The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: www.tandfonline.com/journals/ijmf20

Predicting and preventing preterm birth in Europe: current challenges and gaps

Gian Carlo Di Renzo , José Luis. Bartha , Anna L. David , Roland Devlieger , Loïc Sentilhes , Daniel V. Surbek , Stefan Verlohren & Dilly O. C. Anumba

To cite this article: Gian Carlo Di Renzo , José Luis. Bartha , Anna L. David , Roland Devlieger , Loïc Sentilhes , Daniel V. Surbek , Stefan Verlohren & Dilly O. C. Anumba (2025) Predicting and preventing preterm birth in Europe: current challenges and gaps, The Journal of Maternal-Fetal & Neonatal Medicine, 38:1, 2547687, DOI: 10.1080/14767058.2025.2547687

To link to this article: https://doi.org/10.1080/14767058.2025.2547687

Published online: 21 Aug 2025.

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
2025, VOL. 38, NO. 1, 2547687
https://doi.org/10.1080/14767058.2025.2547687

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS Check for updates

Predicting and preventing preterm birth in Europe: current challenges and gaps

Gian Carlo Di Renzo[a,b], José Luis. Bartha[c], Anna L. David[d], Roland Devlieger[e,f], Loïc Sentilhes[g], Daniel V. Surbek[h], Stefan Verlohren[i] and Dilly O. C. Anumba[j]

[a]PREIS International School, Firenze, Italy; [b]Department of Obstetrics, Gynecology and Perinatal Medicine IM, Sechenov First State University, Moscow, Russia; [c]Department of Obstetrics and Gynecology, University Hospital La Paz, Universidad Autónoma de Madrid, Madrid, Spain; [d]Department of Obstetrics and Maternal Fetal Medicine, University College London, London, United Kingdom; [e]REALIFE Group, Department of Development and Regeneration, KU Leuven, Leuven, Belgium; [f]Department of Obstetrics and Gynaecology, University Hospital Leuven, Leuven, Belgium; [g]Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France; [h]Department of Obstetrics and Gynecology, University Hospital Bern, University of Bern, Bern, Switzerland; [i]Department of Obstetrics, Charité – Universitätsmedizin, Berlin, Germany; [j]Department of Medicine and Public Health, University of Sheffield, Sheffield, UK

ABSTRACT

Objective: Preterm birth (PTB) remains a leading cause of neonatal morbidity and mortality across Europe despite advances in obstetric care. While PTB rates vary widely across the region, overall declines in recent decades have been limited, revealing persistent gaps in risk assessment and prevention.

Methods: Here we review current challenges and disparities in European PTB prediction and prevention, highlighting the complex constellation of maternal, fetal, environmental, and sociodemographic risk factors.

Results: Extending gestational age represents an opportunity to improve outcomes among pregnancies at higher PTB risk. Unfortunately, existing tools for PTB risk assessment and prevention show limited effectiveness arising from the fact that the PTB event is a frequent outcome with various underlying causes.The limitations of existing clinical prediction tools, which can only account for a minority of PTBs, underscore the need for more accurate and accessible screening methods. Although cervical length screening and some biomarkers demonstrate promise for risk stratification, they are not uniformly implemented, and the few effective interventions that risk stratification would implement lack broad consensus or standardization. These interventions, including progesterone therapy, low-dose aspirin, and lifestyle modifications, may require regional approaches reflecting population-specific risk profiles.

Conclusions: The PTB burden is a persistent concern across Europe. Constituent populations are diverse, comprising a mosaic of risk factors of varying significance that fail to predict the majority of PTBs. During this time of evolving demographics in the Europe, assessing PTB risk becomes even more challenging. The stagnation of PTB incidence rates also strongly suggests that new tools are needed to achieve improvements for mothers, babies, public health, and to reduce associated long-term costs of PTB. To move forward, optimizing gestational age and neonatal outcomes in Europe will require more unified guidelines, optimized implementation of known preventative strategies, investment in novel risk assessment tools, and public health policies that address modifiable risk factors both pre- and post-conception. Addressing these gaps is essential to reduce PTB-related health burdens and promote maternal and neonatal well-being across diverse European settings.

ARTICLE HISTORY
Received 22 June 2025
Revised 26 July 2025
Accepted 9 August 2025

KEYWORDS
Preterm birth; neonatal morbidity; neonatal mortality; prevention tools; risk assessment

Introduction

Preterm birth (PTB), defined as birth before 37 weeks of gestation, is a leading cause of perinatal mortality and poses substantial challenges for newborn and child health. Across European countries, a median 6.9% of babies are born preterm [1] (Figure 1), and approximately 75% of neonatal

CONTACT Gian Carlo Di Renzo profgcdr@gmail.com PREIS International School, Firenze, Italy.

mortality occurs in these prematurely born infants [2]. Gestational age at birth correlates most significantly with neonatal survival and morbidity rates, but these outcomes are also influenced by the country of birth and varying definitions of viability limits. After controlling for country-specific data collection methodologies, significant differences in PTB and related morbidity rates remain [3]. For instance, PTB-related neonatal morbidities and functional motor impairment vary markedly among Sweden, England, and France when adjusted for patient-level characteristics [4].

PTB frequency differs widely across Europe, ranging from 5.3%–11.3% of live births in most recent estimates (2019) [1]. Notable differences are seen even among countries with similar economic development and healthcare systems. PTB can be either spontaneous (sPTB) or medically indicated (miPTB). Early labor and spontaneous delivery from 20 to 37 weeks of gestation is commonly defined as sPTB, which in Europe represents between 2.8%–4.8% of births. When births in these same gestational age ranges are iatrogenic and medically indicated (miPTB), they are initiated by healthcare practitioners for overall benefit to maternal and/or fetal health. In Europe, miPTBs represent 1.1%–3.0% of all births. The rates of miPTB are increasing in many high-income European countries, reflecting a greater ability to detect maternal and fetal indications that would benefit from early delivery. In England, for example, over half of PTBs are

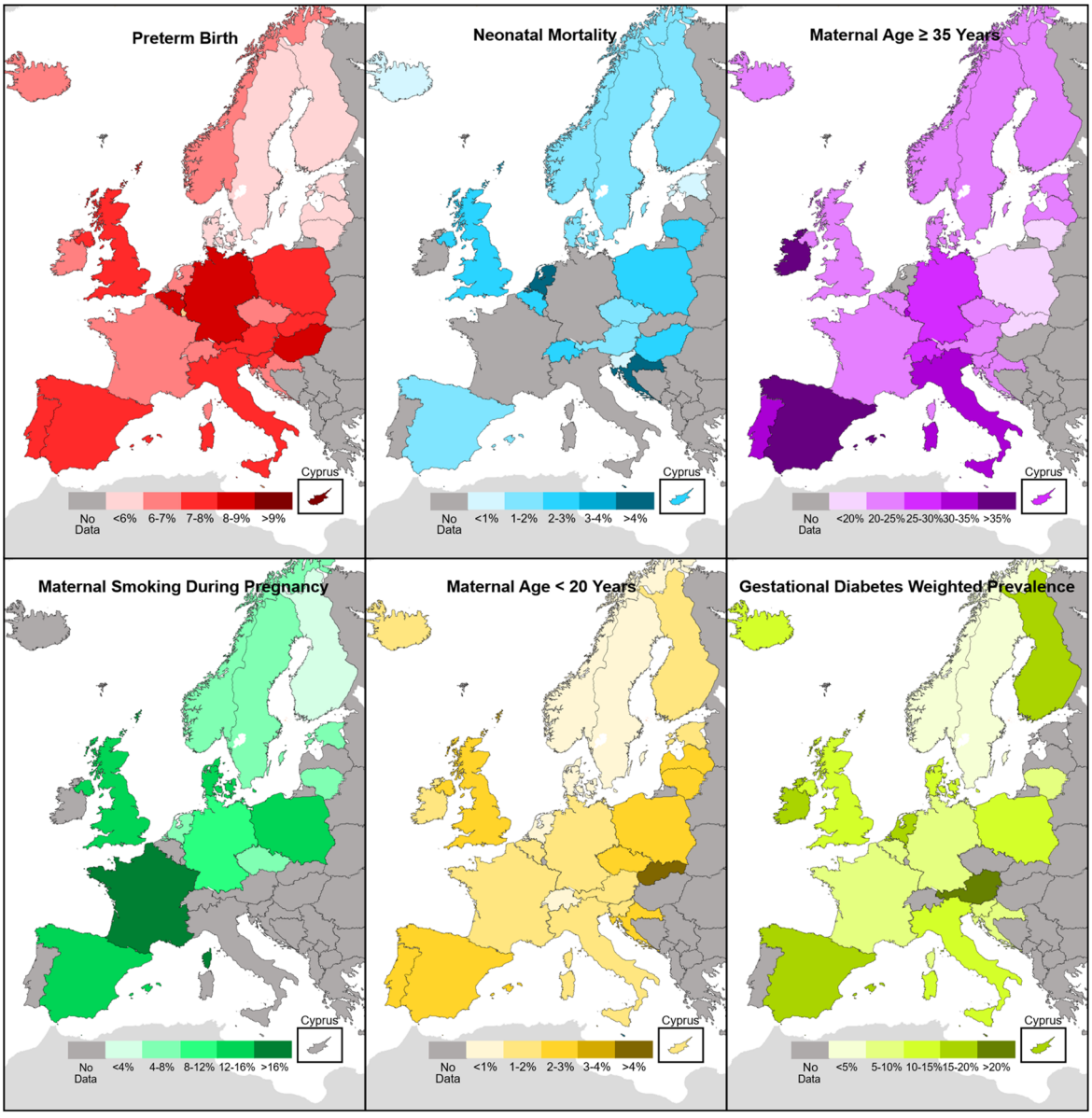

Figure 1. Preterm birth incidence, neonatal mortality, and selected risk factor prevalence across Europe.

miPTBs [5]. Positive trends in PTB incidence may be obscured by an increase in live births at earlier gestational ages due to improvements in perinatal care. (Some of the latter represent miPTBs at extreme preterm gestations to optimize outcomes, such as in cases of early-onset fetal growth restriction [6].)

Despite efforts to reduce PTB and related mortality, rates of both have remain largely unchanged over recent decades. European neonatal mortality rates in 2019 ranged from 0.5–4.3 per 1,000 live births at 22 weeks or more of gestation [1]. Perinatal mortality after 26 weeks of gestation also vary widely, from fewer than 1.0 per 1,000 in Iceland (0.5), Slovenia (0.7), and Estonia (0.9), to 3.0 or more per 1,000 in Malta (4.3), Northern Ireland (3.3), the Netherlands (3.0), and Croatia (3.0) [1] (Figure 1). It is also likely that shifting population risk factors may contribute to neonatal mortality rate stagnation in certain countries [7–9].

PTB is also reflected in higher societal and economic costs to manage associated complications that persist well beyond the acute impacts of prematurity [10]. Neurodevelopmental and other health challenges associated with PTB can persist beyond the age of 5 years, with their frequency being highest in the earliest-born babies [11]. A study of 11 European countries identified significant disparities among countries in the societal costs of PTB by age 5 years [12], with Poland and Sweden reporting the highest total mean costs, and the Netherlands and Germany the lowest. Indeed, as prematurity-related sequela often persist into adolescence or even adulthood, it has been suggested that prematurity be recategorized as a chronic condition to help optimize lifelong medical care [12]. These long-term impacts highlight the pressing public health concern and ongoing need for concerted PTB reduction and mitigation efforts, to improve public health [13].

Risk assessment and risk factors

Extending gestational age represents an opportunity to improve outcomes among pregnancies at higher PTB risk. Unfortunately, existing tools for PTB risk assessment and prevention show limited

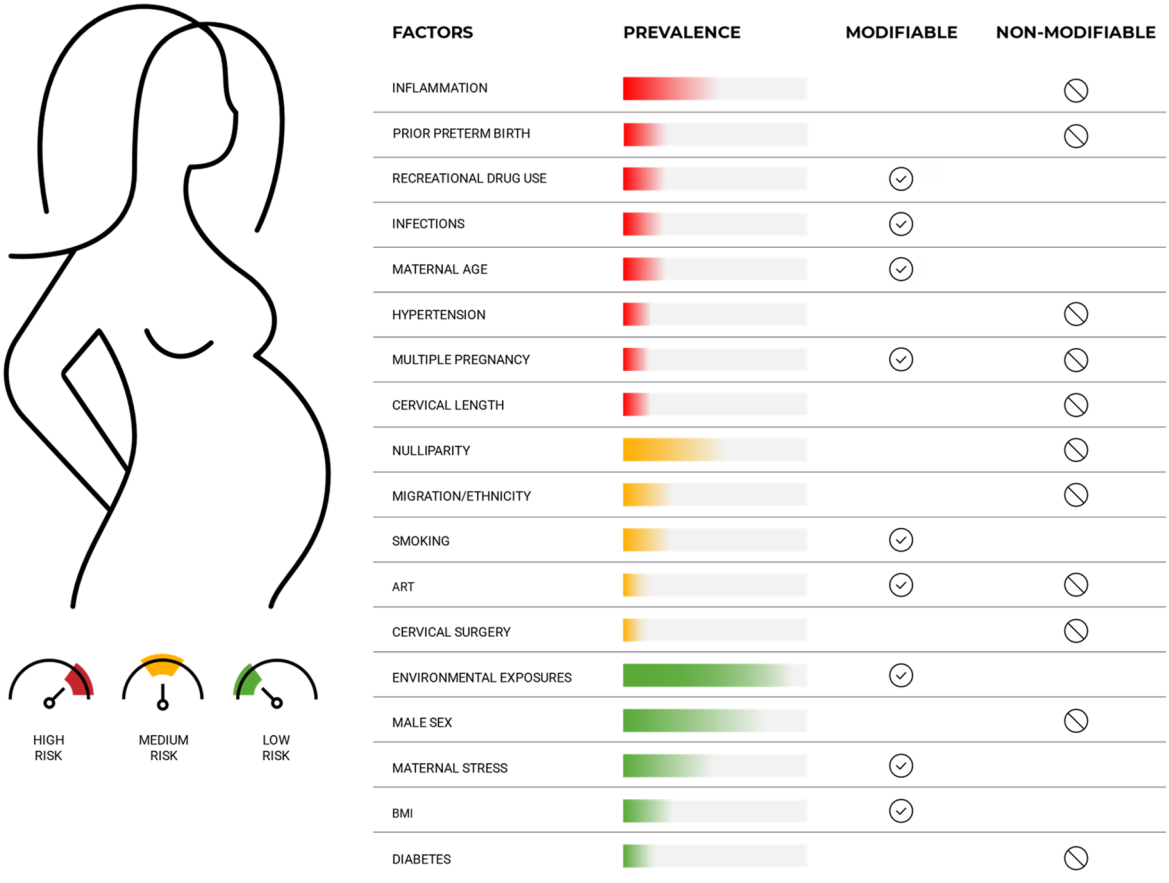

Figure 2. Relative risk factor prevalence and association with preterm birth.

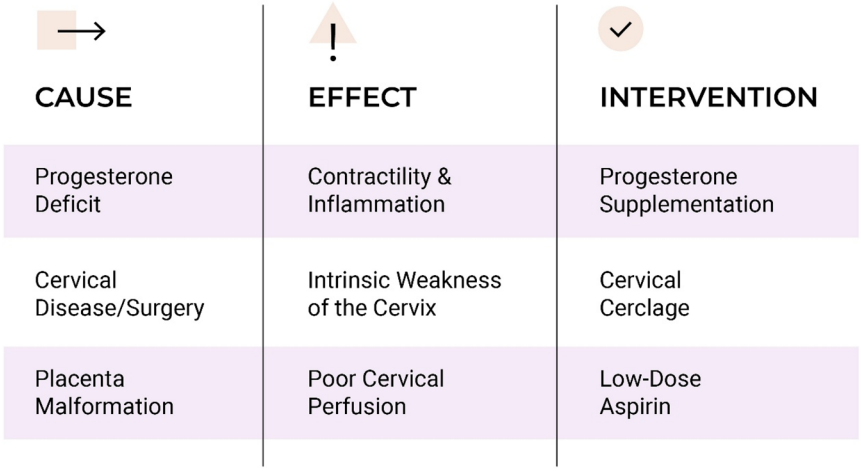

Figure 3. Cervical contributions to preterm birth and evidence-based interventions.

effectiveness arising from the fact that the PTB event is a frequent outcome with various underlying causes.

While PTB is defined as delivery before 37 weeks of gestation, late miscarriages occurring as early as 16 weeks of gestation can be considered PTB due to similarities in presentation, etiologies, and risk factors [14]. Early birth can result from maternal, fetal, and placental causes that exist within a constellation of known risk factors (Figure 2). It is thus helpful to regard PTB as a syndrome of early birth influenced by multiple etiological factors [15,16], and involving varied physiological pathways (Figure 3). Europe's diverse and evolving demographics further complicate the challenges in PTB risk prediction. Evaluation of regional risk factor variations may reveal opportunities to enhance prenatal care, achieve more homogeneous pregnancy outcomes, and reduce the overall PTB burden in Europe. Several known risk factors are relevant to the problem of PTB within the European context (see Table 1).

Pregnancy history

Parity, that is the number of pregnancies carried beyond 20 weeks, is a significant factor when considering risk of PTB. Nulliparity, meaning women who have not had a prior pregnancy, is well known to be associated with a greater risk of PTB when other risk factors are accounted for. Meanwhile, second births are associated with the lowest PTB risk [17]. For multiparous women, a prior PTB, in particular during the previous pregnancy, is the most important risk factor for PTB recurrence in subsequent pregnancies. In one example, a study conducted in Norway found that while 5.6% of first births were preterm, and 3.7% of second births were preterm, women with any PTB history had a recurrence rate of 17.4% [18]. A meta-analysis of 50 000 pregnancies worldwide estimated the overall recurrent risk of sPTB as 30% (95% CI 27–34%), while miPTB risk for women with a sPTB history was only 5% (95% CI 3–7%) [19]. Similarly, a shorter interval between pregnancies has been associated with decreased gestational age at birth; however, trends toward increased spacing between births in Europe have decreased the importance of this risk factor [20].

Maternal age

PTB risk is age-dependent and describes a U-shaped curve, rising among both younger and older pregnant individuals. Young maternal age (<18 years) strongly correlates with sPTB but not with miPTB. Older maternal age (≥35 years) shows the opposite association [21]. Fertility trends across Europe indicate a decline in births among women under 20 years of age, alongside an overall increase among women over 35 years [1]. Recent exceptions include a 0.9% decline in Denmark for mothers aged 35 years or older and increases in mothers under 20 years in Cyprus (0.4%), Malta (0.2%), and Slovenia (0.1%) [1]. Ireland (39.4%) and Spain (40.0%) report the highest percentage of mothers over 35, while Wales (3.9%) and Slovakia (6.2%) show the highest percentages of mothers under 20 [1]. Increased maternal

Table 1. Preterm birth risk factors.

Risk factors			
Risk factor	Description	Risk estimate	Prevalence
Prior Preterm Birth (PTB)	History of spontaneous or medically indicated PTB	OR: 3.4–6.0 [28]	5% to 11.3% of mothers [1]
Multiple Pregnancy	Twin or higher-order gestation	OR: 13 (95% CI: 10.9 – 15.8) [33]	3.3%
Nulliparity	First pregnancy vs second or later	OR sPTB: 1.95 (95% CI: 1.89 – 2.00) [17]	Median 44.2% [1]
Assisted Reproductive Technology	IVF conception (singleton or multiples)	IVF vs non IVF: 1.80 (95% CI: 1.70 – 1.90) [151]	4% [39]
Cervical Surgery or Trauma	Includes CIN excision or full dilation cesarean delivery	Large and very large excisions OR approximately 2 [87]	0.1 – 2.2% [152]
Smoking	Dose-dependent cigarette use during pregnancy	>20 cigarettes daily OR PTB approximately 1.5 [50]	18.4% daily smokers in European population [153]
Recreational Drug Use	Cannabis, cocaine, opioids, amphetamines	Up to 2× increased PTB risk [52]	5% Cannabis use during pregnancy [54]
Maternal Stress	Perceived stress (measured in 2nd/3rd trimester)	Ranges from OR: 1.14 to RR: 1.75 [46]	Approximately 30% [46]
Environmental Exposure	PM2.5, heat, pollutants, heavy metals	PM2.5: OR 1.15 per 10 µg/m^3 [73]	Over 90% in some European countries [154]
Infections	Bacterial or viral (e.g. CMV, HSV, HPV)	Diverse infections associated with 25–70% of PTB [82]	Positive amniotic culture 12.8% [79]
Inflammation	Intra-amniotic or sterile	Present in ≥40% of sPTB [78]	Vast majority of pregnancies will have inflammation at some point.
Migration / Ethnicity	Non-white or immigrant background	OR 1.65 (95% CI: 1.46 – 1.88) for Black women [44]	Minority populations in Europe approximately 15%
Maternal Age	<20 or ≥40 years	≥35 years OR 1.75 [155] <20 years OR 2 [156]	≥35 years 20% <20 years 1.7% [1]
Diabetes	Gestational	RR 1.13 [25]	Gestational DM 10.9% [23]
Hypertension	Chronic or gestational	OR 2 approx. [28]	7.5% [157]
BMI	Underweight <18.5, Obese ≥30	Class IIIb Obesity (≥50): OR ~2.8 [63]	Obesity varies widely in Europe from 26% in Malta to 7.1% in Italy [158]
Fetal Sex	Male fetus	OR: 1.09–1.14 [69]	50% births are male
Cervical Length (CL)	≤25 mm at 18–22 weeks *via* transvaginal ultrasound	RR: 4.6 (95% CI: 2.49 – 8.48) [159]	1.25% [159]
Biomarkers			
Biomarker	Description/measurement	Diagnostic accuracy estimate	
Fetal Fibronectin (fFN)	Quantitative vaginal fluid test in symptomatic pregnancies	Knowledge of fFN results reduces PTB. RR PTB <37 weeks: 0.67 (95% CI: 0.46–0.97) [96]	
Cervical FN	Vaginal protein predictive of sPTB within 7 d	OR 12 (95% CI: 8–16) [160]	
PAMG-1	Vaginal protein predictive of sPTB within 7 d	OR 5.6 (95% CI: 1.5–21.6) for delivery within 7 d [98,161]	
α-fetoprotein	Maternal serum at ≤24 weeks	OR <35 weeks: 3.5 [94]	
Alkaline Phosphatase	Maternal serum at ≤24 weeks	OR PTB <35 weeks: 5.1 [94]	
Corticotropin-Releasing Hormone	Maternal serum at 28 weeks	OR PTB <35 weeks: 3.4 [94]	
IL-6, IL-10,	Serum cytokines (13–26 weeks)	OR IL-6: 2.59; IL-10: 2.15 [101]	
TNF-α, sTNFR1/2	Inflammatory markers (25–33 weeks)	SMD PTB <37 weeks: 1.59 [101]	
IGFBP4/SHBG	2nd trimester maternal serum	AUC: 0.75 (95% CI: 0.56–0.91) [99]	
MMP-9	Biomarker for PPROM	Predicts delivery within 24 h [100]	
HE4 and IL-13 (IVF-specific)	Measured 9–11 d post embryo transfer	Reduced levels predictive of PTB in IVF pregnancies AUC = 0.775 [43]	
GSTT1 Null Genotype	Genetic marker	OR: 1.18 [95]	

age is also associated with the development of medical conditions that themselves are PTB risk factors, such as rheumatoid arthritis, lupus, adenomyosis, asthma, and cardiac conditions [22]. Overall, age-related PTB risk is increasing in Europe, as the rise in older maternal ages has a greater impact than the decline in younger maternal ages. Optimizing interventions for older pregnant women may yield increases in gestational age as trends in maternal age are likely to persist across the Europe.

Diabetes

The incidence of gestational diabetes in Europe is estimated to be 11%. However, the highest incidence in the region occurs in Eastern Europe, at 31.5%[23]. Diabetes is a PTB risk factor most strongly associated with late miPTB, and not significantly associated with early (<32 weeks) PTB [24].

A recent study in Germany found that, although less prevalent, pregestational diabetes is associated with a higher PTB risk than gestational diabetes [25]. Type I pregestational diabetic pregnancies have similar maternal and fetal outcomes to type II [26]. A study conducted in France found that PTBs for pregnancies of women with type I diabetes occurred at a rate of 24% overall, consisting of 9% sPTB and 15% miPTB [27]. The increasing incidence of type 2 diabetes in European countries suggests that diabetes will continue to contribute to PTB rates in Europe.

Hypertension

Chronic hypertension is also a significant risk factor for PTB [28,29]. Similar to diabetes, hypertension can first develop during gestation and is the most common medical disorder encountered during pregnancy [29]. Hypertension during pregnancy can potentially progress to preeclampsia, which presents serious maternal health risks [29]. The evidence that antihypertensive medications can reduce PTB is mixed; however, management of hypertension during pregnancy is based on both maternal and fetal indications [29–31].

Multiple gestations

The risk of PTB is considerably higher in twin and higher-order multiple pregnancies compared to singleton pregnancies [32]. Rates of multiple pregnancies vary across Europe, with some differences likely attributable to variations in maternal age and the differential use of assisted reproductive technologies (ART). A large observational study from Germany in 2015 found that while singleton pregnancies had a PTB rate of approximately 10%, 57.4% of multiple gestation pregnancies were preterm [33].

Placental and umbilical cord abnormalities

Placental abnormalities are significant contributors to PTB, with conditions like placenta previa and abruptio placentae directly increasing the risk. Placental insufficiency also is emerging as a contributor to sPTB, although the mechanisms by which this occurs are not understood.

The most frequently observed placental lesions in patients following PTB are associated with acute inflammation, such as acute chorioamnionitis and funisitis. The second most common placental pathology is vascular lesions [34]. A case-control study, comprising of 210 women, 20% of whom delivered preterm (mean gestational age of 31.4 weeks) and 50% delivered at term, found that 34.1% of women who delivered preterm without preterm prelabor rupture of membranes (PPROM) had vascular lesions in the decidual section of the placenta, compared to 11.8% of normal term deliveries ($p = 0.001$). Of this preterm group, 3% showed evidence of infection and 7.1% showed evidence of mixed infection and vascular pathology. However, the fact that 34.1% had solely vascular lesions suggests an association between placental insufficiency and PTB with intact membranes, independent of the presence of chorioamnionitis [35]. Although some studies have identified both vascular lesions and chorioamnionitis in cases of PPROM and PTB with intact membranes, a subgroup of cases solely exhibit vascular lesions. This subgroup provides strong evidence for a placental etiology in PPROM and PTB with intact membranes [36].

Vasa previa, a condition where unprotected fetal blood vessels run across the cervix, is also strongly linked to PTB. Vasa previa has been identified in 63% of cesarean PTB deliveries, whereas cesarean PTB deliveries without vasa previa comprised 10% PTB [37]. The Royal College of Obstetricians and Gynecologists (RCOG) and others recommend miPTB at 34 to 36 weeks for vasa previa, based upon limited, low-quality evidence [38].

Assisted reproductive technologies

Europe has the highest ART utilization rates globally, with ART births representing over 5% in some countries [39]. Popular ART methods result in higher frequencies of twin and higher-order multiple

pregnancies. In 2006, multiple gestations resulting from ART accounted for 18.3–29.0% of all multiple births in several European countries. However, as of 2018, changes in ART policies have led to the majority of ART procedures in Europe being single-embryo transfers, thereby reducing the number of multiple pregnancies [10]. In 21 European countries, term deliveries (37 weeks or later) achieved with all ART in 2018 were 83.1% for singleton pregnancies, 43.6% for twin pregnancies, and 8.1% for triplet pregnancies. It has been suggested that a recent decline in twin births reflects a broader adoption of single-embryo-transfer ART [1,40]. Engagement with ART differs across Europe, and it has been shown that disparities in ART accessibility in the United Kingdom favors those in socio-economic and geographically advantaged areas [41]. As utilization gradually increases to meet demand, there is opportunity to reduce ART-associated multiple gestations and therefore PTB rates through technological improvements. However, variability in ART outcomes is not solely technique related, also reflecting differences in clinical practice, patient populations, and access to care [42]. Interestingly, singleton *in vitro* fertilization (IVF) pregnancies also show a greater risk of PTB, which persists even after adjusting for maternal age and parity, suggesting that subfertility itself may serve as an independent risk factor [43].

Ethnicity

The reasons for varying PTB rates across different ethnicities remain unclear; however, disparities are regularly observed in broad health outcomes for certain racial and ethnic groups. For instance, Black women experience a higher PTB risk than White women, even after controlling for maternal characteristics, and these racial and ethnic influences do not vary by region [44]. A recent risk prediction model that included "non-white race" showed a sensitivity of 0.85 and specificity of 0.28 for predicting sPTB within 7 d in symptomatic women [45]. Ethnicity and race often correlate with risk factors such as socioeconomic status, BMI, language barriers, self-care, smoking, migration status, substance abuse, and access to adequate antenatal care [33,46]. In addition, PTB risk factors are frequently modified differently by ethnicity [47]. For example, non-white ethnicity and smoking are correlated with an overall increased risk of sPTB; however, in women presenting with symptoms, these factors are linked to a reduced risk of sPTB [45]. Migration, whether within Europe or immigration from elsewhere, has also been identified as a PTB risk factor in relation to ethnicity and race. The implications of migration as a risk factor are influenced by maternal country of origin, reasons for migration, length of residence, and differ for spontaneous and miPTB [48,49]. Current and future trends in the ethnic makeup of Europe should be taken into account when considering overall PTB risk trends.

Smoking and recreational drug use

Smoking habits vary greatly across Europe, and smoking rates during pregnancy reflect this diversity. While complete data from all European countries are lacking, smoking during pregnancy is most frequently reported in Scotland (19.0%), France (17.1%), and Northern Ireland (15.0%), while the lowest reports come from Finland (1.0%), Lithuania (4.5%), and Sweden (4.9%) [48]. A well-established and dose-dependent relationship exists between smoking during pregnancy and increased PTB rates [50]. The dose-dependency of PTB risk associated with maternal smoking is also reflected in the observed increased PTB risk for expectant mothers exposed to secondhand smoke in some studies; however, exposure to secondhand smoke showed no clear effect on gestational length in a large meta-analysis [51].

Recreational drug use has been shown to increase the odds of PTB [52]. Observational evidence finds that opioids, cocaine, cannabis, amphetamine, combinations of these, and other drugs all increase the frequency of PTB [52]. Recreational drug use varies considerably across Europe, for example last-year cannabis prevalence rates for the 15–34 year old demographic ranged from 0.4% in Turkey to 22.1% in France in 2015 [53]. Cannabis is the recreational drug with the highest use rate among pregnant women, with indications that it may be as much as 5%. A study in Spain from 2024 found that cannabis use was associated with a doubling of the risk of PTB [54].

Stress

Evidence from three prospective studies showed that maternal perceived stress significantly correlates with an increased risk of PTB. Measuring perceived stress with various instruments revealed that stress levels assessed during the second and third trimesters provide the strongest predictive value [46]. Employment itself is not a risk factor for PTB; however, working more than 42 h per week, standing for more than 6 h per day, and low job satisfaction have been associated with an increased risk of PTB across 16 European countries [55]. When maternal and paternal occupations are classified by social class, there is an observed increase in PTB rates among service and industrial workers, as well as those lacking employment in Europe [56,57]. Employment classified as sedentary is significantly and negatively associated with sPTB [21,58]. Social determinants of PTB risk likely confound the role of employment related stress. European researchers and stakeholders from diverse backgrounds have demonstrated good consensus on prioritizing additional research regarding the role of stress in PTB [59].

Body mass index

In addition to long-term negative health consequences, a high body mass index (BMI) has been found to correlate positively with miPTB and inversely with sPTB [60,61]. Although comprehensive data are unavailable, estimates of the prevalence of maternal obesity (BMI ≥30 kg/m^2) in European countries ranged from 7% in Poland to 25% in the UK in 2016 [62]. This loosely reflects the overall prevalence of obesity within European populations, which is itself associated with social and educational inequalities. An observational study of almost a half million births in England found that PTB risk associations of obesity are most predictive when stratified by the degree of obesity. The strongest associations with extreme PTB (delivery from 20 to 27 weeks of gestation) were noted in class IIIb obesity (≥50 kg/m^2), where, after adjusting for other risk factors, these mothers were 2.8 times more likely to experience an extreme preterm delivery [63]. The risk of sPTB also rises at lower BMI (<18 kg/m^2), with the lowest PTB risks occurring at a BMI of 22.5 kg/m^2 for nulliparous women and 25.9 kg/m^2 for multiparous women [33,64]. Obesity more strongly associated with late preterm birth, most often miPTB, and was not identified as an independent risk factor for early (<32 weeks) PTB [24]. Bariatric surgery is an effective surgical option to decrease BMI, and it may improve fertility through restoration of ovulation following weight loss. Pregnancies following bariatric surgery are becoming increasingly common and preliminary evidence suggests that a history of bariatric surgery increases PTB risk [65,66]. Efforts to address the obesity epidemic are largely outside the influence of obstetric practice however broader public health efforts to decrease BMI throughout Europe populations could yield improved health outcomes, including decreased PTB rates.

Sex of the fetus

Singleton pregnancies of males are found to be at higher risk of PTB [67–69]. In higher-risk pregnancies that include a history of late miscarriage, PTB, or significant cervical surgery, this disparity has not been noted [70]. Sex-based influences on risk factors for decreased gestation have also been recognized, with PPROM occurring more commonly in women carrying a male fetus, while those carrying a female fetus are at greater risk of preeclampsia [71]. More recently, it has been discovered that the increased risk of PTB for male fetuses is modified by ethnicity, with Asian pregnancies exhibiting a greater sex disparity in PTB risk compared to Mediterranean or African ethnicities [47]. In most cases, the sex of the fetus is not considered in evaluations as an independent risk factor for PTB.

Environmental factors

Environmental conditions and related changes represent significant risk factors that vary across the region. A large study in Denmark found seasonal variations in PTB, with autumn and summer births

having the most extremely PTBs (22 to 28 weeks gestation) [72]. Air pollution and climate have also shown impacts on PTB rates. A meta-analysis of 20 studies revealed a 15% increase in the risk of PTB for each 10 μg/m^3 rise in PM2.5 [73]. Additionally, heat exposure elevates the risk of PTB, particularly late in pregnancy when extreme heat is a notable concern. More temperate EU countries, such as Sweden, are less likely to exhibit this association; however, the climate is changing rapidly at higher latitudes [74]. The intersection of air pollution and climate change, driven by increases in wildfire smoke pollution, poses potential synergistic effects on PTB rates in the Europe [73,74].

Potentially hazardous exposures, including to organic pollutants and heavy metals, can be faced during pregnancy through the air, water, soil, food, and domestic products. Lead and cadmium exposures have been linked to a higher incidence of PTB [75], as have perfluoroalkyl substances [76]. It is probable that other environmental constituents can increase the risk of PTB, however such associations require direct evidence.

Infection and inflammation

Intra-amniotic inflammation, which may or may not be accompanied by microbial infection, is linked to PTB through proposed immune-mediated mechanisms. It stands as the most recognized risk factor for preterm labor and sPTB [77,78]. Microbiological analyses of amniotic fluid indicate that at least 25% of all sPTB occurs within the context of a generally asymptomatic infection while symptomatic intrauterine inflammation has been implicated in 40% to 70% of all PTB worldwide [16]. While a definitive mechanism remains elusive, various preclinical evidence supports the causal roles of infection in PTB [79]. Distinct microbiome signatures have been associated with preterm labor, however the relative contribution of microbiota diversity, quantity to PTB is unclear [80]. Findings of intra-amniotic sludge at second cervical ultrasound are thought to be associated with microbial biofilms and are significant and independent predictors of PTB within 14 d [81]. The prevalence of sterile intra-amniotic inflammation, which produces similar PTB and neonatal outcomes, strongly suggests that maternal inflammation plays a role in the proposed mechanisms; however, these two inflammatory states possess some inherent differences [77].

Furthermore, several non-genital tract bacterial infections are associated with PTB, including asymptomatic bacteriuria, pyelonephritis, pneumonia, periodontal disease, syphilis and appendicitis [82]. Periodontitis and oral health have been correlated to a greater frequency of poor neonatal outcomes. While oral health indices may not be independent predictors of preterm birth, oral health may contribute indirectly to PTB through systemic inflammation [83,84].

Viral infections of the maternal-fetal interface and viral cervical infections are also linked to PTB [85]. Cytomegalovirus (CMV), herpes simplex virus (HSV), human papillomavirus (HPV), influenza, and hepatitis B virus (HPV) have all been associated with PTB. These associations are not as well supported by an inflammation-mediated mechanism however animal models suggest a similar but even more complex immune-mediated mechanism [85].

Alcohol consumption

Similar to smoking, the frequency of alcohol consumption during pregnancy varies significantly across the Europe. While alcohol consumption during pregnancy greatly increases the risk of serious morbidity, it does not show an association with increased PTB risk [86].

Clinical risk assessment captures only a portion of PTBs. Some women delivering prematurely show no known risk factors, while others have significant risk factors that remain undetected or unscreened. Despite improvements in perinatal care, comprehensive prediction algorithms based on known risk factors can account for only one-third of PTBs. Established risk factors fail to identify most PTBs, and women who deliver prematurely often lack recognized risk factors. Comprehensive prediction algorithms based on known risk factors account for less than one-third of PTBs [28]. It is possible that changing influences of various risk factors, including BMI, migration, increasing maternal age, and the greater use of ART, may be masking these improvements. Fortunately, there

is potential to reduce certain PTB risk factors through maternal education particularly preconception, lifestyle changes, and policy modifications to lessen the impact of decreased gestational age on public health [28].

Cervical surgery and/or trauma

A history of some surgical procedures has been found to increase PTB risk. Women with cervical intraepithelial neoplasia have an increased PTB risk and surgical excision of disease further increases risk. Larger excisions and more radical excisional techniques increase treatment success but also pose greater risk of subsequent PTBs, and the observed increase risk does not decrease with time [87–89]. A cesarean section at full dilation also increases PTB risk for subsequent pregnancies. This procedure is increasingly common in Europe, and the implications for surveillance and management of subsequent pregnancies remain unclear [90].

Cervical length

A shortened cervix can lead to cervical insufficiency, or the decreased ability of the cervix to retain the fetus in the absence of contractions (Figure 3). Ultrasound cervical length measurement identifies otherwise asymptomatic pregnancies that are at increased risk of PTB during early gestational periods (16 to 24 weeks), providing adequate time for preventative interventions [91,92]. In addition, risk prediction that combines ultrasound assessments of cervical length and texture has shown an area under the curve (AUC) of 0.77 for predicting birth before 34 weeks [93]. As an established PTB risk factor, cervical length measurement will continue to play a role in identifying patients who may benefit from preventative care.

Molecular biomarkers

Identifying highly predictive molecular biomarkers could potentially address limitations in the predictive power of known PTB risk factors. Desirable biomarkers should be assessable at early gestational timepoints in asymptomatic pregnancies to provide at least comparable clinical utility to known PTB risk factors. A summary of some potentially useful biomarkers is included in the second part of Table 1.

Exploratory associations have been established with alkaline phosphatase, α-fetoprotein, and corticotropin-releasing hormone, which can independently distinguish PTB risk at <35 weeks and ≥37 weeks of gestation. However, such studies are considered hypothesis-generating and have not yet demonstrated clinical utility [94]. A meta-analysis of nine case-control studies found an 18% greater risk of PTB associated with the *GSTT1* null genotype [95]. Subgroup analyses indicated that the association may be stronger among certain ethnic groups. While this genetic marker provides ample time for interventions, its positive predictive value (PPV) is not particularly useful [95]. It has been demonstrated that biomarkers can augment the predictive power of other known risk factors. For example, when known risk factors are used in combination with quantitative vaginal fluid fetal fibronectin (fFN), in symptomatic pregnancies, the AUC attains 0.89 (95% CI 0.84 to 0.94) [45]. Optimal management of asymptomatic women with a positive fFN test (over 50 ng/mL) has not been established [96,97]. Another biomarker from cervico-vaginal fluid, PAMG-1 (placental alpha microglobulin-1), has a greater positive predictive value for sPTB within 7 d as compared to fFN [98], Unfortunately, the aforementioned biomarker studies are only predictive for symptomatic pregnancies within 7 d, providing a limited opportunity to initiate preventative interventions [45]. Proteomic approaches have been explored to identify PTB predictive biomarkers at earlier gestations to facilitate targeted preventative interventions. One commercially available proteomic test in the United States measures the ratio of two maternal blood biomarkers in the second trimester and has consistently demonstrated an AUC of 0.75 (95% CI 0.56 to 0.91) for predicting birth before 37 weeks of gestation [99].

Decreased gestational age at birth in IVF pregnancies may have distinct etiologies, and PTB predictive biomarkers for these pregnancies have been identified, suggesting that suboptimal implantation from IVF could be a risk factor. The most predictive biomarkers identified in one study of IVF pregnancies were reductions in human epididymal protein 4 (HE4) and interleukin-13 (IL-13) at 9 to 11 d after embryo transfer. The potential for broader applicability of biomarkers associated with peri-implantation events remains unknown [43].

Surrogate molecular markers, markers of infection and inflammation, have also been investigated for predicting PTB [100,101]. Recently, a network meta-analysis of randomized controlled trials prioritized potentially informative biomarkers for predicting infectious PTB. These small studies, most of which were conducted in non-European populations, provided evidence that the biomarkers most predictive of infectious sPTB were sTNFR2, TNF-α, and IL-10 [101]. PPROM is an infrequent complication, occurring in approximately 0.4% to 0.7% of all pregnancies, yet it accounts for as many as a third of preterm deliveries. Matrix metalloproteinase-9 (MMP-9) is an effective marker for PPROM, and therefore a surrogate marker for PTB. While MMP-9 provides informative insights regarding the etiology of PTB, its clinical utility is limited as it predicts delivery within 24 h [100]. There are several accurate diagnostic tests for PPROM; none, however, necessarily provide an opportunity to prevent PTB for asymptomatic pregnancies, and prolonging pregnancy in cases of PPROM presents its own risks [102].

A comprehensive accounting for risk factors, biomarkers, and biophysical assessments that offer sufficient predictive power, along with adequate time for interventions to effectively extend gestation, is a critical step toward to reducing PTB incidence.

Interventions

Medical interventions

PTB prediction is useful only in the presence of effective interventions to extend gestation. Several exist (Figure 4), but broad consensus on their most effective implementation is limited. Differing

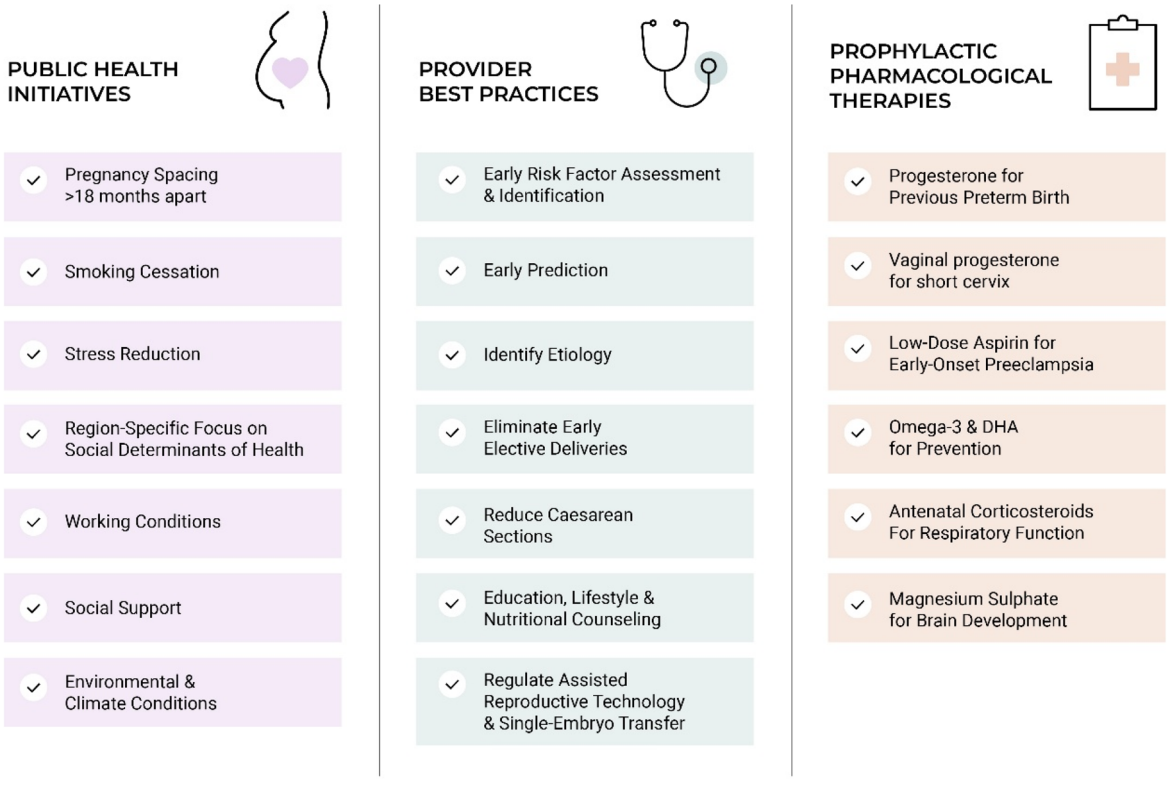

Figure 4. Evidence-based interventions to address preterm birth risk.

population risk profiles within Europe suggest that interventions will have varying effect sizes depending on where they are implemented.

One of the few interventions that consistently demonstrate safe reductions in PTB frequency is vaginal progesterone for women with singleton pregnancies identified as having high sPTB risk, and multiple gestations with a short cervical length [103]. FIGO, the French College of Gynecologists and Obstetricians (CNGOF), guidelines from the National Health Service (NHS), consensus guidelines from the German, Austrian, and Swiss societies for gynecology and obstetrics (DGGG, OEGGG, and SGGG), and the National Institute for Health and Care Excellence (NICE) recommend progesterone for women with a singleton pregnancy and a short cervix [104–108]. The guidelines differ regarding the definition of a short cervix, whether a history of sPTB is an indication for vaginal progesterone, and whether cervical cerclage should be offered as an alternative to this same patient population [104–108]. More risk indicators, alongside cervical length and history, might better identify pregnancies that would benefit from vaginal progesterone.

Expectant management of PPROM, is a relatively new approach to provide more extended gestational benefits to the newborn without increasing rates of neonatal sepsis when compared to medically indicated induction of late PTB. Adoption of expectant management of PPROM guidelines, a conservative approach utilizing corticosteroids, antibiotics, and individualized management, is expected to reduce PTB rates in Europe [109]. Similarly, for pre-eclampsia and fetal growth restriction diagnosed between 34 and 37 weeks expectant management is used to optimize maternal and neonatal outcomes. The impact of this clinical approach on overall PTB rates is unclear as the timing of birth is dependent on individualized risk assessments [110,111].

Cerclage remains a common surgical option for pregnancies at high risk of preterm delivery in the presence of cervical dilation detected by ultrasound or physical examination between 16 and 24 weeks of gestation (Figure 4). It is also a preventative intervention for short cervical length presentations, usually defined as <20 mm at 16–24 weeks of gestation; however, most of these cases will deliver at or near term [112,113].

Low-dose aspirin has consistently shown an approximate 10% reduction in PTB and perinatal mortality in large, high-quality clinical trials of women at risk for preeclampsia [114,115]. This inexpensive and safe preventive intervention decreases the risk of proteinuric pre-eclampsia by 18% and neonatal death by 14% when initiated before 20 weeks of gestation and it is possible that these benefits could be extended through newer, more accurate methods of preterm preeclampsia risk screening and risk standardization [116,117]. Low-dose aspirin has also demonstrated utility in reducing recurrent PTB [118]. Given the association with somewhat increased postpartum hemorrhage and potentially an elevated risk of placental abruption with low-dose aspirin PTB prophylaxis, further improvements in identifying pregnancies most likely to benefit from low-dose aspirin is necessary [114].

Data collected during the influenza H1N1 and the COVID 19 pandemics support the role of vaccination in reducing rates of PTB [85,119]. A randomized controlled trial out of Finland also suggests that the HPV vaccine may reduce PTB rates [120]. Ensuring that safe vaccination programs are broadly available to pregnant women could help reduce PTB rates, especially during pandemics.

Placement of a cervical pessary has been examined as a possible PTB prevention intervention for pregnant women with a cervical length of 20 mm or less at 16 to 24 weeks gestation. A recent definitive randomized controlled trial demonstrated that a cervical pessary did not reduce PTB incidence, however, and may be associated with an increased risk of fetal or neonatal mortality [121].

Care management (lifestyle changes)

A focus on preconception health and reproductive planning, for both men and women, has the potential for substantial reductions in PTB. Smoking cessation, normalization of BMI, and optimization of maternal medical pathologies for expectant mothers and their partners can also provide both short- and long-term benefits beyond PTB reduction. Consensus regarding preconception care effectiveness needs to be strengthened in order to determine the priority of interventions and how exactly to deliver this important care to maximize its potential specific to PTB [122,123]. Undoubtedly, the most effective methods will differ throughout Europe as a reflection of the variety of languages,

cultures, and prevalence of risk factors. Lifestyle changes that reduce PTB incidence can be encouraged during any healthcare point of contact.

Local obstetric practices have an opportunity to address certain modifiable risk factors to extend overall gestation after conception. Since BMI is associated with an increased risk of PTB, efforts have been made to evaluate the potential for controlling gestational weight gain. The most widely accepted recommendations for gestational weight gain are 12.5–18 kg for underweight women (BMI <18.5); 11.5–16 kg for normal-weight women (BMI 18.5–24.9); 7–11 kg for overweight women (BMI 25–29.9); and 5–9 kg for obese women (BMI ≥30) [124,125]. Excessive gestational weight gain can lead to negative maternal and neonatal outcomes, creating an opportunity for interventions that could mitigate long-term health consequences, including perinatal complications in subsequent pregnancies. However, conflicting evidence exists regarding management strategies for gestational weight gain that effectively reduce sPTB [62,124,125]. Additionally, gestational weight gain below the recommended amounts is linked to an increased risk of PTB; however, there is insufficient evidence for management strategies aimed at increasing gestational weight gain in these mothers [124].

Diet and nutrition can play an elemental role in PTB prevention. Assigning pregnant women to a diet rich in omega-3 long-chain polyunsaturated fatty acids—typically found in fish and fish oils—has shown a significant risk reduction in PTB before 37 weeks (RR = 0.88, 95% CI 0.81 to 0.95) in a meta-analysis of multiple high-quality studies [126]. More recent trials suggest that the decrease is significant only in women with very low baseline omega-3 levels who were randomized to receive omega-3 supplementation, while the benefits for multiparous women and those with a history of sPTB remain unestablished [127–129]. Nevertheless, omega-3 supplementation is considered a safe, affordable, and effective intervention to lower the risk of sPTB when initiated before 20 weeks of gestation in women with inadequate dietary intake [127].

Micronutrient deficiencies, including iron deficiency anemia, are common among women of reproductive potential, especially for those in low to middle income countries. In particular, iron deficiency complicates nearly 50% of pregnancies and increases risk of PTB (OR 1.54; 95% CI [1.36 to 1.76]) [130]. Iron and other nutritional deficiencies are exacerbated during pregnancy due to increased requirements of the growing fetus, placenta, maternal tissues and supplementation can help meet these increased demands. Pregnant women who supplement their diet with multiple micronutrients, including iron and folic acid, have fewer PTBs [131]. Europeans have a wide variety of diets and continued changes in diet trends could impact regional PTB risk where supplements and fortified foods could play a role in PTB prevention [132].

Despite findings that some employment conditions correlate with sPTB, the guidelines from DGGG, OEGGG, and SGGG as well as those from CNGOF do not recommend reducing prolonged working hours, standing, or physical labor unless the specific working conditions pose an unjustifiable risk [21,105,107]. Some stress reduction interventions have shown significant improvements in PTB outcomes for low-risk pregnant women; however, higher-quality evidence is necessary [133].

Regardless of previous smoking frequency, smoking cessation continues to lower the risk of PTB, with greater reductions achieved when quitting early [134]. Quitting smoking during pregnancy, even after smoking in a prior pregnancy, is also effective in reducing PTB risk [135]. DGGG, OEGGG, and SGGG as well as those from CNGOF advocate for smoking cessation as a preventive measure against PTB [107,136].

Simple interventions can limit pregnant mothers' exposure to environmental conditions that increase the risk of PTB. Ensuring that pregnant women have access to climate-controlled, indoor spaces with adequate air filtration can help minimize exposure to factors that elevate the possibility of PTB. No standard guidelines recommend air conditioning or staying indoors based on reported air quality. Gaps in the current prevention care path.

Differences among clinical practice guidelines do not fully reflect the extent of suboptimal PTB prevention, as the barriers to implementing guideline recommendations also vary within Europe. Current clinical practices exhibit both similarities and differences across the region, and some standardization may improve outcomes [137]. In practice, guidelines from NICE and North America are frequently followed in Europe.

Standardized risk screening

Guidelines and resources provided vary across Europe; however, most focus on PTB management and overlook the potential for prediction to enhance the targeting of effective management strategies. Risk factors and biomarkers are useful only when used systematically to identify at-risk pregnancies, yet clinical practice guidelines across Europe and the UK do not agree on the most effective screening and prevention strategies. Guidelines from Germany, Austria, and Switzerland advocate for comprehensive risk factor evaluation even before conception, emphasizing modifiable risk factors [105]. The diversity in family planning strategies within Europe suggests a range in adherence to preconception risk assessments and associated preventive measures.

Despite promising preliminary evidence, no biochemical biomarker tests have been integrated into routine clinical practice in the EU or UK to stratify PTB risk and safely extend gestation. Several institutions, including DGGG, OEGGG, and SGGG recommend only the optional use of predictive biomarkers from cervico-vaginal secretions for symptomatic pregnancies to forecast PTB within 7 d of onset [105]. The identification, introduction, and implementation of a standard biomarker test that correlates with decreased gestation for asymptomatic pregnancies, independently from known risk factors, could provide a starting point for more personalized PTB prevention strategies.

Guidelines from the Italian Society of Ultrasound in Obstetrics and Gynecology (SIEOG) and the UK's NICE, along with DGGG, OEGGG, and SGGG, and the CNGOF, do not currently recommend universal cervical length screening [104,105,107]. There is uncertainty as to whether universal cervical length screening is cost-effective across entire populations, however the evidence landscape is evolving [138,139]. Some studies suggest that expanding the indications for mid-trimester cervical length screening could reduce PTB [139,140], and similar diagnostic ultrasound markers may provide even greater predictive power.

Additional markers that may increase the utility of ultrasound investigations for PTB risk include strain elastography, shear wave elastography, hardness ratio, cervical consistency index, uterocervical angle, cervical funneling, cervical gland area, and amniotic fluid sludge [141–144]. To date, these anatomic aspects of the cervix have not been recommended for PTB risk assessment in European guidelines. In addition, the availability of the required transvaginal sonography and expertise for these sonography assessments across Europe is unclear.

Screening and treatment approaches for infections associated with PTB also differ among European countries [145]. Although the association between infections and PTB has long been established, clinical evidence for the efficacy of screening and treating infections during pregnancy remains mixed [146–150]. Similarly, evidence for the efficacy of periodontal treatment for periodontitis remains mixed [84]. It has yet to be determined whether adherence to any particular infection screening and treatment protocol offers opportunities to reduce the PTB risk, which may partially explain the lack of uniformity across international practices.

Conclusions

The PTB burden is a persistent concern across Europe. Constituent populations are diverse, comprising a mosaic of risk factors of varying significance that fail to predict the majority of PTBs. During this time of evolving demographics in the Europe, assessing PTB risk becomes even more challenging. The stagnation of PTB incidence rates also strongly suggests that new tools are needed to achieve improvements for mothers, babies, public health, and to reduce associated long-term costs of PTB.

The clinical utility of current risk analysis assessments remain suboptimal. While opportunities exist for reducing PTB rates during pregnancy through changes in modifiable risk factors such as smoking, environmental exposures, and diet, the potential for improvements remains limited. Cervical length screening and related ultrasound investigations provide the only recommended and most successful evidence-based screening methods for which effective preventative interventions for asymptomatic pregnancies exist. Unfortunately, the magnitude of improvement we can expect from optimizing the implementation of current solutions is again limited.

While perhaps the largest opportunities for improvement exist by focusing attention on optimizing preconception health, these broader public health goals are outside the scope of obstetric practice.

One clear potential area for development is identifying and implementing a consistent PTB risk stratification protocol for pregnancies, aimed at effectively targeting the few available effective preventative interventions. There is a lack of more sensitive and specific indicators of PTB risk that are independent of known PTB risk factors.

Acknowledgments

The authors acknowledge medical writing assistance from Jennifer Logan, PhD and Rob Edge, PhD.

Author contributions

CRediT: **Gian Carlo Di Renzo**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **José Luis. Bartha**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **Anna L. David**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **Roland Devlieger**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **Loïc Sentilhes**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **Daniel V. Surbek**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **Stefan Verlohren**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **Dilly O. C. Anumba**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

References

[1] Euro-Peristat Network. The European perinatal health report, 2015–2019. 2022 [cited 2024 Jul 23]. Available from: https://www.europeristat.com/index.php/reports/ephr-2019.html.

[2] Draper ES, Manktelow BN, Cuttini M, et al. Variability in very preterm stillbirth and in-hospital mortality across Europe. Pediatrics. 2017;139(4):e20161990. doi: 10.1542/peds.2016-1990.

[3] Torchin H, Morgan AS, Ancel PY. International comparisons of neurodevelopmental outcomes in infants born very preterm. Semin Fetal Neonatal Med. 2020;25(3):101109. doi: 10.1016/j.siny.2020.101109.

[4] Morgan AS, Zeitlin J, Källén K, et al. Birth outcomes between 22 and 26 weeks' gestation in national population-based cohorts from Sweden, England and France. Acta Paediatr. 2022;111(1):59–75. doi: 10.1111/apa.16084.

[5] Aughey H, Jardine J, Knight H, et al. Iatrogenic and spontaneous preterm birth in England: a population-based cohort study. BJOG. 2023;130(1):33–41. doi: 10.1111/1471-0528.17291.

[6] Ancel P-Y, Goffinet F, Kuhn P, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. JAMA Pediatr. 2015;169(3):230–238. doi: 10.1001/jamapediatrics.2014.3351.

[7] Nath S, Hardelid P, Zylbersztejn A. Are infant mortality rates increasing in England? The effect of extreme prematurity and early neonatal deaths. J Public Health (Oxf). 2021;43(3):541–550. doi: 10.1093/pubmed/fdaa025.
[8] Taylor-Robinson D, Lai ETC, Wickham S, et al. Assessing the impact of rising child poverty on the unprecedented rise in infant mortality in England, 2000-2017: time trend analysis. BMJ Open. 2019;9(10):e029424. doi: 10.1136/bmjopen-2019-029424.
[9] Trinh NTH, de Visme S, Cohen JF, et al. Recent historic increase of infant mortality in France: a time-series analysis, 2001 to 2019. Lancet Reg Health Eur. 2022;16:100339. doi: 10.1016/j.lanepe.2022.100339.
[10] Raju TNK, Buist AS, Blaisdell CJ, et al. Adults born preterm: a review of general health and system-specific outcomes. Acta Paediatr. 2017;106(9):1409–1437. doi: 10.1111/apa.13880.
[11] Pierrat V, Marchand-Martin L, Marret S, et al. Neurodevelopmental outcomes at age 5 among children born preterm: EPIPAGE-2 cohort study. BMJ. 2021;373:n741. doi: 10.1136/bmj.n741.
[12] Kim SW, Andronis L, Seppänen A-V, et al. Economic costs at age five associated with very preterm birth: multinational European cohort study. Pediatr Res. 2022;92(3):700–711. doi: 10.1038/s41390-021-01769-z.
[13] Zeitlin J, Alexander S, Barros H, et al. Perinatal health monitoring through a European lens: eight lessons from the Euro-Peristat report on 2015 births. BJOG. 2019;126(13):1518–1522. doi: 10.1111/1471-0528.15857.
[14] Glover AV, Manuck TA. Screening for spontaneous preterm birth and resultant therapies to reduce neonatal morbidity and mortality: a review. Semin Fetal Neonatal Med. 2018;23(2):126–132. doi: 10.1016/j.siny.2017.11.007.
[15] Di Renzo GC. The great obstetrical syndromes. J Matern Fetal Neonatal Med. 2009;22(8):633–635. doi: 10.1080/14767050902866804.
[16] Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. BJOG. 2006;113 Suppl 3(Suppl 3):17–42. doi: 10.1111/j.1471-0528.2006.01120.x.
[17] Koullali B, van Zijl MD, Kazemier BM, et al. The association between parity and spontaneous preterm birth: a population based study. BMC Pregnancy Childbirth. 2020;20(1):233. doi: 10.1186/s12884-020-02940-w.
[18] Tingleff T, Vikanes Å, Räisänen S, et al. Risk of preterm birth in relation to history of preterm birth: a population-based registry study of 213 335 women in Norway. BJOG. 2022;129(6):900–907. doi: 10.1111/1471-0528.17013.
[19] Phillips C, Velji Z, Hanly C, et al. Risk of recurrent spontaneous preterm birth: a systematic review and meta-analysis. BMJ Open. 2017;7(6):e015402. doi: 10.1136/bmjopen-2016-015402.
[20] Schummers L, Hutcheon JA, Hernandez-Diaz S, et al. Association of short interpregnancy interval with pregnancy outcomes according to maternal age. JAMA Intern Med. 2018;178(12):1661–1670. doi: 10.1001/jamainternmed.2018.4696.
[21] Meis PJ, Michielutte R, Peters TJ, et al. Factors associated with preterm birth in Cardiff, Wales. II. Indicated and spontaneous preterm birth. Am J Obstet Gynecol. 1995;173(2):597–602. doi: 10.1016/0002-9378(95)90288-0.
[22] Correa-de-Araujo R, Yoon SSS. Clinical outcomes in high-risk pregnancies due to advanced maternal age. J Womens Health (Larchmt). 2021;30(2):160–167. doi: 10.1089/jwh.2020.8860.
[23] Paulo MS, Abdo NM, Bettencourt-Silva R, et al. Gestational diabetes mellitus in Europe: a systematic review and meta-analysis of prevalence studies. Front Endocrinol (Lausanne). 2021;12:691033. doi: 10.3389/fendo.2021.691033.
[24] Martius JA, Steck T, Oehler MK, et al. Risk factors associated with preterm (<37 + 0 weeks) and early preterm birth (<32 + 0 weeks): univariate and multivariate analysis of 106 345 singleton births from the 1994 statewide perinatal survey of Bavaria. Eur J Obstet Gynecol Reprod Biol. 1998;80(2):183–189. doi: 10.1016/S0301-2115(98)00130-4.
[25] Reitzle L, Heidemann C, Baumert J, et al. Pregnancy complications in women with pregestational and gestational diabetes mellitus. Dtsch Arztebl Int. 2023;120(6):81–86. doi: 10.3238/arztebl.m2022.0387.
[26] Balsells M, García-Patterson A, Gich I, et al. Maternal and fetal outcome in women with type 2 versus type 1 diabetes mellitus: a systematic review and metaanalysis. J Clin Endocrinol Metab. 2009;94(11):4284–4291. doi: 10.1210/jc.2009-1231.
[27] Lepercq J, Coste J, Theau A, et al. Factors associated with preterm delivery in women with type 1 diabetes: a cohort study. Diabetes Care. 2004;27(12):2824–2828. doi: 10.2337/diacare.27.12.2824.
[28] Ferrero DM, Larson J, Jacobsson B, et al. Cross-country individual participant analysis of 4.1 million singleton births in 5 countries with very high human development index confirms known associations but provides no biologic explanation for 2/3 of all preterm births. PLoS One. 2016;11(9):e0162506. doi: 10.1371/journal.pone.0162506.
[29] Mustafa R, Ahmed S, Gupta A, et al. A comprehensive review of hypertension in pregnancy. J Pregnancy. 2012. 2012;2012:105918.
[30] Abalos E, Duley L, Steyn DW, et al. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2018;10(10):CD002252. doi: 10.1002/14651858.CD002252.pub4.
[31] Tita AT, Szychowski JM, Boggess K, et al. Treatment for mild chronic hypertension during pregnancy. N Engl J Med. 2022;386(19):1781–1792. doi: 10.1056/NEJMoa2201295.

[32] Fuchs F, Senat MV. Multiple gestations and preterm birth. Semin Fetal Neonatal Med. 2016;21(2):113–120. doi: 10.1016/j.siny.2015.12.010.
[33] Weichert A, Weichert TM, Bergmann RL, et al. Factors for preterm births in Germany—an analysis of representative German data (KiGGS). Geburtshilfe Frauenheilkd. 2015;75(8):819–826. doi: 10.1055/s-0035-1557817.
[34] Romero R, Kusanovic JP, Chaiworapongsa T, et al. Placental bed disorders in preterm labor, preterm PROM, spontaneous abortion and abruptio placentae. Best Pract Res Clin Obstet Gynaecol. 2011;25(3):313–327. doi: 10.1016/j.bpobgyn.2011.02.006.
[35] Arias F, Rodriquez L, Rayne SC, et al. Maternal placental vasculopathy and infection: two distinct subgroups among patients with preterm labor and preterm ruptured membranes. Am J Obstet Gynecol. 1993;168(2):585–591. doi: 10.1016/0002-9378(93)90499-9.
[36] Jaiman S, Romero R, Bhatti G, et al. The role of the placenta in spontaneous preterm labor and delivery with intact membranes. J Perinat Med. 2022;50(5):553–566. doi: 10.1515/jpm-2021-0681.
[37] Yeaton-Massey A, Girsen AI, Mayo JA, et al. Vasa previa and extreme prematurity: a population-based study. J Perinatol. 2019;39(3):475–480. doi: 10.1038/s41372-019-0319-8.
[38] McMahon C, Laiu S, Oyelese Y, et al. Vasa previa guidelines and their supporting evidence. J Perinat Med. 2025;53(4):411–417. doi: 10.1515/jpm-2024-0473.
[39] Chambers GM, Dyer S, Zegers-Hochschild F, et al. International committee for monitoring assisted reproductive technologies world report: assisted reproductive technology, 2014†. Hum Reprod. 2021;36(11):2921–2934. doi: 10.1093/humrep/deab198.
[40] European IVF-Monitoring Consortium for the European Society of Human Reproduction and Embryology (ESHRE), et al. ART in Europe 2022: results generated from European registries by ESHRE. Hum Reprod Open. 2018;2022(3):hoac022.
[41] Jones B, Peri-Rotem N, Mountford-Zimdars A. Geographic opportunities for assisted reproduction: a study of regional variations in access to fertility treatment in England. Hum Fertil (Camb). 2023;26(3):494–503. doi: 10.1080/14647273.2023.2190040.
[42] Chambers GM, Sullivan EA, Ishihara O, et al. The economic impact of assisted reproductive technology: a review of selected developed countries. Fertil Steril. 2009;91(6):2281–2294. doi: 10.1016/j.fertnstert.2009.04.029.
[43] Kanninen TT, Sisti G, Ramer I, et al. Predictive biomarkers of preterm delivery in women with ongoing IVF pregnancies. J Reprod Immunol. 2015;112:58–62. doi: 10.1016/j.jri.2015.05.004.
[44] Sheikh J, Allotey J, Kew T, et al. Effects of race and ethnicity on perinatal outcomes in high-income and upper-middle-income countries: an individual participant data meta-analysis of 2 198 655 pregnancies. Lancet. 2022;400(10368):2049–2062. doi: 10.1016/S0140-6736(22)01191-6.
[45] Stock SJ, Horne M, Bruijn M, et al. Development and validation of a risk prediction model of preterm birth for women with preterm labour symptoms (the QUIDS study): a prospective cohort study and individual participant data meta-analysis. PLoS Med. 2021;18(7):e1003686. doi: 10.1371/journal.pmed.1003686.
[46] Staneva A, Bogossian F, Pritchard M, et al. The effects of maternal depression, anxiety, and perceived stress during pregnancy on preterm birth: a systematic review. Women Birth. 2015;28(3):179–193. doi: 10.1016/j.wombi.2015.02.003.
[47] Peelen MJCS, Kazemier BM, Ravelli ACJ, et al. Ethnic differences in the impact of male fetal gender on the risk of spontaneous preterm birth. J Perinatol. 2021;41(9):2165–2172. doi: 10.1038/s41372-021-01024-7.
[48] Delnord M, Blondel B, Zeitlin J. What contributes to disparities in the preterm birth rate in European countries? Curr Opin Obstet Gynecol. 2015;27(2):133–142. doi: 10.1097/GCO.0000000000000156.
[49] Khanolkar AR, Wedrén S, Essén B, et al. Preterm and postterm birth in immigrant- and Swedish-born parents: a population register-based study. Eur J Epidemiol. 2015;30(5):435–447. doi: 10.1007/s10654-014-9986-0.
[50] Andres RL, Day MC. Perinatal complications associated with maternal tobacco use. Semin Neonatol. 2000;5(3):231–241. doi: 10.1053/siny.2000.0025.
[51] Leonardi-Bee J, Smyth A, Britton J, et al. Environmental tobacco smoke and fetal health: systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2008;93(5):F351–61. doi: 10.1136/adc.2007.133553.
[52] Baer RJ, Chambers CD, Ryckman KK, et al. Risk of preterm and early term birth by maternal drug use. J Perinatol. 2019;39(2):286–294. doi: 10.1038/s41372-018-0299-0.
[53] Mounteney J, Griffiths P, Sedefov R, et al. The drug situation in Europe: an overview of data available on illicit drugs and new psychoactive substances from European monitoring in 2015. Addiction. 2016;111(1):34–48. doi: 10.1111/add.13056.
[54] Brik M, Sandonis M, Hernández-Fleury A, et al. Cannabis exposure during pregnancy and perinatal outcomes: a cohort study. Acta Obstet Gynecol Scand. 2024;103(6):1083–1091. doi: 10.1111/aogs.14818.
[55] Saurel-Cubizolles MJ, Zeitlin J, Lelong N, et al. Employment, working conditions, and preterm birth: results from the Europop case-control survey. J Epidemiol Community Health. 2004;58(5):395–401. doi: 10.1136/jech.2003.008029.
[56] Ancel PY, Saurel-Cubizolles MJ, Di Renzo GC, et al. Very and moderate preterm births: are the risk factors different? Br J Obstet Gynaecol. 1999;106(11):1162–1170. doi: 10.1111/j.1471-0528.1999.tb08142.x.
[57] Ancel PY, Saurel-Cubizolles MJ, Di Renzo GC, et al. Social differences of very preterm birth in Europe: interaction with obstetric history. Europop Group. Am J Epidemiol. 1999;149(10):908–915. doi: 10.1093/oxfordjournals.aje.a009734.

[58] Di Renzo GC, Giardina I, Rosati A, et al. Maternal risk factors for preterm birth: a country-based population analysis. Eur J Obstet Gynecol Reprod Biol. 2011;159(2):342–346. doi: 10.1016/j.ejogrb.2011.09.024.
[59] Zeitlin J, Sentenac M, Morgan AS, et al. Priorities for collaborative research using very preterm birth cohorts. Arch Dis Child Fetal Neonatal Ed. 2020;105(5):538–544. doi: 10.1136/archdischild-2019-317991.
[60] Hendler I, Goldenberg RL, Mercer BM, et al. The Preterm Prediction Study: association between maternal body mass index and spontaneous and indicated preterm birth. Am J Obstet Gynecol. 2005;192(3):882–886. doi: 10.1016/j.ajog.2004.09.021.
[61] Savitz DA, Dole N, Herring AH, et al. Should spontaneous and medically indicated preterm births be separated for studying aetiology? Paediatr Perinat Epidemiol. 2005;19(2):97–105. doi: 10.1111/j.1365-3016.2005.00637.x.
[62] Devlieger R, Benhalima K, Damm P, et al. Maternal obesity in Europe: where do we stand and how to move forward?: a scientific paper commissioned by the European Board and College of Obstetrics and Gynaecology (EBCOG). Eur J Obstet Gynecol Reprod Biol. 2016;201:203–208. doi: 10.1016/j.ejogrb.2016.04.005.
[63] Slack E, Best KE, Rankin J, et al. Maternal obesity classes, preterm and post-term birth: a retrospective analysis of 479,864 births in England. BMC Pregnancy Childbirth. 2019;19(1):434. doi: 10.1186/s12884-019-2585-z.
[64] Cornish RP, Magnus MC, Urhoj SK, et al. Maternal pre-pregnancy body mass index and risk of preterm birth: a collaboration using large routine health datasets. BMC Med. 2024;22(1):10. doi: 10.1186/s12916-023-03230-w.
[65] Shawe J, Ceulemans D, Akhter Z, et al. Pregnancy after bariatric surgery: consensus recommendations for periconception, antenatal and postnatal care. Obes Rev. 2019;20(11):1507–1522. doi: 10.1111/obr.12927.
[66] Stephansson O, Johansson K, Näslund I, et al. Bariatric surgery and preterm birth. N Engl J Med. 2016;375(8):805–806. doi: 10.1056/NEJMc1516566.
[67] Cooperstock M, Campbell J. Excess males in preterm birth: interactions with gestational age, race, and multiple birth. Obstet Gynecol. 1996;88(2):189–193. doi: 10.1016/0029-7844(96)00106-8.
[68] Di Renzo GC, Rosati A, Sarti RD, et al. Does fetal sex affect pregnancy outcome? Gend Med. 2007;4(1):19–30. doi: 10.1016/s1550-8579(07)80004-0.
[69] Zeitlin J, Saurel-Cubizolles M-J, De Mouzon J, et al. Fetal sex and preterm birth: are males at greater risk? Hum Reprod. 2002;17(10):2762–2768. doi: 10.1093/humrep/17.10.2762.
[70] Teoh PJ, Ridout A, Seed P, et al. Gender and preterm birth: is male fetal gender a clinically important risk factor for preterm birth in high-risk women? Eur J Obstet Gynecol Reprod Biol. 2018;225:155–159. doi: 10.1016/j.ejogrb.2018.04.025.
[71] Elsmen E, et al. Fetal gender and gestational-age-related incidence of pre-eclampsia. Acta Obstet Gynecol Scand. 2006;85(11):1285–1291.
[72] Hviid A, Laksafoss A, Hedley P, et al. Assessment of seasonality and extremely preterm birth in Denmark. JAMA Netw Open. 2022;5(2):e2145800. doi: 10.1001/jamanetworkopen.2021.45800.
[73] Sapkota A, Chelikowsky AP, Nachman KE, et al. Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. Air Qual Atmos Health. 2012;5(4):369–381. doi: 10.1007/s11869-010-0106-3.
[74] Masters C, Wu C, Gleeson D, et al. Scoping review of climate drivers on maternal health: current evidence and clinical implications. AJOG Glob Rep. 2025;5(1):100444. doi: 10.1016/j.xagr.2025.100444.
[75] Khanam R, Kumar I, Oladapo-Shittu O, et al. Prenatal environmental metal exposure and preterm birth: a scoping review. Int J Environ Res Public Health. 2021;18(2):573. doi: 10.3390/ijerph18020573.
[76] Qin X-D, Zhou Y, Bloom MS, et al. Prenatal exposure to PFAS, associations with preterm birth and modification by maternal estrogen levels: the maoming birth study. Environ Health Perspect. 2023;131(11):117006. doi: 10.1289/EHP11377.
[77] Gomez-Lopez N, Galaz J, Miller D, et al. The immunobiology of preterm labor and birth: intra-amniotic inflammation or breakdown of maternal-fetal homeostasis. Reproduction. 2022;164(2):R11–R45. doi: 10.1530/REP-22-0046.
[78] Romero R, Espinoza J, Gonçalves LF, et al. The role of inflammation and infection in preterm birth. Semin Reprod Med. 2007;25(1):21–39. doi: 10.1055/s-2006-956773.
[79] Romero R, Gómez R, Chaiworapongsa T, et al. The role of infection in preterm labour and delivery. Paediatr Perinat Epidemiol. 2001;15 Suppl 2:41–56. doi: 10.1046/j.1365-3016.2001.00007.x.
[80] Doyle RM, Alber DG, Jones HE, et al. Term and preterm labour are associated with distinct microbial community structures in placental membranes which are independent of mode of delivery. Placenta. 2014;35(12):1099–1101. doi: 10.1016/j.placenta.2014.10.007.
[81] Bujold E, Pasquier J-C, Simoneau J, et al. Intra-amniotic sludge, short cervix, and risk of preterm delivery. J Obstet Gynaecol Can. 2006;28(3):198–202. doi: 10.1016/S1701-2163(16)32108-9.
[82] Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75–84. doi: 10.1016/S0140-6736(08)60074-4.

[83] Temur I, Temur KT, Dönertas SN, et al. The relationship between maternal oral health parameters, inflammatory blood markers, and the evaluation of their effects on preterm low birth weight. BMC Pregnancy Childbirth. 2025;25(1):231. doi: 10.1186/s12884-025-07337-1.
[84] Xu H, Cai M, Xu H, et al. Role of periodontal treatment in pregnancy gingivitis and adverse outcomes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2025;38(1):2416595. doi: 10.1080/14767058.2024.2416595.
[85] Racicot K, Mor G. Risks associated with viral infections during pregnancy. J Clin Invest. 2017;127(5):1591–1599. doi: 10.1172/JCI87490.
[86] Meis PJ, Goldenberg RL, Mercer BM, et al. The preterm prediction study: risk factors for indicated preterm births. Maternal-fetal medicine units network of the National Institute of Child Health and Human Development. Am J Obstet Gynecol. 1998;178(3):562–567. doi: 10.1016/s0002-9378(98)70439-9.
[87] Castanon A, Landy R, Brocklehurst P, et al. Risk of preterm delivery with increasing depth of excision for cervical intraepithelial neoplasia in England: nested case-control study. BMJ. 2014;349(v05 3):g6223–g6223. doi: 10.1136/bmj.g6223.
[88] Castanon A, Brocklehurst P, Evans H, et al. Risk of preterm birth after treatment for cervical intraepithelial neoplasia among women attending colposcopy in England: retrospective-prospective cohort study. BMJ. 2012;345:e5174–e5174. doi: 10.1136/bmj.e5174.
[89] Athanasiou A, Veroniki AA, Efthimiou O, et al. Comparative effectiveness and risk of preterm birth of local treatments for cervical intraepithelial neoplasia and stage IA1 cervical cancer: a systematic review and network meta-analysis. Lancet Oncol. 2022;23(8):1097–1108. doi: 10.1016/S1470-2045(22)00334-5.
[90] Watson HA, Carter J, David AL, et al. Full dilation cesarean section: a risk factor for recurrent second-trimester loss and preterm birth. Acta Obstet Gynecol Scand. 2017;96(9):1100–1105. doi: 10.1111/aogs.13160.
[91] Goldenberg RL, Iams JD, Mercer BM, et al. The preterm prediction study: toward a multiple-marker test for spontaneous preterm birth. Am J Obstet Gynecol. 2001;185(3):643–651. doi: 10.1067/mob.2001.116752.
[92] Granese R, Gitto E, D'Angelo G, et al. Preterm birth: seven-year retrospective study in a single centre population. Ital J Pediatr. 2019;45(1):45. doi: 10.1186/s13052-019-0643-9.
[93] Burgos-Artizzu XP, Baños N, Coronado-Gutiérrez D, et al. Mid-trimester prediction of spontaneous preterm birth with automated cervical quantitative ultrasound texture analysis and cervical length: a prospective study. Sci Rep. 2021;11(1):7469. doi: 10.1038/s41598-021-86906-8.
[94] Moawad AH, Goldenberg RL, Mercer B, et al. The Preterm Prediction Study: the value of serum alkaline phosphatase, alpha-fetoprotein, plasma corticotropin-releasing hormone, and other serum markers for the prediction of spontaneous preterm birth. Am J Obstet Gynecol. 2002;186(5):990–996. doi: 10.1067/mob.2002.121727.
[95] Liu Y, Tang Y-B, Chen J, et al. Meta-analysis of GSTT1 null genotype and preterm delivery risk. Int J Clin Exp Med. 2014;7(6):1537–1541.
[96] Berghella V, Saccone G. Fetal fibronectin testing for reducing the risk of preterm birth. Cochrane Database Syst Rev. 2019;7(7):CD006843. doi: 10.1002/14651858.CD006843.pub3.
[97] Chandiramani M, Di Renzo GC, Gottschalk E, et al. Fetal fibronectin as a predictor of spontaneous preterm birth: a European perspective. J Matern Fetal Neonatal Med. 2011;24(2):330–336. doi: 10.3109/14767058.2010.496879.
[98] Melchor JC, Khalil A, Wing D, et al. Prediction of preterm delivery in symptomatic women using PAMG-1, fetal fibronectin and phIGFBP-1 tests: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;52(4):442–451. doi: 10.1002/uog.19119.
[99] Branch DW, VanBuren JM, Porter TF, et al. Prediction and prevention of preterm birth: a prospective, randomized intervention trial. Am J Perinatol. 2023;40(10):1071–1080. doi: 10.1055/s-0041-1732339.
[100] Goldenberg RL, Goepfert AR, Ramsey PS. Biochemical markers for the prediction of preterm birth. Am J Obstet Gynecol. 2005;192(5 Suppl):S36–S46. doi: 10.1016/j.ajog.2005.02.015.
[101] Li J, Ge J, Ran N, et al. Finding the priority and cluster of inflammatory biomarkers for infectious preterm birth: a systematic review. J Inflamm (Lond). 2023;20(1):25. doi: 10.1186/s12950-023-00351-0.
[102] Tchirikov M, Schlabritz-Loutsevitch N, Maher J, et al. Mid-trimester preterm premature rupture of membranes (PPROM): etiology, diagnosis, classification, international recommendations of treatment options and outcome. J Perinat Med. 2018;46(5):465–488. doi: 10.1515/jpm-2017-0027.
[103] Care A, Nevitt SJ, Medley N, et al. Interventions to prevent spontaneous preterm birth in women with singleton pregnancy who are at high risk: systematic review and network meta-analysis. BMJ. 2022;376:e064547. doi: 10.1136/bmj-2021-064547.
[104] NICE. NICE guideline: preterm labour and birth. 2022 [2025 Feb 18]. Available from: https://www.nice.org.uk/guidance/ng25
[105] Berger R, Abele H, Bahlmann F, et al. Prevention and therapy of preterm birth. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry Number 015/025, February 2019) - Part 2 with recommendations on the tertiary prevention of preterm birth and the management of preterm premature rupture of membranes. Geburtshilfe Frauenheilkd. 2019;79(8):813–833. doi: 10.1055/a-0903-2735.

[106]North West Guideline. NHS guideline: preterm birth. 2023 [2025 Feb 18]. Available from: https://www.england.nhs.uk/north-west/wp-content/uploads/sites/48/2023/05/NW-Preterm-Birth-guideline-FINAL-V1-April-2023-1.pdf.
[107]Sentilhes L, Sénat M-V, Ancel P-Y, et al. Prevention of spontaneous preterm birth: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol. 2017;210:217–224. doi: 10.1016/j.ejogrb.2016.12.035.
[108]Shennan A, Suff N, Leigh Simpson J, et al. FIGO good practice recommendations on progestogens for prevention of preterm delivery. Int J Gynaecol Obstet. 2021;155(1):16–18. doi: 10.1002/ijgo.13852.
[109]Bouchet N, Joal A, Gayet-Ageron A, et al. Impact of the new guidelines on the management of premature rupture of membranes for the prevention of late preterm birth: an 11-year retrospective study. J Perinat Med. 2019;47(3):341–346. doi: 10.1515/jpm-2018-0324.
[110]Chappell LC, Cluver CA, Kingdom J, et al. Pre-eclampsia. Lancet. 2021;398(10297):341–354. doi: 10.1016/S0140-6736(20)32335-7.
[111]Boers KE, Vijgen SMC, Bijlenga D, et al. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). BMJ. 2010;341:c7087–c7087. doi: 10.1136/bmj.c7087.
[112]Guzman ER, Walters C, Ananth CV, et al. A comparison of sonographic cervical parameters in predicting spontaneous preterm birth in high-risk singleton gestations. Ultrasound Obstet Gynecol. 2001;18(3):204–210. doi: 10.1046/j.0960-7692.2001.00526.x.
[113]Heath VC, Southall TR, Souka AP, et al. Cervical length at 23 weeks of gestation: prediction of spontaneous preterm delivery. Ultrasound Obstet Gynecol. 1998;12(5):312–317. doi: 10.1046/j.1469-0705.1998.12050312.x.
[114]Duley L, Meher S, Hunter KE, et al. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev. 2019;2019(10):CD004659. doi: 10.1002/14651858.CD004659.pub3.
[115]Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med. 2017;377(7):613–622. doi: 10.1056/NEJMoa1704559.
[116]Tan MY, Wright D, Syngelaki A, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. Ultrasound Obstet Gynecol. 2018;51(6):743–750. doi: 10.1002/uog.19039.
[117]Hoffman MK, Goudar SS, Kodkany BS, et al. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. Lancet. 2020;395(10220):285–293. doi: 10.1016/S0140-6736(19)32973-3.
[118]Kupka E, Hesselman S, Hastie R, et al. Low-dose aspirin use in pregnancy and the risk of preterm birth: a Swedish register-based cohort study. Am J Obstet Gynecol. 2023;228(3):336 e1–336–e9. doi: 10.1016/j.ajog.2022.09.006.
[119]Rahmati M, Yon DK, Lee SW, et al. Effects of COVID-19 vaccination during pregnancy on SARS-CoV-2 infection and maternal and neonatal outcomes: A systematic review and meta-analysis. Rev Med Virol. 2023;33(3):e2434. doi: 10.1002/rmv.2434.
[120]Kalliala I, Eriksson T, Aro K, et al. Preterm birth rate after bivalent HPV vaccination: registry-based follow-up of a randomized clinical trial. Prev Med. 2021;146:106473. doi: 10.1016/j.ypmed.2021.106473.
[121]Hoffman MK, Clifton RG, Biggio JR, et al. Cervical pessary for prevention of preterm birth in individuals with a short cervix: the TOPS randomized clinical trial. JAMA. 2023;330(4):340–348. doi: 10.1001/jama.2023.10812.
[122]Dean SV, Mason E, Howson CP, et al. Born too soon: care before and between pregnancy to prevent preterm births: from evidence to action. Reprod Health. 2013;10 Suppl 1(Suppl 1):S3. doi: 10.1186/1742-4755-10-S1-S3.
[123]Benedetto C, Borella F, Divakar H, et al. FIGO preconception checklist: preconception care for mother and baby. Int J Gynaecol Obstet. 2024;165(1):1–8. doi: 10.1002/ijgo.15446.
[124]Goldstein RF, Abell SK, Ranasinha S, et al. Association of gestational weight gain with maternal and infant outcomes: a systematic review and meta-analysis. JAMA. 2017;317(21):2207–2225. doi: 10.1001/jama.2017.3635.
[125]Muktabhant B, et al. Diet or exercise, or both, for preventing excessive weight gain in pregnancy. Cochrane Database Syst Rev. 2015;2015(6):CD007145.
[126]Middleton P, Gomersall JC, Gould JF, et al. Omega-3 fatty acid addition during pregnancy. Cochrane Database Syst Rev. 2018;11(11):CD003402. doi: 10.1002/14651858.CD003402.pub3.
[127]Best KP, Gibson RA, Makrides M. ISSFAL statement number 7 - Omega-3 fatty acids during pregnancy to reduce preterm birth. Prostaglandins Leukot Essent Fatty Acids. 2022;186:102495. doi: 10.1016/j.plefa.2022.102495.
[128]Carlson SE, Gajewski BJ, Valentine CJ, et al. Higher dose docosahexaenoic acid supplementation during pregnancy and early preterm birth: A randomised, double-blind, adaptive-design superiority trial. EClinicalMedicine. 2021;36:100905. doi: 10.1016/j.eclinm.2021.100905.
[129]Makrides M, Best K, Yelland L, et al. A randomized trial of prenatal n-3 fatty acid supplementation and preterm delivery. N Engl J Med. 2019;381(11):1035–1045. doi: 10.1056/NEJMoa1816832.

[130] Benson AE, Shatzel JJ, Ryan KS, et al. The incidence, complications, and treatment of iron deficiency in pregnancy. Eur J Haematol. 2022;109(6):633–642. doi: 10.1111/ejh.13870.
[131] Keats EC, Haider BA, Tam E, et al. Multiple-micronutrient supplementation for women during pregnancy. Cochrane Database Syst Rev. 2019;3(3):CD004905. doi: 10.1002/14651858.CD004905.pub6.
[132] Schüpbach R, Wegmüller R, Berguerand C, et al. Micronutrient status and intake in omnivores, vegetarians and vegans in Switzerland. Eur J Nutr. 2017;56(1):283–293. doi: 10.1007/s00394-015-1079-7.
[133] Janssen LE, Gieskes AA, Kok M, et al. Stress-reducing interventions in pregnancy for the prevention of preterm birth: a systematic review and meta-analysis. J Psychosom Obstet Gynaecol. 2023;44(1):2281238. doi: 10.1080/0167482X.2023.2281238.
[134] Mainous AG, 3rd, Hueston WJ. The effect of smoking cessation during pregnancy on preterm delivery and low birthweight. J Fam Pract. 1994;38(3):262–266.
[135] Soneji S, Beltrán-Sánchez H. Association of maternal cigarette smoking and smoking cessation with preterm birth. JAMA Netw Open. 2019;2(4):e192514. doi: 10.1001/jamanetworkopen.2019.2514.
[136] Berger R, Abele H, Bahlmann F, et al. Prevention and therapy of preterm birth. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry Number 015/025, September 2022) - part 2 with recommendations on the tertiary prevention of preterm birth and on the management of preterm premature rupture of membranes. Geburtshilfe Frauenheilkd. 2023;83(5):569–601. doi: 10.1055/a-2044-0345.
[137] Gizzi C, Gagliardi L, Trevisanuto D, et al. Variation in delivery room management of preterm infants across Europe: a survey of the Union of European Neonatal and Perinatal Societies. Eur J Pediatr. 2023;182(9):4173–4183. doi: 10.1007/s00431-023-05107-9.
[138] Berghella V, Saccone G. Cervical assessment by ultrasound for preventing preterm delivery. Cochrane Database Syst Rev. 2019;9(9):CD007235. doi: 10.1002/14651858.CD007235.pub4.
[139] Hessami K, D'Alberti E, Mascio DD, et al. Universal cervical length screening and risk of spontaneous preterm birth: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2024;6(5S):101343. doi: 10.1016/j.ajogmf.2024.101343.
[140] Son M, Miller ES. Predicting preterm birth: cervical length and fetal fibronectin. Semin Perinatol. 2017;41(8):445–451. doi: 10.1053/j.semperi.2017.08.002.
[141] Sapiens Global L. The global library of women's medicine. London; Dumfries: Sapiens Global Library Limited; 2023.
[142] Adanir I, Ozyuncu O, Gokmen Karasu AF, et al. Amniotic fluid "sludge"; prevalence and clinical significance of it in asymptomatic patients at high risk for spontaneous preterm delivery. J Matern Fetal Neonatal Med. 2018;31(2):135–140. doi: 10.1080/14767058.2016.1277700.
[143] Bohiltea RE, et al. A debate about ultrasound and anatomic aspects of the cervix in spontaneous preterm birth. J Med Life. 2016;9(4):342–347.
[144] Meyer JA, Limaye M, Roman AS, et al. Assessing the multifaceted cervix: examining cervical gland area at cervical length screening to predict spontaneous preterm birth. Am J Obstet Gynecol MFM. 2024;6(7):101390. doi: 10.1016/j.ajogmf.2024.101390.
[145] Werter DE, Dehaene I, Gurney L, et al. Differences in clinical practice regarding screening and treatment of infections associated with spontaneous preterm birth: An international survey. Eur J Obstet Gynecol Reprod Biol. 2021;266:83–88. doi: 10.1016/j.ejogrb.2021.09.009.
[146] Bretelle F, Loubière S, Desbriere R, et al. Effectiveness and costs of molecular screening and treatment for bacterial vaginosis to prevent preterm birth: the AuTop randomized clinical trial. JAMA Pediatr. 2023;177(9):894–902. doi: 10.1001/jamapediatrics.2023.2250.
[147] Farr A, Kiss H, Hagmann M, et al. Routine use of an antenatal infection screen-and-treat program to prevent preterm birth: long-term experience at a tertiary referral center. Birth. 2015;42(2):173–180. doi: 10.1111/birt.12154.
[148] Jeffcoat M, Parry S, Sammel M, et al. Periodontal infection and preterm birth: successful periodontal therapy reduces the risk of preterm birth. BJOG. 2011;118(2):250–256. doi: 10.1111/j.1471-0528.2010.02713.x.
[149] Kiss H, Petricevic L, Husslein P. Prospective randomised controlled trial of an infection screening programme to reduce the rate of preterm delivery. BMJ. 2004;329(7462):371. doi: 10.1136/bmj.38169.519653.EB.
[150] Klebanoff MA, Schuit E, Lamont RF, et al. Antibiotic treatment of bacterial vaginosis to prevent preterm delivery: systematic review and individual participant data meta-analysis. Paediatr Perinat Epidemiol. 2023;37(3):239–251. doi: 10.1111/ppe.12947.
[151] Sazonova A, Källen K, Thurin-Kjellberg A, et al. Obstetric outcome after in vitro fertilization with single or double embryo transfer. Hum Reprod. 2011;26(2):442–450. doi: 10.1093/humrep/deq325.
[152] Sabale U, Reuschenbach M, Takyar J, et al. Epidemiological, economic and humanistic burden of cervical intraepithelial neoplasia in Europe: A systematic literature review. Eur J Obstet Gynecol Reprod Biol X. 2025;25:100360. doi: 10.1016/j.eurox.2024.100360.
[153] Eurostat. Tobacco consumption statistics. 2019 [cited 2025 Jun 3]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Tobacco_consumption_statistics#:~:text=Daily%20smokers%20of%20cigarettes,-Men%20were%20more&text=In%202019%2C%2018.4%20%25%20of%20people,Bulgaria%20(see%20Table%201).

[154] Our World in Data. Share of the population exposed to air pollution levels above WHO guidelines. 2017 [cited 2025 Jun 3]. Available from: https://ourworldindata.org/grapher/share-above-who-pollution-guidelines?time=latest.
[155] Waldenström U, Cnattingius S, Vixner L, et al. Advanced maternal age increases the risk of very preterm birth, irrespective of parity: a population-based register study. BJOG. 2017;124(8):1235–1244. doi: 10.1111/1471-0528.14368.
[156] Voigt M, Briese V, Carstensen M, et al. Age-specific preterm birth rates after exclusion of risk factors–an analysis of the german perinatal survey. Z Geburtshilfe Neonatol. 2010;214(4):161–166.
[157] Olié V, Moutengou E, Grave C, et al. Prevalence of hypertensive disorders during pregnancy in France (2010–2018): the Nationwide CONCEPTION Study. J Clin Hypertens. 2021;23(7):1344–1353. doi: 10.1111/jch.14254.
[158] Eurostat. Obesity rate by body mass index (BMI). 2022 [cited 2025 Jun 3]. Available from: https://ec.europa.eu/eurostat/databrowser/view/sdg_02_10/default/table?lang=en.
[159] Ferrari F, Melis B, Basile L, et al. Second trimester cervical length screening, in a low-risk European population. J Matern Fetal Neonatal Med. 2025;38(1):2436099.
[160] Lucaroni F, Morciano L, Rizzo G, et al. Biomarkers for predicting spontaneous preterm birth: an umbrella systematic review. J Matern Fetal Neonatal Med. 2018;31(6):726–734. doi: 10.1080/14767058.2017.1297404.
[161] Ehsanipoor RM, Swank ML, Jwa SC, et al. Placental alpha-microglobulin-1 in vaginal secretions of women with evidence of preterm labor. Am J Perinatol. 2016;33(2):208–213. doi: 10.1055/s-0035-1563710.