high transmission settings) [7]	High quality evidence specifically for PTB is lacking

HIV Human immunodeficiency virus, *PTB* Preterm birth, *ART* Antiretroviral therapy, *ITPp* Intermittent preventive therapy in pregnancy, *UTI* Urinary tract infection, *ASB* Asymptomatic bacteriuria, *STIs* Sexually transmitted infections, *BV* Bacterial vaginosis, *CMV* Cytomegalovirus, *HSV* Herpes simplex virus, *HIC* High-income setting, *OR* Odds ratio, *aOR* Adjusted odds ratio, *RR* Risk ratio

3.3 Syphilis

Infection with syphilis-causing bacteria, *Treponeda pallidum,* is more common in LMIC than HIC settings. Syphilis is associated with an increased risk of PTB where mothers present late to antenatal care (OR 2.09; 95% CI:1.09–4.00) [9].

3.4 Urinary Tract Infections (UTI)

UTIs are frequently reported as a risk factor for PTB, with studies stating odds ratios (OR) of 1.8 (95% CI: 1.4–2.1) [10], 1.8 (95% CI: 1.3–2.4) [11] and 5.05 (95% CI: 1.16–21.8) [12, 13]. Low quality evidence from a systematic review and meta-analysis conducted across 21 East African countries reported an OR of 5.27 (95% CI: 2.98–9.31) [8]. Symptomatic urinary tract infections should be treated with antibiotics, and repeated urine testing is advised in low- and high-risk women [8].

3.5 Asymptomatic Bacteriuria (ASB)

Many infections during pregnancy present *subclinically or are asymptomatic*, subsequently delaying treatment and diagnosis. Untreated ASB is associated with PTB (aOR 1.6; 95% CI: 1.5–1.7) and has been shown to develop into acute pyelonephritis, itself an independent risk factor for PTB (OR: 2.6; 95% CI: 1.7–3.9) [7, 14, 26]. Increased rates of spontaneous PTB in patients with pyelonephritis have been reported (10.3% vs 7.9%; OR:1.3; 95% CI:1.2–1.5) [27]. Routine urine dipstick testing is not advised by the WHO due to high false-positive rates (118/1000) leading to unnecessary treatment and antimicrobial resistance [7].

3.6 Sexually Transmitted Infections (STIs)

STIs of the lower genital tract have been linked to increased risk of PTB; the most robust evidence available reports an OR of 1.3 (95% CI:1.1–1.4) [17] in cases of trichomoniasis (caused by the *Trichomonas vaginalis* parasite). However, Gulmezoglu and Azhar (2011) reported *T. vaginalis* treatment with metronidazole to appear to increase risk of PTB (RR 1.78; 95%CI:1.19 to 2.66) [21, 28]. Odds ratios of 2.2 (95% CI:1.03–4.78) and 3.2 (95% CI:1.08–9.57) at <37 weeks delivery and < 35 weeks delivery, respectively, are reported where infection with *Chlamydia trachomatis* bacteria has been diagnosed [18, 19].

3.7 Bacterial Vaginosis (BV)

A 2014 prospective cohort study found a significant increase in PTB risk in women with higher levels of BV-associated bacteria and a previous history of PTB, adjusted OR (aOR) 16.4 (95% CI: 4.3–62.7) [22]. Strategies to treat BV have failed to lower PTB risk [4].

3.8 Systemic Viral Pathogens

Infection with some systemic viral pathogens is a risk factor for PTB; the available best evidence reports odds ratios for cytomegalovirus (CMV), 1.6 (95% CI:1.14–2.27) [24], any herpesvirus, 1.51 (95% CI:1.08–2.10) [24], and influenza A (H1N1), 2.21 (95% CI:1.47–3.33) [25].

3.9 Factors Not Yet Shown to Be Associated with Increased Risk of Preterm Birth

- A systematic review and meta-analysis including one study of periodontal disease (PD) carried out in East Africa reported it as a risk factor for PTB (aOR 2.32; 95% CI:1.33–4.35) [8]. Currently, there is insufficient evidence to directly establish a connection between PTB and periodontal infection [4].
- There is limited evidence suggesting infection by *Neisseria gonorrhoea* bacteria as a risk factor for PTB (OR 2.50; 95% CI:1.39–4.50) [19].
- Estimations of global burden of tuberculosis (TB) found little evidence of increased risk of PTB in TB-infected pregnant women [29].
- Colonisation by Group B *Streptococcus* (GBS) has previously been described as a risk factor for PTB; a 1989 meta-analysis found non-bacteriuric patients had half the risk of PTB as those with ASB resulting from GBS colonisation (RR 0.5; 95% CI:0.36–0.70) [30]; however, more recent evidence is lacking.

4 Practical Clinical Risk Assessment Instructions for PTB

Health-care workers conducting the antenatal booking assessment should determine the risk of infections linked to PTB. This enquiry should determine likelihood of specific infections known to be risk factors for PTB to inform testing and management as follows:

- Urinary tract infections (UTI): UTIs and progression to pyelonephritis are risk factors for PTB. Information on frequency of urination and presence of dysuria or suprapubic pain should be sought. Point of care dipstick testing should be undertaken where symptomatic bacteriuria is suspected.
- Pyelonephritis: Along with determining symptoms of a UTI, detail of any fever or loin pain should also be elicited where pyelonephritis is suspected.
- Asymptomatic bacteriuria (ASB): A urine specimen, preferably a clean catch urine (CCU) specimen, should be collected from all women at the antenatal booking clinic. Where not feasible, a midstream urine (MSU) specimen will suffice. Dipstick testing should not be performed due to a lack of sensitivity. CCU/MSU should be sent to the laboratory for culturing.
- Bacterial vaginosis (BV): Routine screening is not recommended for asymptomatic BV. Symptomatic BV information should be elicited through asking pregnant women about any changes to odour or consistency of vaginal discharge and/or vaginal itching.
- Syphilis, HIV, and hepatitis B: Routine blood testing should be offered to all women at the booking clinic for syphilis, HIV, and hepatitis B. Both syphilis and HIV have been shown to be risk factors for PTB.

Enquiries and testing, where appropriate, should lead to categorisation of risk of PTB and appropriate treatment and management.

Table 2 Benefit statements of infection interventions to reduce PTB risk

- **Moderate (clear) benefit** [7, 16].
  - Testing for HIV, malaria, and syphilis.
  - Screening for lower genital tract infections <37wks without signs of labour, bleeding, or infection.
  - Antibiotics for pregnant women with UTIs.
- **Low (possible) benefit** [7].
  - Screening for asymptomatic bacteriuria.
  - Antibiotics for pregnant women with asymptomatic bacteriuria.
- **No benefit** [23].
  - Metronidazole for low- or high-risk women with bacterial vaginosis.

5 Interventions for Evidenced Risk Factors for PTB

The evidenced effective interventions to address infections associated with preterm birth are shown in Table 1.

6 Summary of ANC Infection Interventions to Reduce PTB

These are depicted in Table 2.

7 Research and Clinical Practice Recommendation

Clinical practice should focus on promoting awareness of infections prior to and during pregnancy rather than routine testing of all infections linked to PTB. Further research is required to consider routine testing for chlamydia in target populations and effectiveness of dipstick testing for ASB in LMIC settings.

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Nutritional Status and the Risk of Preterm Birth

Bronwen Gillespie

1 Background

The pregnancy booking visit affords the health-care professional an opportunity to assess a pregnant woman's risk of PTB, among other potential adverse pregnancy outcomes. This guidance is aimed to facilitate early identification of women likely to experience PTB, especially in LMICs settings, and to highlight risk factors for PTB that should signpost care pathways to try to reduce the risk and improve birth outcomes. A woman's body mass index (BMI) and nutritional status, covered in this section, affect her risk of spontaneous PTB and should be assessed.

2 Evidence Statement

- Iron, folic acid, and calcium (in specific contexts) are necessary supplements for pregnancy in general and also have potential benefits for reducing the risk of PTB. In undernourished populations, balanced energy and protein dietary supplementation, as well as nutrition education, is recommended for pregnant women to improve broad pregnancy outcomes. Likewise, for populations at risk of low levels of vitamin D, supplementation may be recommended to improve general pregnancy outcomes.
- The benefit of other micronutrients, vitamins, and minerals to reduce the risk of PTB is unclear. Low-certainty evidence links low dietary zinc to PTB risks, but there is no definitive evidence in support of routine zinc supplementation for all

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D. O. Anumba, S. M. Jayasooriya (eds.), *Evidence Based Global Health Manual for Preterm Birth Risk Assessment*,
https://doi.org/10.1007/978-3-031-04462-5_6

pregnant women. However, in settings where there are low dietary or maternal zinc levels, women may benefit from zinc supplementation. Nutrition is a marker of general health and until clearer evidence is available regarding the benefit of supplementing with specific nutrients, caregivers should explore and address access to balanced diets and food security in general during the pregnancy risk assessment.

3 Synopsis of best Evidenced Nutrition-Related Risk Factors for Preterm Birth

For a summary of the evidence of these nutrition-related risk factors for preterm birth, please see Table 1, in Sect. 5, below.

3.1 Body Mass Index (BMI)

(i) *Low BMI.*

Low BMI is associated with an increased risk of PTB (BMI <19 kg/m^2 relative risk (RR): 1.29, 95% CI: 1.15–1.46) [1, 2]. A systematic review of 78 studies involving 1,025,794 women found that the overall risk of PTB was increased in underweight women (adjusted RR 1.29, 95% CI 1.15–1.46), as were the risks of spontaneous PTB (adjusted RR 1.32, 95% CI 1.10–1.57) and induced PTB (adjusted RR 1.21, 95% CI 1.07–1.36) [2]. However, when limited to developing countries (5/52, 10% of cohort studies), no significant association was found (RR: 0.99, 95% CI: 0.67–1.45) [2].

(ii) *High BMI.*

Overweight (OR 1.20, 95% CI 1.04–1.38), obese (OR 1.60, 95% CI 1.32–1.94), and morbidly obese (OR 2.42, 95% CI 1.46–4.05) have been shown to increase risks of PTB [15]. Data from LMICs is absent. In one systematic review on maternal BMI which included 39 studies (1,788,633 women), findings suggested that obese women (BMI, 35–40) have an increased risk for PTB in general (aOR = 1.33, 95% CI: 1.12–1.57), as well as for moderate (aOR = 2.43, 95% CI: 1.46–4.05) and very PTB (AOR = 1.96, 95% CI: 1.66–2.31). Very obese women (BMI > 40) have an even higher risk (AOR = 2.27, 95%CI: 1.76–2.94) [5].

Table 1 Summary of evidenced risk factors and interventions for PTB

Evidenced risk factor for preterm birth	Evidence of risk	Recommended action for risk factor for preterm birth	Evidence of effectiveness of action
Low BMI	Low-certainty evidence [1, 2]. When limited to LMIC settings, no significant association has been found	Booking visit height and weight (not specific to PTB)	Moderate-certainty evidence reduces SGA neonates (7 trials, 4408 women; RR: 0.79, 95% CI: 0.69–0.90) and stillbirths (5 trials, 3408 women RR: 0.60, 95% CI: 0.39–0.94), no proven effect on PTB (5 trials, 3384 women; RR: 0.96, 95% CI: 0.80–1.16). Most studies were in LMIC settings [3]
		Balanced energy and protein dietary supplementation [3]	May reduce low-birth-weight neonates, little or no effect on SGA neonates, stillbirths, or neonatal deaths, low certainty for evidence on PTB [3]. One LMIC setting included
		Nutrition education on increasing daily energy and protein intake [3]	Lower relative risk of PTB (2 trials, 449 women; risk ratio (RR) 0.46, 95% CI 0.21 to 0.98, low-quality evidence) [4]
High BMI	Low-certainty evidence [5]. Does not include LMIC studies	Diet and exercise advice at booking (not specific to PTB) [3]	Systematic review (5 trials, 2713 women), risk of PTB reduced in women enrolled to diet and exercise (RR 0.71, 95% CI 0.55–0.93) [6], low-certainty evidence. Not specified whether these include LMICs
Dietary patterns	Low certainty (observational) [7] limited data from LMIC settings		
Anemia/iron deficiency	Maternal anemia is associated with PTB (RR, 1.56 (95% CI: 1.25–1.95)) [1]. (moderate-certainty evidence). Over half of included studies were LMIC settings, primarily Asia	Routine elemental iron [8] and folic acid [3] supplementation (routine or intermittent) in settings with a high prevalence of anemia in pregnancy [3]	High-certainty evidence shows that iron may reduce the risk of PTB less than 34 weeks (5 trials including LMIC settings, 3749 women; RR: 0.51, 95% CI: 0.29–0.91) [8] [9] Intermittent iron and folic acid produce similar outcomes as daily supplementation. All studies from LMIC settings [10]

(continued)

Table 1 (continued)

Evidenced risk factor for preterm birth	Evidence of risk	Recommended action for risk factor for preterm birth	Evidence of effectiveness of action
Folic acid	This is not established to be a risk factor for PTB but beneficial in the prevention of neural tube defects	Daily folic acid supplementation with 400 μg (0.4 mg) is advised for all pregnancies [3, 11]	Conflicting low-certainty evidence that folic acid supplement initiated after pregnancy may reduce risk of PTB (RR = 0.68, 95%CI, 0.52–0.90), it may not if initiated before conception (RR = 0.89, 95%CI, 0.80–1.01) [12]. Study included limited LMIC settings (China) [12]
Calcium	Calcium deficiency is associated with increased risk of pre-eclampsia [13] and low quality evidence. LMIC settings included	Daily calcium supplementation recommended for pregnant women from populations at high risk of low calcium intake [3]	Low quality evidence and high proportion of LMIC studies included [13] Moderate-certainty evidence shows that high-dose calcium supplementation may reduce PTB (12 trials, 15,479 women; RR: 0.81, 95% CI: 0.66–0.99) [3, 14] and some trials in LMIC settings [14]

PTB Preterm birth, *BMI* Body mass index, *LMIC* Low- and middle-income countries, *SGA* Small for gestational age, *RR* Relative risk, *CI* Confidence interval

3.2 Dietary Patterns

A systematic review of observational studies on maternal dietary patterns and birth outcomes found that unhealthy dietary patterns characterized by high intakes of refined grains, processed meat, and foods high in saturated fat or sugar were associated with a trend towards a higher risk of PTB (OR: 1.17; 95% CI: 0.99, 1.39; I2 = 76%). Healthy dietary patterns—characterized by high intakes of vegetables, fruits, whole grains, low-fat dairy, and lean protein foods—were associated with a lower risk of PTB (OR for top compared with bottom tercile: 0.79; 95% CI: 0.68, 0.91; I2 = 32%) [7].

3.3 Nutrient and Mineral Deficiencies Definitely *Associated with an Increased Risk of Preterm Birth*

Observational studies suggest that pre-conceptional and periconceptional intake of some vitamin and mineral supplements are associated with a reduced risk of PTB [8]. Further evidence examines specific supplements for nutrient deficiencies:

(i) *Maternal Anemia and/or Iron Deficiency.*

- A meta-analysis of 18 prospective and retrospective studies with a combined sample size of 932,090 showed a significant relationship between maternal anemia during pregnancy and PTB (OR 1.56 [95% CI: 1.25–1.95]) [16].
- WHO guidelines recommend daily oral iron but suggest that weekly iron should be considered for a) cases where daily iron is not acceptable due to side effects and b) populations with anemia in pregnancy prevalence of less than 20% (as this is not considered public health risk) [3].

(ii) *Folic Acid.*

- Evidence that folic acid supplementation reduces the risk of PTB is conflicting [17], with one systematic review suggesting that supplementation is associated with a significant reduction in the risk of PTB only when being initiated after conception [12]. However, folate supplementation has established benefits for reducing birth defects.

(iii) *Calcium.*

- The WHO recommends that in populations with low dietary calcium intake pregnant women should receive daily calcium supplementation to reduce the risk of pre-eclampsia [3].
- One review found that high-dose calcium supplementation (at least 1 g/day) may reduce the risk of pre-eclampsia and PTB, particularly for women with low calcium diets (low-quality evidence) [13]. The average risk of PTB was reduced in the calcium supplementation group (11 trials, 15,275 women: RR 0.76, 95% CI 0.60 to 0.97; low-quality evidence); this reduction was greatest among women at higher risk of developing pre-eclampsia (four trials, 568 women: average RR 0.45, 95% CI 0.24 to 0.83). Most studies were carried out in LMIC settings [13].
- A review examining the effect of calcium supplementation on pregnancy outcomes other than hypertension and pre-eclampsia showed no clear additional benefits on preventing PTB [14]. However, when evidence is stratified by dose (<1000 mg vs ≥1000 mg), high-dose calcium supplementation appears to reduce PTB (12 trials, 15,479 women; RR: 0.81, 95% CI: 0.66–0.99) [3]. Current WHO guidelines recommend calcium supplementation only to reduce the risk of developing pregnancy-induced hypertension [3, 14].

3.4 Nutrient and Mineral Deficiencies Possibly *Associated with an Increased Risk of Preterm Birth in Specific Situations*

Supplementing the following nutrient factors is not clearly established to reduce the risk of PTB. However, for some of these factors, the evidence is conflicting, and for others, further research is required.

(i) *Vitamin D.*

- The WHO does not recommend vitamin D supplementation to improve maternal and perinatal outcomes, advising that sunlight is the most important source of vitamin D [3]. In some countries such as the UK, supplementation with 10 micrograms of vitamin D per day for population groups at increased risk of vitamin D deficiency (those with darker skin or experiencing low sunlight exposure) and pregnant and lactating women is recommended [11].
- Evidence (22 trials, 3725 pregnant women) suggests that supplementation with vitamin D alone during pregnancy probably reduces the risk of pre-eclampsia, gestational diabetes, and low birthweight but may make little or no difference to the risk of having PTB (RR 0.66, 95% CI 0.34 to 1.30; 7 trials, 1640 women) [18]. An earlier review (9 trials, 1916 pregnant women) suggests that supplementation with vitamin D combined with calcium may reduce the risk for pre-eclampsia but may actually increase the risk of PTB (RR 1.52, 95% CI 1.01 to 2.28; 5 trials, 942 women), consistent with an earlier version [19] which it updated which showed that the combination increased the risk of delivery prior to 37 weeks of gestation compared to women who received no treatment or placebo (RR 1.57; 95% CI 1.02 to 2.43; 3 studies, 798 women, moderate quality), but that supplementation of vitamin D alone reduces the risk of PTB compared to no intervention or placebo (8.9% versus 15.5%; RR 0.36; 95% CI 0.14 to 0.93; 3 trials, 477 women, moderate quality). These reviews included studies from LMIC settings (Bangladesh, India, Brazil, Iran) [18, 19].
- Given conflicting findings between systematic reviews of observational studies and those examining the effectiveness of vitamin D from randomized control trials (RCTs) which showed no effect, it is suggested that low vitamin D levels may reflect poor general maternal health status for which attention to general health rather than vitamin D supplementation is required [20].

(ii) *Zinc.*

- Maternal zinc supplementation is contentious—while WHO guidelines recommend further research regarding zinc supplementation for pregnant women [3], low-to-moderate-certainty evidence suggests that zinc supplementation may reduce PTB (16 trials, 7637 women; RR: 0.86, 95% CI: 0.76–0.97) in women with presumed low zinc intake or poor nutrition (14 trials mostly from LMIC settings, 7099 women; RR: 0.87, 95% CI: 0.77–0.98) [21], rather than as a routine supplement for all pregnant women.

(iii) *Vitamin B12.*

- A systematic review found that B12 deficiency (<148 pmol/L) was associated with a higher risk of low birth weight (adjusted risk ratio = 1.15, 95% confidence interval (CI): 1.01, 1.31) and PTB (adjusted risk ratio = 1.21, 95% CI: 0.99, 1.49) [22].

(iv) *Multiple Micronutrient (MMN) Supplements.*

- According to WHO guidelines, there is high-certainty evidence that shows that MMN supplements make little or no difference to PTB rates (14 trials; RR: 0.95, 95% CI: 0.88–1.03) [3]. However, recent evidence indicates that MMN (added to iron and folic acid) may slightly reduce the risk of PTB (average RR 0.95, 95% CI 0.90 to 1.01; 18 trials, 91,425 participants; moderate-quality evidence) and very PTB (average RR 0.81, 95% CI 0.71 to 0.93; 4 trials, 37,701 participants) when compared to iron, with or without folic acid [23].

(v) *Vitamin A.*

- Vitamin A deficiency is not linked to PTB and is not generally recommended in pregnancy as it can be teratogenic [11]. However, it is appropriate to supplement pregnant women in areas where vitamin A deficiency is a severe public health problem, to prevent night blindness [3].

(vi) *Omega-3 Fatty Acids.*

- One systematic review of RCTs has shown that women who received omega-3 LCPUFA experienced less PTB < 37 weeks (13.4% versus 11.9%; RR 0.89, 95% CI 0.81 to 0.97; 26 RCTs, 10,304 participants; high-quality evidence) and early PTB < 34 weeks (4.6% versus 2.7%; RR 0.58, 95% CI 0.44 to 0.77; 9 RCTs, 5204 participants; high-quality evidence) than those who did not receive omega-3 [24].

(vii) *Restricting Coffee Intake.*

- Low-certainty evidence from one trial suggests that restricting caffeine intake may have little or no effect on PTB (1153 neonates; RR: 0.81, 95% CI: 0.48–1.37); however, those with high intake are recommended to reduce it for better pregnancy outcomes in general [3]. Some studies indicate that high caffeine consumption is associated with low birth weight and/or prematurity [25].

3.5 Nutrient and Mineral Deficiencies Not Shown to be Associated *with an Increased Risk of Preterm Birth [3]*

Supplementation is not recommended for vitamin B6 (pyridoxine), vitamin E and C (moderate-certainty evidence shows little or no effect on PTB; 11 trials, 20,565 neonates; RR: 0.98, 95% CI: 0.88–1.09), and high protein (1 study, 505 women; RR: 1.14, 95% CI: 0.83–1.56).

4 Practical Clinical Risk Assessment Instructions for PTB

As part of the general evaluation of pregnant women, some routine nutritional assessment is carried out during antenatal booking in most contexts. However, information obtained is seldom employed to undertake a formal risk assessment for PTB. Therefore, we highlight below routine data that should be collected to enable formal evaluation of a women's risk of PTB.

- BMI: Low and high body mass index (BMI) are risk factors for PTB. Maternal weight and height should be measured at the booking appointment, and the woman's BMI should be calculated.
- Dietary patterns: A well-balanced diet during pregnancy may reduce risk of PTB. Knowledge of and access to a well-balanced diet should be assessed during pregnancy.

Nutrient and mineral deficiencies: Iron deficiency anemia is a risk for PTB. Pregnant women should be offered screening for anemia early in pregnancy and at 28 weeks when other blood screening tests are being performed [11]. In a context where calcium deficiency may exist, or risk of pre-eclampsia is deemed substantial, or there is suspicion of low dietary calcium levels, calcium supplementation should be offered. Populations at high risk of vitamin D deficiency should be offered vitamin D supplementation to improve pregnancy outcomes generally.

5 Evidenced Risk Factors and Interventions for PTB

These are outlined in Table 1.

6 Summary of Nutrition Interventions to Reduce PTB

These are shown in Table 2.

7 Research and Clinical Practice Recommendation

To clarify outcomes for PTB, further RCTs are recommended that target populations with a high prevalence of vitamin D deficiency. It would be helpful if future trials were to evaluate whether the increase of serum 25-hydroxyvitamin D concentration supplementation early in pregnancy is associated with improved maternal and infant outcomes in populations with different BMI, skin pigmentation, vitamin D status, and setting [18]. Research should also evaluate the PTB risk of combining calcium and vitamin D. Further research is also required to look at zinc and omega-3 fatty acids in relation to PTB.

Table 2 Benefit statements of nutrition interventions to reduce preterm birth

Very clear benefit
• Women at high risk of deficiency—Iron (daily oral iron with 30 mg to 60 mg of elemental iron) [3].
• Folic acid (daily folic acid supplementation with 400 μg (0.4 mg)) [3] for general pregnancy health and outcomes may not affect PTB risk.
• Alternative if unable to tolerate daily dosing or prevalence of anemia in pregnancy is not high (less than 20%) intermittent oral iron and folic acid with 120 mg of elemental iron and 2800 μg (2.8 mg) of folic acid once weekly [3].
• If a woman is diagnosed with anemia during pregnancy, her daily elemental iron should be increased to 120 mg until her Hb concentration rises to normal (Hb 110 g/L or higher) [3].
Moderate benefit
• In undernourished populations, balanced energy and protein dietary supplementation is recommended for pregnant women (to reduce the risk of stillbirths and SGA, not specifically for PTB) [3].
• Daily calcium supplementation (1.5–2.0 g oral elemental calcium) for populations with low dietary calcium intake (to reduce the risk of pre-eclampsia). NOTE: Negative interactions between iron and calcium supplements may occur. The two nutrients should preferably be administered several hours apart rather than concomitantly [3].
Possible benefit
• Vitamin D (for women without pre-existing conditions) for populations at risk of deficiency, for general pregnancy outcomes, not PTB specifically. NOTE: Vitamin D may not to be combined with calcium; risk of PTB may be increased.
• Zinc supplementation may reduce the risk of PTB if dietary zinc is low. However, further research is required.
• Nutrition education (access to a well-balanced diet is advised above and beyond MMN and/or zinc supplementation).
• Exercise advice.

However, the most important focus should be on promoting a good quality diet in general, rather than a specific supplementation regime. Studies to address ways of improving the overall nutritional status of populations in impoverished areas, rather than focusing on micronutrient and or zinc supplementation, are required [21]. The role of maternal BMI on PTB risks in LMICs warrants further study.

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Evaluating Alcohol, Tobacco, and Other Substance Use in Pregnant Women

Shumona Sharmin Salam and Caroline Mitchell

1 Background

Substance use disorder in pregnancy is a critical public health concern that is linked with several adverse maternal and newborn health outcomes including preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA) babies. The most widely used substances in pregnancy in high-, low-, and middle-income countries (LMICs) include tobacco, alcohol, cannabis, opiates, cocaine, and other illicit substances. This guidance has been developed to help health-care providers in identifying and managing smoking, alcohol, and substance use disorders in pregnant women and thereby reducing the risks of PTB and other adverse maternal and child health outcomes.

This guideline summarises information from the WHO, other guidance (where available), and recently conducted systematic reviews on the risks of and interventions for antenatal exposure to smoking, alcohol, and substance use for PTB.

2 Evidence Statement

Use of alcohol, tobacco, and other psychoactive substances during pregnancy leads to an increased risk of health problems for mother and child such as spontaneous abortion, stillbirth, low birth weight, birth defects, and prematurity (Table 1). Concurrent

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D. O. Anumba, S. M. Jayasooriya (eds.), *Evidence Based Global Health Manual for Preterm Birth Risk Assessment*,
https://doi.org/10.1007/978-3-031-04462-5_7

Table 1 Summary of evidenced tobacco, alcohol, and other substance use-related risk factors and interventions for PTB

Evidenced risk factor for preterm birth	Evidence of risk	Recommended action for evidenced risk factor for preterm birth*	Evidence of effectiveness of action
Alcohol and substance use			
Generic measures	Screening and brief interventions for substance use: All pregnant women should be asked about their alcohol and illicit substance use at every antenatal visit and offered brief interventions.		Evidence related to PTB or birth outcomes unavailable. Reviews of brief interventions for alcohol use among pregnant women (low-quality evidence) indicate a reduction in use [24–26].
Alcohol	Moderate drinking (18 g or 1.5 drinks/day: No effect [4] 36 g or 3 drinks/day: RR 1.23 (95% CI 1.05–1.44) [4]	**Psychosocial interventions** (e.g. motivational interviewing, cognitive behavioural therapy and contingency management) [13]: Pregnant women with alcohol or other substance use disorders should be provided individualised care **Detoxification or quitting programmes** for substance dependence in pregnancy [13]: • All pregnant women should be advised to quit and offered/referred to detoxification services as applicable. • Opiates: Opioid substitution treatment as available and not detoxification. • Pregnant women with alcohol withdrawal symptoms should be managed with the short-term use of a long-acting benzodiazepine. • Psychopharmacological medications may be useful to assist with symptoms of psychiatric disorders in withdrawal management but are not routinely required. **Pharmacological treatment** (maintenance and relapse prevention) for substance dependence in pregnancy [13]: • Not recommended for dependence on amphetamine-type stimulants, cannabis, cocaine, or volatile agents in pregnant patients. • Due to lack of evidence on the safety and efficacy of alcohol dependency treatment medications in pregnancy, an individual risk-benefit analysis should be conducted for each woman. • Opioid maintenance therapy with methadone or buprenorphine recommended for opiate dependence.	**Psychosocial interventions:** • Conditionally recommend by WHO due to lack of evidence [13]. • Evidence related to birth outcomes is limited. Systematic review indicates no difference in PTB rates (RR 0.71, 95% CI 0.34–1.51: Three trials, 264 participants, moderate quality evidence [27]. No difference in abstinence in any intervention group compared to control [27]. **Detoxification or quitting programmes** • Recommendations based on narrative synthesis of evidence and highly recommended [13]. • Systematic reviews report no differences in rates of PTB between opioid detoxification and other treatment groups such as opioid substitution treatment. Due to increased risk of relapse with opioid detoxification, opioid substitution therapy is recommended [28–31]. **Pharmacological treatment:** • Due to lack of evidence, pharmacological treatment is not recommended (conditional) for alcohol, amphetamine-type stimulants, cannabis, cocaine, or volatile agents in pregnant women [13]. • Although opioid maintenance therapy is beneficial in pregnant women, systematic review provides inconclusive evidence of the superiority of one treatment over another (low-quality evidence, studies conducted in high-income settings) [13, 30]. • Pharmacological treatment should be combined with psychosocial interventions [13].
Crack cocaine	OR 2.22 (95% CI 1.59–3.10) [10]		
Cocaine	OR 3.38 (95% CI 2.72–4.21) [11]		
Opioid	OR 2.86 (95% cl 1.11–7.36) [7]		
Cannabis	Pooled OR 1.29 (95% CI 0.80–2.08) [6]		
Marijuana	Unadjusted pooled RR 1.32 (95% CI 1.14–1.54) [5] Adjusted pooled RR 1.08 (95% CI 0.82–1.43) [5]		
Amphetamine	Unadjusted OR 4.11 (95% CI 3.05–5.55) [12]		

Tobacco and exposure to second-hand smoke (SHS)			
Generic measures	Screening for tobacco use and exposure to SHS [14]: Pregnant women should be asked about their tobacco use and exposure to SHS at every antenatal care visit		
Smoking	Pooled OR 1.27 (95% CI 1.21–1.33) [1]	**Psychosocial interventions** (e.g. counselling, feedback, health education, incentives, peer/social support) should be regularly offered to pregnant women who are either current tobacco users or have recently quit [14] **Pharmacological interventions** for cessation of tobacco use [14]: • Inconclusive regarding the recommendation on related to use or non-use of NRT to support cessation of tobacco use in pregnancy. • Bupropion or varenicline to support tobacco-use cessation in pregnancy is not recommended. • Further research needed to assess safety, efficacy, and compliance to pharmacotherapeutic cessation agents. **Interventions for exposure to SHS in pregnancy** [14]**:** • Public places: All public places including health-care facilities, workplaces, and public transports should be smoke-free to protect everyone including pregnant women. Homes: Pregnant women, their partners and household members should be given advice and information on risks of SHS and strategies to reduce SHS including smoking cessation support.	**Psychosocial interventions:** • Although previous reviews indicated reductions in preterm birth [14, 32, 33], recent Cochrane review (high-quality evidence) indicates uncertainty in whether women who received psychosocial interventions had reductions in PTB or not compared to the control group (RR 0.93, 95% CI 0.77–1.11, 19 RCTs, $n = 9222$). None of the studies included in assessing PTB were from LMICs [34]. **Pharmacological interventions:** • Cochrane review indicated insufficient evidence to determine the impact of NRT on rates of PTB (RR 0.81, 95% CI 0.59–1.11, 7 studies, 2182 women, low-quality evidence) [35]. No studies explored the use of varenicline and electronic cigarettes and only two studies explored bupropion. All studies were conducted in HICs [35]. I**nterventions for exposure to SHS in pregnancy:** • Implementation of various smoke-free legislation was associated with reductions in rates of PTB (risk change −3.77%, 95% CI -6.37 to −1.16, ten studies, $n = 27{,}530{,}183$) [36]; (risk change −10.4% 95% CI -8.9 to −2.0, four studies, $n = 1366\,862$) [37]. The majority of the studies are from HICs. Systematic reviews explored several interventions targeted to either the women or partner (e.g. educational and behaviour change interventions, smoking cessation support) to reduce SHS in homes [38–41]. Results varied and studies were of low quality with moderate to high risk of bias and did not have a standardised way of assessing exposure or outcome. None explored the effect on birth outcomes. Some studies were from LMIC settings.
Passive smoking	At any place: OR 1.20 (95%CI 1.07–1.34) [2] Home: OR 1.16 (95%CI 1.04–1.30) [2]		
Smokeless tobacco (India)	Pooled OR 1.39, 95% CI 1.01–1.91) [3]		

PTB Preterm birth, *LMIC* Low- and middle-income countries, *RR* Relative risk, *CI* Confidence interval, *NRT* Nicotine replacement therapy, *SHS* Second-hand smoke

use of these substances (i.e. poly substance use) further increases the risk of adverse outcomes in all settings.

This guideline proposes interventions (Table 1) for the identification and management of the following:

(i) Tobacco smoking and exposure to second-hand smoke (SHS) (protection from SHS in homes and public places, screening, psychosocial, and pharmacological).
(ii) Alcohol and illicit substance use (screening and dependency management) in pregnant women during the antenatal period.

Despite gaps in research and knowledge, the potential benefits of the recommended actions may help improve PTB and other birth outcomes.

3 Synopsis of the best Evidenced Risk Factors for Preterm Birth

For a summary of the evidence of tobacco, alcohol, and substance use-related risk factors for preterm birth, please see Table 1, in Sect. 5.

3.1 Smoking and Exposure to Second-Hand Smoke

(i) A systematic review and meta-analysis (2000) of prospective studies for any *maternal tobacco smoking* versus no maternal smoking and preterm delivery found the pooled odds ratio to be 1.27 (95% CI 1.21–1.33, 20 studies, >100,000 participants) [1]. All the studies were conducted in high-income countries (HICs).
(ii) A meta-analysis (2016) reported the ORs of PTB for women who were ever exposed to *passive tobacco smoking* versus women who had never been exposed to passive smoking at *any place* and at *home* were 1.20 (95% CI 1.07–1.34, 24 studies, 88,200 participants) and 1.16 (95% CI 1.04–1.30, 11 studies, 73,211 participants), respectively [2]. The associations were statistically significant for studies conducted in Asia (OR 1.26, 95% CI 1.05–1.52) [2]. Several studies were from low- and middle-income countries (LMICs) including China, India, Korea, and Indonesia.
(iii) A systematic review and meta-analysis of observational studies in India also indicated that 0.19 million PTB (6% of all PTBs) could be attributed to the use *smokeless tobacco (SLT)* (pooled OR 1.39, 95% CI 1.01–1.91, 2 studies, 1800 participants) [3].

3.2 Alcohol Use

A dose-response relationship between *alcohol consumption* during pregnancy and the risks of PTB was observed in a meta-analysis (2011) of 14 observational studies (n = 280,443 pregnant women) primarily in HICs [4]. Compared with mothers who do not drink, the overall dose-response relationships for PTB showed (i) no effect up to 18 g pure alcohol or an average of 1.5 drinks/day and (ii) 23% increase in risk at an average of three drinks or 36 g/day (RR 1.23, 95% CI 1.05–1.44) [4].

3.3 Substance Use

(i) Two systematic reviews (2016) were identified that explored maternal *cannabis/marijuana* use and the risks of preterm birth [5, 6]. No association was demonstrated between in utero exposure to marijuana/cannabis and PTB (pooled OR 1.29, 95% CI 0.80–2.08, 9 studies) compared to non-users [6]. Three studies included in the review showed an increase in odds of PTB, while six showed no association. Only two studies included were from LMICs—Iran and Jamaica [6]. Although marijuana use during pregnancy was associated with an increased risk of PTB in the pooled unadjusted analysis, (15.3% compared with 9.6%, pooled RR 1.32, 95% CI 1.14–1.54), results were found to be insignificant after adjusting for tobacco use and other confounding factors (pooled RR 1.08, 95% CI 0.82–1.43) [5].

(ii) *Opiate use* (heroin, opium) is associated with an increased risk of premature birth and a number of other maternofoetal adverse outcomes. Findings from observational studies show that, compared to cocaine or opiate non-users, opiate users were 2.86 times as likely (95% Cl 1.11–7.36; p = 0.03) to deliver preterm [7]. Similar results were also seen in other observational studies conducted in Iran [8] and low-income, multi-ethnic US population [9].However research is heavily skewed to high-income country settings.

(iii) *Crack cocaine* use during pregnancy was associated with significantly higher odds of preterm delivery (OR 2.22, 95% CI 1.59–3.10) [10]. Eight observational studies were included (n = 5761) in the meta-analysis; only one was from a LMIC (Iran) [10]. Systematic review and meta-analysis of 24 observational studies in HICs (n = 39,860) shows that *cocaine* use during pregnancy was associated with significantly higher odds of PTB (OR 3.38, 95% CI 2.72–4.21) [11].

(iv) A significant increase in unadjusted risks of PTB (OR 4.11, 95% CI 3.05–5.55, 5 studies, n = 62,070) was identified among women exposed to *amphetamines* in pregnancy. All five studies included in the review were from HICs [12].

4 Practical Clinical Risk Assessment Instructions for PTB

4.1 Health-care providers should ask all pregnant women about their use of alcohol and other substances (past and present) early in pregnancy and at every antenatal visit. WHO recommends the use of validated screening instruments for this purpose [13, 14]. There may be cultural taboos which compound stigma and other difficulties in disclosure of substance use such as fear of judgement by health-care providers, breach of confidentiality, and fear of child removal after the birth.

4.2 All guidance encourages health-care practitioners to explore these issues sensitively, using a non-judgemental approach and in a confidential environment. There may, however, be child safeguarding issues which arise during this assessment which should be dealt with using in-country mechanisms, while optimising maternal physical and mental health. The presence of family members during maternal health checks may also act as a barrier to full disclosure.

4.3 Listed below are screening instruments that have been suggested to be used for prenatal assessment of pregnant women [13, 14]. There are variations in the tools regarding number of items, administration method (paper and pencil, computer), training needed, and location (prenatal clinic/outpatient/inpatient). Although some of the tools were validated, they will need to be further validated before use in an LMIC context.

- Tobacco, alcohol, and substances: Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST Version 3.0); Pregnancy Information Program (PIP).
- Alcohol and General Substance Use: 4P's Plus [15]; Substance Use Risk Profile—Pregnancy (SURP-P) [16].
- Alcohol: Alcohol Use Disorder Identification Test (AUDIT) [17]; Alcohol Use Disorder Identification Test—Consumption (AUDIT-C) [18]; CAGE [19]; Short Michigan Alcohol Screening Test (SMAST) [20]; Ten Question Drinking History (TQDH) [21]; T-ACE [22]; TWEAK [23].

5 Evidenced Effective Interventions for Risk Factors for Preterm Birth

These are summarised in Table 1.

6 Summary of Interventions for Smoking and Second-Hand Exposure to Smoke (Table 2)

7 Summary of Interventions for Alcohol and Substance Use (Table 3)

Table 2 Benefits statements of effectiveness of smoking cessation interventions to prevent preterm birth

Low (possible) benefit
• Identification of tobacco use and second-hand smoke (SHS) exposure in pregnancy [14].
• Psychosocial interventions (as per local in-country clinical guidelines and resources) [14].
• Pharmacological interventions (as per local in-country clinical guidelines and resources) [14].
• Protection from second-hand smoke in pregnancy (homes and public places) [14].

Table 3 Benefits statements of effective interventions to promote harm reduction to prevent preterm birth

Low (possible) benefit
• Screening and brief intervention [13].
• Psychosocial interventions (as per local in-country clinical guidelines and resources) [13].
• Detoxification or quitting programmes (as per local in-country clinical guidelines and resources) [13].
• Pharmacological treatment (as per local in-country clinical guidelines and resources) [13].

8 Research and Clinical Practice Recommendation

There is strong consensus within the literature about the negative effects of alcohol, tobacco, and substance use during pregnancy, and all women should receive necessary interventions to stop (preferably) or reduce use. The evidence is of low quality, and further primary research and controlled trials are needed on effective ways to assess exposure and the use of alcohol, tobacco (including second-hand exposure), and substances; measure the effect on maternal and child health outcomes and for determining the effectiveness and cost-effectiveness of recommended interventions in pregnancy. Additionally, there is also a dearth of studies conducted in LMICs. Assessment methods should include and integrate findings from policy, public health, behavioural and implementation science, and trials of interventions where PTB is the primary outcome measure. In addition, longitudinal cohort studies which include consideration of multi-factorial psychosocial factors are needed to assess the risks on women, children, and future generations.

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