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The global epidemiology of preterm birth

Joshua P. Vogel [a, *], Saifon Chawanpaiboon [b], Ann-Beth Moller [a], Kanokwaroon Watananirun [b], Mercedes Bonet [a], Pisake Lumbiganon [c]

[a] *UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland*
[b] *Maternal Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
[c] *Department of Obstetrics & Gynaecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*

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A B S T R A C T

This article is a part of a series that focuses on the current state of evidence and practice related to preterm birth prevention. We provide an overview of current knowledge (and limitations) on the global epidemiology of preterm birth, particularly around how preterm birth is defined, measured, and classified, and what is known regarding its risk factors, causes, and outcomes. Despite the reported associations between preterm birth and a wide range of socio-demographic, medical, obstetric, fetal, and environmental factors, approximately two-thirds of preterm births occur without an evident risk factor. Efforts to standardize definitions and compare preterm birth rates internationally have yielded important insights into the epidemiology of preterm birth and how it could be prevented.

How is preterm birth defined?

The World Health Organization (WHO) defines preterm birth as births before 37 completed weeks of gestation or fewer than 259 days from the first date of a woman's last menstrual period (LMP) [1]. It

* Corresponding author.
E-mail address: vogeljo@who.int (J.P. Vogel).

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is a condition defined by the failure of a gestation to reach a certain length of time, rather than by the presence of specific signs or symptoms [2]. Depending on one's point of view, preterm birth may be considered as an adverse pregnancy outcome (where a fetus is unable to fulfill its *in utero* growth potential) or a preferred outcome (e.g., where a miscarriage or nonviable prematurity has been successfully avoided). Even in healthy women with low-risk pregnancies, a proportion of babies can be expected to be born preterm. For example, a WHO-led multicenter study assessed fetal growth through serial ultrasound examinations in 1387 well-nourished women with low-risk pregnancies and reported preterm birth rates ranging from 3.6% in Germany to 14.7% in Egypt [3]. In the multicountry fetal growth longitudinal study (INTERGROWTH) that involved 4321 healthy pregnancies, the preterm birth rate was 5% [4]. For the newborn, preterm birth is a risk factor that has an impact on health, welfare, and development in adult life.

Fetal development is a continuum; some normal variation in fetal growth between individuals is to be expected. A specific cut-off (such as <37 weeks) that classifies all women or babies into two, mutually exclusive groups is convenient for epidemiology and research; however, a group of preterm fetuses will inevitably contain some that are more developmentally advanced than others. In aggregate, the mortality and morbidity outcomes of infants who are born preterm are poorer than those of those who are born at term, with the worst outcomes seen in the shortest gestations [5,6]. The <37 week cut-off for preterm birth is somewhat arbitrary, as some adverse health outcomes for babies born at 37 and 38 weeks are significantly higher than for those born at 39 and 40 weeks [2,7]. This has led to the distinction between "early term" and "full term," which can be important when communicating with women about pregnancy duration and risk [8,9].

How is gestational age measured?

The method by which a pregnant woman's gestational age (GA) is determined is an important factor. In general, in pregnancy, the later the GA is estimated, the greater is the uncertainty [10]. Early pregnancy ultrasound is considered the gold standard for GA assessment. Other methods such as calculation from the date of LMP, symphysis–fundal height measurement, postnatal examination of the newborn, or use of birthweight as a GA surrogate are often used in settings without access to ultrasound or with low rates of early antenatal care (ANC) participation [11]. Many settings use a "best obstetric estimate" (OE) of GA, using a combination algorithm of ultrasound and LMP; however, the specifics of that algorithm can vary [12].

Different GA estimation methods have been shown to affect population-level preterm birth rates. Barradas et al. analyzed 165,148 singleton births in California and demonstrated that the prevalence of preterm birth was higher when early ultrasound was used (8.1%) than when the best OE was used (7.1%) [13]. Similarly, the USA national reporting of preterm birth for 2014 has moved away from the historical LMP-based approach, in favor of OE of gestation at birth. The 2015 preterm birth rate for the USA (based on OE-based data) was 9.62%, whereas the LMP-based data for the same year were 11.29% [14]. The impact of the GA assessment method on estimating preterm birth rates, as well as comparing rates between countries, is thus likely a significant confounder.

Another important variation is the definition of the lower GA threshold of viability. For the purposes of preterm birth reporting, the International Classification of Diseases (ICD-10) system does not state a lower limit for fetal viability, rather advises that "signs of life" should define a live birth (regardless of GA) [15]. For international comparisons of stillbirth rates, WHO employs a definition of late fetal deaths, defined as stillbirths of birthweight $\geq$ 1000 g, or if birthweight is unknown, stillbirths at $\geq$28 weeks of gestation [16]. In many (but certainly not all) lower resource settings, 28 weeks is a common threshold for fetal viability, whereas in higher resource settings, 23–24 weeks is often the norm.

How is preterm birth monitored and reported?

WHO and other United Nations (UN) agencies have developed standardized global indicators to optimize collection, reporting, and international comparisons of data on conditions and diseases. WHO uses the indicator "live births before 37 completed weeks (whether singleton or multiple) per 100 live births" for estimates of preterm birth [17,18]. In practice, countries often report preterm birth using different operational definitions—for example, preterm birth in singleton pregnancies only. Inclusion or exclusion of stillbirths from preterm birth reporting will also have a varying effect on preterm birth rates depending on the income level of that country [19].

Definitions and practices regarding fetal viability reflect available obstetric and newborn interventions, local clinical protocols, likelihood of survival, and socio-cultural norms and beliefs about pregnancy—all of which may vary between countries and settings. International differences in preterm birth rates between countries, settings, and over time may reflect variations in definitions, rather than "true" epidemiological differences. It is important to standardize measurement and reporting so that the effects of population and health system risk factors on preterm rates can be assessed consistently and comparably [20]. For example, a comparison of the prevalence of singleton births before 32 weeks (whether stillbirth or live birth) in routine data from 30 high-income countries concluded that exclusion of births at 22–23 weeks (as well as pregnancy terminations) was necessary to allow standardized international comparisons [21].

How is preterm birth classified?

Classification systems are developed through the systematic assembly, storage, and retrieval of basic information on a health event [22]. Multiple classification systems have been developed around preterm birth for different applications: to guide research on causes and determinants, to better identify at-risk populations, to implement and monitor prevention strategies, to facilitate preterm birth surveillance, and to allow standardized local and international data comparisons. It would be difficult (if not impossible) to design a preterm birth classification system suitable for all applications; however, some systems have been applied to different purposes beyond their original design.

Common preterm classification systems include the following: GA sub-groups (such as extremely preterm, very preterm, moderate preterm, and late preterm), mode of preterm birth (spontaneous versus provider initiated), etiology, or pathophysiological pathways [2]. Preterm birth may be spontaneous (due to spontaneous preterm labor and/or preterm prelabor rupture of membranes) or provider initiated (by cesarean or labor induction) [23]. Common indications for provider-initiated preterm birth include maternal (such as pre-eclampsia, eclampsia, placental abruption, and placenta previa) or fetal (such as intrauterine growth restriction or fetal distress) conditions [24].

Although the literature often quotes a relative proportion of 70% spontaneous preterm births and 30% provider-initiated preterm births [23], the contribution of provider-initiated preterm births varies between region and countries [25,26]. A recent detailed classification system by Villar et al. classified all preterm births (including stillbirths and terminations of pregnancies) based on phenotypes [27]. However, even with detailed classification systems, many preterm cases are difficult to classify—there are cases with no pre-existing pathological conditions, cases with multiple conditions, or cases where a condition is present but not causally linked to the occurrence of preterm birth.

The global burden of preterm birth

The first global and regional estimates of preterm birth were published in 2010 by Beck et al. (for the year 2005), followed by the global-, regional-, and national-level estimates in 2012 (for the year 2010) by Blencowe et al. [17,28] Beck et al. identified data from 92 countries and estimated the global prevalence at 9.6% (95% confidence interval [CI]: 9.1%–10.1%) for the year 2005 [28]. Blencowe et al. identified data from 99 countries and estimated the 2010 global prevalence at 11.1% (95% CI: 9.1%–13.4%). Although their estimation methods differed, the global prevalence estimates are similar. Blencowe et al also reported estimates of preterm birth rates at the national level, which ranged from approximately 5% in some European countries to 18% in some African countries. One clear message from both analyses is that low- and middle-income countries (LMICs) account for the majority of the world's preterm births—60% of preterm births occur in sub-Saharan African or South Asian countries [17].

Limitations in estimating the global burden of preterm birth

Estimates are helpful in understanding preterm birth epidemiology, developing and implementing health policies, raising awareness, and mobilizing resources. However, they are often developed in the absence of reliable, population-representative data, which can paradoxically obscure the need for additional investment to develop or improve data collection and monitoring systems, as well as data quality [29]. Even in countries with robust civil registration and vital statistics (CRVS) systems, GA assessment at birth and preterm birth are often neither prioritized nor routinely captured. Where they are reported, they may be subject to the quality issues (such as misclassification and incompleteness) known to affect other global maternal and newborn health indicators [30]. Misclassification of live births, stillbirths, and neonatal deaths has a direct impact on the calculation of the liveborn preterm rate [31].

The preterm birth data available to estimate the global burden is predominantly derived from national CRVS systems in higher income countries [17,28]. These data may not generalize to LMICs with different demographics, socio-cultural norms, levels of nutrition, patterns of disease, and lower availability of health workers and resources. In the absence of CRVS data, data from research studies or household-representative surveys in LMICs are used as data inputs for modeling (with acknowledgment of their limitations) [16,18,28]. Observational studies containing preterm birth data are often facility based (generally higher level facilities) and are generally not nationally or population representative (particularly in countries where institutional birth rates are low). Disadvantaged sub-populations (such as poor, rural-dwelling, or less educated women, who often give birth in community settings) may have higher rates of preterm birth owing to the higher prevalence of some risk factors, as well as less access to health facilities for childbirth (where GA can be estimated and recorded) [32]. Participation bias is plausible—women who agree to participate in studies may not be representative of the population they are recruited from [33]. Conversely, higher level health facilities may have larger numbers of women with medical and obstetric complications, thus leading to over-representation of preterm birth. Well-designed, population-representative cohort studies from low- and middle-income countries that define, measure, and report preterm birth in a standardized way are thus needed to address preterm birth data gaps in these settings.

Trends in preterm birth rates

In some (mostly higher income) countries, preterm birth rates appear to be increasing. Blencowe et al. reported that for 65 countries with reliable preterm birth data, 62 countries had experienced increases between 2000 and 2010 [17]. A few methodological considerations should be remembered. Preterm birth definitions may change over time—a reduction in the lower threshold of fetal viability (i.e., when management of extremely preterm births changes over time) will create an apparent increase in the preterm birth rate overall [17,34]. Similarly, concomitant reductions in stillbirth rates (in favor of live births) could lead to an apparent increase in the liveborn preterm birth rate [19]. Changes in the coverage and quality of birth data capture over time can also affect the preterm birth rate. Focusing on trends in the overall preterm birth rate may obscure other trends in subgroups. For example, an analysis of national data from 19 European countries (2004–2008) found that while preterm birth rates increased in most countries, half had either no change or a decrease in the singleton preterm birth rate [26]. The preterm birth rate changes in that analysis were instead driven by higher multiple birth rates, as well as a higher rates of preterm birth among multiples.

Why does preterm birth occur?

Although many socio-demographic, nutritional, medical, obstetric, and environmental factors have been shown to increase the risk of spontaneous preterm birth, its etiology remains imperfectly understood [23,35]. When considering the literature on preterm risk factors, it is worthwhile keeping some general limitations in mind.

Despite the plethora of reported risk factors, the majority of preterm births have no clear risk factor. An individual participant data (IPD) meta-analysis of 4.1 million singleton births in five high-income countries reported that approximately 65% of all preterm births exhibited none of 21 prespecified risk factors [36]. The magnitude of risk associations is often modest (less than twofold increase in risk), and the biological mechanisms and pathways are not always evident or known. Meta-analyses of observational studies are often unable to adjust for important confounders (such as participant characteristics, comorbidities, method of GA measurement, and definition of preterm birth indicator) and thus may be subject to bias. Meta-analyses do not always report results separately for singleton and twin pregnancies—however, the risk of preterm birth among multiples compared to singletons is ninefold greater [37]. Although it seems logical that preventing or treating risk factors would reduce preterm birth rates overall, this is not always the case—for example, systematic reviews of periodontal disease treatments and antibiotics for bacterial vaginosis in pregnancy have not shown an effect on preterm birth rates [38,39]. Interventions for preterm birth prevention are explored in more detail in other papers in this series.

Risk factors for preterm birth

A 2013 systematic review assessed the association between ethnic groups and preterm birth and reported an odds ratio (OR) of 2.0 (95% CI: 1.8–2.2) for black ethnicity; no significant associations were seen for Asian, Hispanic, or Caucasian women [40]. The risk of preterm birth appears higher in both adolescent pregnancies and advanced maternal age [41–43]. A meta-analysis of cohort studies found that nulliparous women below 18 years of age had the highest risk of preterm birth across all age/parity categories (OR: 1.52, 95% CI: 1.40–1.66) [44]. Low maternal education has also been associated with preterm birth, although this can be difficult to disentangle from low maternal age alone [45]. Preterm birth in a previous pregnancy is a strong risk factor for preterm birth in a subsequent pregnancy, as is maternal nulliparity [36,46]. Male newborns are also at greater risk [36].

A 2012 meta-analysis by Wendt et al. assessed 12 studies and reported increased odds of preterm birth at <6 months and <12 months inter-pregnancy interval [47]. Hypothesized mechanisms include maternal nutritional depletion, folate depletion, cervical insufficiency, and vertical infection transmission [48]. Short cervical length (measured by transvaginal ultrasonography) is associated with preterm birth—a length less than 25 mm is a commonly used cut-off; the shorter the cervical length, the greater is the risk [49,50]. Singletons and twins formed through in vitro fertilization (IVF) have independently higher risks of preterm birth than spontaneously conceived singleton and twin pregnancies [51,52].

Smoking in pregnancy increases the likelihood of preterm birth similar to the use of recreational and illicit drugs (such as heavy alcohol use, cannabis, and cocaine) [53–56]. During pregnancy, infectious conditions that have been linked to preterm birth include HIV, bacterial vaginosis, *Chlamydia trachomatis* infection, chorioamnionitis, urinary tract infections (particularly pyelonephritis), hepatitis C, malaria, and syphilis [57–64]. Other maternal conditions complicating pregnancy that are associated with preterm birth include pre-eclampsia, pregestational and gestational diabetes, cervical incompetence, periodontal disease, maternal anemia, obesity, short stature, and low maternal vitamin D [36,49,65–71]. Rarer conditions such as systemic lupus erythematosus, polycystic ovarian syndrome, epilepsy, bipolar disorder, and pregnancy-related depression, stress, and anxiety also increase the likelihood of preterm birth [72–76]. Although women with cervical intraepithelial neoplasia (CIN) have an increased risk of preterm birth, treatment of CIN may increase that risk, particularly if treatment occurs during pregnancy [77,78].

Placental, uterine, or fetal conditions such as placental abruption, placenta previa, polyhydramnios, uterine anomalies, leiomyoma, and fetal birth defects have also been associated with preterm birth [79–84]. There is a debate as to whether previous surgical uterine evacuation (such as for termination of pregnancy or management of spontaneous abortion) increases the risk of preterm birth or not—although systematic reviews have reported modest associations for prior surgical uterine evacuation, they were unable to adjust for all potential confounders [85,86].

Two meta-analyses have reported that outdoor air pollution (where the particulate matter has an aerodynamic diameter of 2.5 μm or greater) is associated with increased preterm birth [87,88]. Preterm birth has also been associated with socio-economic disadvantage and disruptive life events affecting a pregnant woman [89,90]. Intimate partner violence (IPV) during pregnancy is also associated with increased odds of low birth weight (LBW) (OR: 1.18, 95% CI: 1.05–1.31) and preterm birth (OR: 1.42, 95% CI: 1.21–1.63), but not intrauterine growth restriction (IUGR) [91].

The consequences of preterm birth

Since 1990, the under-five mortality rate has dropped dramatically, from 93 deaths per 1000 live births in 1990 to 41 deaths per 1000 live births in 2016 [92]. Neonatal mortality (death in the first 28 days of life) has also steadily reduced, although at a disproportionately slower rate than under-five mortality. Consequently, the determinants of neonatal mortality (including preterm birth) have become a greater contributor to the mortality rate in children below five years of age over time. The latest estimates suggest that complications of preterm birth were the leading cause of death in children below five years of age globally in 2016 and account for approximately 16% of all deaths in children below five years of age and 35% of deaths among newborns [92]. Under-recognition of the prevalence of preterm birth (particularly in countries where neonatal mortality is high) may bias these estimates.

Shorter term complications of prematurity include increased risks of neonatal respiratory conditions (such as respiratory distress syndrome and bronchopulmonary dysplasia), necrotizing enterocolitis, sepsis, neurological conditions (such as periventricular leukomalacia, seizures, intraventricular hemorrhage, cerebral palsy, and hypoxic ischemic encephalopathy), as well as feeding difficulties and visual and hearing problems [93–95]. Newborns born late preterm (34-<37 weeks) have significantly higher risks of adverse outcomes than term newborns [5,6]. Preterm birth has been linked to poorer neurodevelopmental outcomes, higher rates of hospital admissions, as well as behavioral, social-emotional, and learning difficulties in childhood [96–98]. It also leads to significant, long-term health systems costs as well as causes considerable psychological and financial hardship for the families of preterm newborns [99,100].

Implications for practice, policy, and research

It is clear that further discovery research is needed on the mechanisms of spontaneous preterm birth, so that it can be better predicted and prevented. Several methodological issues related to international comparisons of preterm birth (such as definitional differences in indicators and differences in measurement of GA) could be addressed through better, standardized reporting of preterm data, as well as efforts to collect and report reliable GA data from resource-limited settings. Ideally, preterm birth reports (particularly from CRVS systems) would clearly delineate numbers and rates of preterm births in singletons and multiples, how the preterm birth rate was calculated, live births and stillbirths, and GA subgroups. This should be linked to broader efforts to optimize the quality and completeness of perinatal data monitoring and reporting in health statistics infrastructure. This could also make CRVS data a more useful source for assessing the effect of interventions on preterm birth (such as the introduction of health policies or clinical guidelines).

Summary

Preterm birth remains an important public health priority worldwide. Evidence-based strategies to prevent prematurity from occurring, as well as mitigating its effects on preterm newborns, are needed, particularly in low-resource settings.

The quantity and quality of preterm birth data reported in most countries is inadequate, thus impeding accurate estimation at global, regional, and national levels; however, standardization of definitions, measurement, and reporting would allow international comparisons of available data.

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None.

Conflicts of interest

None.

Research agenda

- Discovery research on mechanisms of spontaneous preterm birth, so that it can be better predicted and prevented.
- Better tools for measuring gestational age and identifying preterm births.
- Developing preventive interventions that are safe, effective, and scalable in low-resource settings, where the majority of preterm-associated child mortality is occurring.

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References

[1] WHO. Recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. Acta Obstet Gynecol Scand 1977;56(3):247–53.
[2] Kramer MS, Papageorghiou A, Culhane J, Bhutta Z, Goldenberg RL, Gravett M, et al. Challenges in defining and classifying the preterm birth syndrome. Am J Obstet Gynecol 2012;206(2):108–12.
[3] Kiserud T, Piaggio G, Carroli G, Widmer M, Carvalho J, Neerup Jensen L, et al. The world health organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. PLoS Med 2017;14(1). e1002220.
[4] Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Cheikh Ismail L, Lambert A, et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet 2014;384(9946):869–79.
[5] Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008; 371(9608):261–9.
[6] Teune MJ, Bakhuizen S, Gyamfi Bannerman C, Opmeer BC, van Kaam AH, van Wassenaer AG, et al. A systematic review of severe morbidity in infants born late preterm. Am J Obstet Gynecol 2011;205(4). 374–e1–9.
[7] Zhang X, Kramer MS. Variations in mortality and morbidity by gestational age among infants born at term. J Pediatr 2009;154(3):358–62. 62.e1.
[8] ACOG Committee Opinion No 579. Definition of term pregnancy. Obstet Gynecol 2013;122(5):1139–40.
[9] Yang J, Baer RJ, Berghella V, Chambers C, Chung P, Coker T, et al. Recurrence of preterm birth and early term birth. Obstet Gynecol 2016;128(2):364–72.
[10] Lynch CD, Zhang J. The research implications of the selection of a gestational age estimation method. Paediatr Perinat Epidemiol 2007;21(Suppl. 2):86–96.
[11] Moller AB, Petzold M, Chou D, Say L. Early antenatal care visit: a systematic analysis of regional and global levels and trends of coverage from 1990 to 2013. Lancet Glob Health 2017;5(10):e977–83.
[12] Blondel B, Morin I, Platt RW, Kramer MS, Usher R, Bréart G. Algorithms for combining menstrual and ultrasound estimates of gestational age: consequences for rates of preterm and postterm birth. BJOG 2002;109(6):718–20.
[13] Barradas DT, Dietz PM, Pearl M, England LJ, Callaghan WM, Kharrazi M. Validation of obstetric estimate using early ultrasound: 2007 California birth certificates. Paediatr Perinat Epidemiol 2014;28(1):3–10.
[14] Hamilton B, Martin J, Osterman M. National vital statistics reports. Births: preliminary data for 2015. US Department o Health and Human Services; 2015.
[15] World Health Organization. ICD-10: international statistical classification of diseases and related health problems - instruction manual. Geneva, Switzerland: World Health Organization; 2004. p. 2 [Accessed 09.November.2009], http://www.who.int/classifications/icd/icdonlineversions/en/index.html.
[16] Blencowe H, Cousens S, Jassir FB, Say L, Chou D, Mathers C, et al. National, regional, and worldwide estimates of stillbirth rates in 2015, with trends from 2000: a systematic analysis. Lancet Glob Health 2016;4(2):e98–108.
[17] Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379(9832):2162–72.
[18] Vogel JP, Chawanpaiboon S, Watananirun K, Lumbiganon P, Petzold M, Moller AB, et al. Global, regional and national levels and trends of preterm birth rates for 1990 to 2014: protocol for development of World Health Organization estimates. Reprod Health 2016;13(1):76.
[19] Morisaki N, Ganchimeg T, Vogel JP, Zeitlin J, Cecatti JG, Souza JP, et al. Impact of stillbirths on international comparisons of preterm birth rates: a secondary analysis of the WHO multi-country survey of Maternal and Newborn Health. BJOG 2017; 124(9):1346–54.

[20] 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):133–42.
[21] Delnord M, Hindori-Mohangoo AD, Smith LK, Szamotulska K, Richards JL, Deb-Rinker P, et al. Variations in very preterm birth rates in 30 high-income countries: are valid international comparisons possible using routine data? BJOG 2017;124(5):785–94.
[22] Flenady V, Frøen JF, Pinar H, Torabi R, Saastad E, Guyon G, et al. An evaluation of classification systems for stillbirth. BMC Pregnancy Childbirth 2009;9:24.
[23] Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008;371(9606):75–84.
[24] Souza RT, Cecatti JG, Passini R, Tedesco RP, Lajos GJ, Nomura ML, et al. The burden of provider-initiated preterm birth and associated factors: evidence from the brazilian multicenter study on preterm birth (EMIP). PLoS One 2016;11(2). e0148244.
[25] Vogel JP, Lee AC, Souza JP. Maternal morbidity and preterm birth in 22 low- and middle-income countries: a secondary analysis of the WHO Global Survey dataset. BMC Pregnancy Childbirth 2014;14:56.
[26] Zeitlin J, Szamotulska K, Drewniak N, Mohangoo AD, Chalmers J, Sakkeus L, et al. Preterm birth time trends in Europe: a study of 19 countries. BJOG Int J Obstet Gynaecol 2013;120(11):1356–65.
[27] Villar J, Papageorghiou AT, Knight HE, Gravett MG, Iams J, Waller SA, et al. The preterm birth syndrome: a prototype phenotypic classification. Am J Obstet Gynecol 2012;206(2):119–23.
[28] Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ 2010;88(1):31–8.
[29] AbouZahr C, Boerma T, Hogan D. Global estimates of country health indicators: useful, unnecessary, inevitable? Glob Health Action 2017;10(Suppl. 1):1290370.
[30] WHO. UNFPA, World bank group and the United Nations population division. Trends in maternal mortality: 1990 to 2015. Geneva: World Health Organization; 2015.
[31] Liu L, Kalter HD, Chu Y, Kazmi N, Koffi AK, Amouzou A, et al. Understanding misclassification between neonatal deaths and stillbirths: empirical evidence from Malawi. PLoS One 2016;11(12). e0168743.
[32] World Health Organization. State of inequality: reproductive, maternal, newborn and child health. Geneva: World Health Organization; 2015.
[33] Kramer MS, Wilkins R, Goulet L, Séguin L, Lydon J, Kahn SR, et al. Investigating socio-economic disparities in preterm birth: evidence for selective study participation and selection bias. Paediatr Perinat Epidemiol 2009;23(4):301–9.
[34] Bonet M, Cuttini M, Piedvache A, Boyle EM, Jarreau PH, Kollée L, et al. Changes in management policies for extremely preterm births and neonatal outcomes from 2003 to 2012: two population-based studies in ten European regions. BJOG 2017;124(10):1595–604.
[35] Muglia LJ, Katz M. The enigma of spontaneous preterm birth. N Engl J Med 2010;362(6):529–35.
[36] Ferrero DM, Larson J, Jacobsson B, Di Renzo GC, Norman JE, Martin JN, 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.
[37] Heino A, Gissler M, Hindori-Mohangoo AD, Blondel B, Klungsøyr K, Verdenik I, et al. Variations in multiple birth rates and impact on perinatal outcomes in europe. PLoS One 2016;11(3). e0149252.
[38] Brocklehurst P, Gordon A, Heatley E, Milan SJ. Antibiotics for treating bacterial vaginosis in pregnancy. Cochrane Database Syst Rev 2013;(1). CD000262.
[39] Iheozor-Ejiofor Z, Middleton P, Esposito M, Glenny AM. Treating periodontal disease for preventing adverse birth outcomes in pregnant women. Cochrane Database Syst Rev 2017;6. CD005297.
[40] Schaaf JM, Liem SM, Mol BW, Abu-Hanna A, Ravelli AC. Ethnic and racial disparities in the risk of preterm birth: a systematic review and meta-analysis. Am J Perinatol 2013;30(6):433–50.
[41] Smith GC, Pell JP. Teenage pregnancy and risk of adverse perinatal outcomes associated with first and second births: population based retrospective cohort study. BMJ 2001;323(7311):476.
[42] Waldenström U, Aasheim V, Nilsen AB, Rasmussen S, Pettersson HJ, Schytt E, et al. Adverse pregnancy outcomes related to advanced maternal age compared with smoking and being overweight. Obstet Gynecol 2014;123(1):104–12.
[43] Carolan M. Maternal age ≥45 years and maternal and perinatal outcomes: a review of the evidence. Midwifery 2013;29(5):479–89.
[44] Kozuki N, Lee AC, Silveira MF, Sania A, Vogel JP, Adair L, et al. The associations of parity and maternal age with small-for-gestational-age, preterm, and neonatal and infant mortality: a meta-analysis. BMC Public Health 2013;13(Suppl. 3):S2.
[45] Ruiz M, Goldblatt P, Morrison J, Kukla L, Švancara J, Riitta-Järvelin M, et al. Mother's education and the risk of preterm and small for gestational age birth: a DRIVERS meta-analysis of 12 European cohorts. J Epidemiol Community Health 2015;69(9):826–33.
[46] Kazemier BM, Buijs PE, Mignini L, Limpens J, de Groot CJ, Mol BW, et al. Impact of obstetric history on the risk of spontaneous preterm birth in singleton and multiple pregnancies: a systematic review. BJOG 2014;121(10):1197–208. discussion 209.
[47] Wendt A, Gibbs CM, Peters S, Hogue CJ. Impact of increasing inter-pregnancy interval on maternal and infant health. Paediatr Perinat Epidemiol 2012;26(Suppl. 1):239–58.
[48] Conde-Agudelo A, Rosas-Bermudez A, Castaño F, Norton MH. Effects of birth spacing on maternal, perinatal, infant, and child health: a systematic review of causal mechanisms. Stud Fam Plann 2012;43(2):93–114.
[49] Committee on Practice Bulletins—Obstetrics TeACoOaG. Practice bulletin no. 130: prediction and prevention of preterm birth. Obstet Gynecol 2012;120(4):964–73.
[50] Barros-Silva J, Pedrosa AC, Matias A. Sonographic measurement of cervical length as a predictor of preterm delivery: a systematic review. J Perinat Med 2014;42(3):281–93.
[51] Qin JB, Sheng XQ, Wu D, Gao SY, You YP, Yang TB, et al. Worldwide prevalence of adverse pregnancy outcomes among singleton pregnancies after in vitro fertilization/intracytoplasmic sperm injection: a systematic review and meta-analysis. Arch Gynecol Obstet 2017;295(2):285–301.

[52] Qin JB, Sheng XQ, Wang H, Chen GC, Yang J, Yu H, et al. Worldwide prevalence of adverse pregnancy outcomes associated with in vitro fertilization/intracytoplasmic sperm injection among multiple births: a systematic review and meta-analysis based on cohort studies. Arch Gynecol Obstet 2017;295(3):577–97.
[53] Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. Nicotine Tob Res 2004;6(Suppl. 2):S125–40.
[54] Faber T, Kumar A, Mackenbach JP, Millett C, Basu S, Sheikh A, et al. Effect of tobacco control policies on perinatal and child health: a systematic review and meta-analysis. Lancet Public Health 2017;2(9):e420–37.
[55] Forray A. Substance use during pregnancy. F1000Res 2016:5.
[56] Kesmodel U, Olsen SF, Secher NJ. Does alcohol increase the risk of preterm delivery? Epidemiology 2000;11(5):512–8.
[57] Haahr T, Ersbøll AS, Karlsen MA, Svare J, Sneider K, Hee L, et al. Treatment of bacterial vaginosis in pregnancy in order to reduce the risk of spontaneous preterm delivery - a clinical recommendation. Acta Obstet Gynecol Scand 2016;95(8): 850–60.
[58] Olson-Chen C, Balaram K, Hackney DN. Chlamydia trachomatis and adverse pregnancy outcomes: meta-analysis of patients with and without infection. Matern Child Health J 2018 Jun;22(6):812–21.
[59] Galinsky R, Polglase GR, Hooper SB, Black MJ, Moss TJ. The consequences of chorioamnionitis: preterm birth and effects on development. J Pregnancy 2013;2013:412831.
[60] Cunnington M, Kortsalioudaki C, Heath P. Genitourinary pathogens and preterm birth. Curr Opin Infect Dis 2013;26(3): 219–30.
[61] Xiao PL, Zhou YB, Chen Y, Yang MX, Song XX, Shi Y, et al. Association between maternal HIV infection and low birth weight and prematurity: a meta-analysis of cohort studies. BMC Pregnancy Childbirth 2015;15:246.
[62] Huang QT, Huang Q, Zhong M, Wei SS, Luo W, Li F, et al. Chronic hepatitis C virus infection is associated with increased risk of preterm birth: a meta-analysis of observational studies. J Viral Hepat 2015;22(12):1033–42.
[63] Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, et al. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis 2007;7(2):93–104.
[64] Qin J, Yang T, Xiao S, Tan H, Feng T, Fu H. Reported estimates of adverse pregnancy outcomes among women with and without syphilis: a systematic review and meta-analysis. PLoS One 2014;9(7):e102203.
[65] Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. Lancet 2016;387(10022): 999–1011.
[66] Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. Am J Clin Nutr 2016; 103(2):495–504.
[67] Corbella S, Taschieri S, Francetti L, De Siena F, Del Fabbro M. Periodontal disease as a risk factor for adverse pregnancy outcomes: a systematic review and meta-analysis of case-control studies. Odontology 2012;100(2):232–40.
[68] Marchi J, Berg M, Dencker A, Olander EK, Begley C. Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews. Obes Rev 2015;16(8):621–38.
[69] Kozuki N, Katz J, Lee AC, Vogel JP, Silveira MF, Sania A, et al. Short maternal stature increases risk of small-for-gestational-age and preterm births in low- and middle-income countries: individual participant data meta-analysis and population attributable fraction. J Nutr 2015;145(11):2542–50.
[70] Ray JG, Vermeulen MJ, Shapiro JL, Kenshole AB. Maternal and neonatal outcomes in pregestational and gestational diabetes mellitus, and the influence of maternal obesity and weight gain: the DEPOSIT study. Diabetes Endocr Pregnancy Outcome Study Tor QJM 2001;94(7):347–56.
[71] Wei SQ, Qi HP, Luo ZC, Fraser WD. Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2013;26(9):889–99.
[72] Wei S, Lai K, Yang Z, Zeng K. Systemic lupus erythematosus and risk of preterm birth: a systematic review and meta-analysis of observational studies. Lupus 2017;26(6):563–71.
[73] Kjerulff LE, Sanchez-Ramos L, Duffy D. Pregnancy outcomes in women with polycystic ovary syndrome: a metaanalysis. Am J Obstet Gynecol 2011;204(6). 558–e1–6.
[74] Viale L, Allotey J, Cheong-See F, Arroyo-Manzano D, Mccorry D, Bagary M, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. Lancet 2015;386(10006):1845–52.
[75] Bodén R, Lundgren M, Brandt L, Reutfors J, Andersen M, Kieler H. Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. BMJ 2012;345: e7085.
[76] Staneva A, Bogossian F, Pritchard M, Wittkowski A. The effects of maternal depression, anxiety, and perceived stress during pregnancy on preterm birth: a systematic review. Women Birth 2015;28(3):179–93.
[77] Kyrgiou M, Athanasiou A, Paraskevaidi M, Mitra A, Kalliala I, Martin-Hirsch P, et al. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. BMJ 2016;354:i3633.
[78] Danhof NA, Kamphuis EI, Limpens J, van Lonkhuijzen LR, Pajkrt E, Mol BW. The risk of preterm birth of treated versus untreated cervical intraepithelial neoplasia (CIN): a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2015;188:24–33.
[79] Ananth CV, Berkowitz GS, Savitz DA, Lapinski RH. Placental abruption and adverse perinatal outcomes. JAMA 1999; 282(17):1646–51.
[80] Crane JM, van den Hof MC, Dodds L, Armson BA, Liston R. Neonatal outcomes with placenta previa. Obstet Gynecol 1999; 93(4):541–4.
[81] Many A, Hill LM, Lazebnik N, Martin JG. The association between polyhydramnios and preterm delivery. Obstet Gynecol 1995;86(3):389–91.
[82] Fox NS, Roman AS, Stern EM, Gerber RS, Saltzman DH, Rebarber A. Type of congenital uterine anomaly and adverse pregnancy outcomes. J Matern Fetal Neonatal Med 2014;27(9):949–53.
[83] Chen YH, Lin HC, Chen SF. Increased risk of preterm births among women with uterine leiomyoma: a nationwide population-based study. Hum Reprod 2009;24(12):3049–56.

[84] Purisch SE, DeFranco EA, Muglia LJ, Odibo AO, Stamilio DM. Preterm birth in pregnancies complicated by major congenital malformations: a population-based study. Am J Obstet Gynecol 2008;199(3). :287–e1–8.
[85] Saccone G, Perriera L, Berghella V. Prior uterine evacuation of pregnancy as independent risk factor for preterm birth: a systematic review and metaanalysis. Am J Obstet Gynecol 2016;214(5):572–91.
[86] Lemmers M, Verschoor MA, Hooker AB, Opmeer BC, Limpens J, Huirne JA, et al. Dilatation and curettage increases the risk of subsequent preterm birth: a systematic review and meta-analysis. Hum Reprod 2016;31(1):34–45.
[87] Sapkota A, Chelikowsky A, Nachman K, Cohen A, Ritz B. Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. Air Qual Atmos Health 2012 December;5(4):369–81.
[88] Lamichhane DK, Leem JH, Lee JY, Kim HC. A meta-analysis of exposure to particulate matter and adverse birth outcomes. Environ Health Toxicol 2015;30. e2015011.
[89] Khashan AS, McNamee R, Abel KM, Mortensen PB, Kenny LC, Pedersen MG, et al. Rates of preterm birth following antenatal maternal exposure to severe life events: a population-based cohort study. Hum Reprod 2009;24(2):429–37.
[90] Vos AA, Posthumus AG, Bonsel GJ, Steegers EA, Denktaş S. Deprived neighborhoods and adverse perinatal outcome: a systematic review and meta-analysis. Acta Obstet Gynecol Scand 2014;93(8):727–40.
[91] Hill A, Pallitto C, McCleary-Sills J, Garcia-Moreno C. A systematic review and meta-analysis of intimate partner violence during pregnancy and selected birth outcomes. Int J Gynaecol Obstet 2016;133(3):269–76.
[92] Levels and trends in child mortality: report 2017, Estimates developed by the UN inter-agency group for child mortality estimation. New York: United Nations Children's Fund; 2017.
[93] Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet 2012;379(9814):445–52.
[94] Araujo BF, Zatti H, Madi JM, Coelho MB, Olmi FB, Canabarro CT. Analysis of neonatal morbidity and mortality in late-preterm newborn infants. J Pediatr (Rio J) 2012;88(3):259–66.
[95] Platt MJ. Outcomes in preterm infants. Public Health 2014;128(5):399–403.
[96] Orchinik LJ, Taylor HG, Espy KA, Minich N, Klein N, Sheffield T, et al. Cognitive outcomes for extremely preterm/extremely low birth weight children in kindergarten. J Int Neuropsychol Soc 2011;17(6):1067–79.
[97] Moreira RS, Magalhães LC, Alves CR. Effect of preterm birth on motor development, behavior, and school performance of school-age children: a systematic review. J Pediatr (Rio J) 2014;90(2):119–34.
[98] Johnson S, Evans TA, Draper ES, Field DJ, Manktelow BN, Marlow N, et al. Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study. Arch Dis Child Fetal Neonatal Ed 2015;100(4):F301–8.
[99] Singer LT, Salvator A, Guo S, Collin M, Lilien L, Baley J. Maternal psychological distress and parenting stress after the birth of a very low-birth-weight infant. JAMA 1999;281(9):799–805.
[100] Petrou S, Abangma G, Johnson S, Wolke D, Marlow N. Costs and health utilities associated with extremely preterm birth: evidence from the EPICure study. Value Health 2009;12(8):1124–34.