Seminars in Fetal and Neonatal Medicine 24 (2019) 3–10

Contents lists available at ScienceDirect

Seminars in Fetal and Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Epidemiology of late preterm and early term births – An international perspective

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ARTICLE INFO

Keywords:
Preterm birth
Late preterm birth
Early term birth
Risk factors
Neonatal mortality
Neonatal morbidity

ABSTRACT

Late preterm (34–36 weeks of gestational age (GA)), and early term (37–38 weeks GA) birth rates among singleton live births vary from 3% to 6% and from 15% to 31%, respectively, across countries, although data from low- and middle-income countries are sparse. Countries with high preterm birth rates are more likely to have high early term birth rates; many risk factors are shared, including pregnancy complications (hypertension, diabetes), medical practices (provider-initiated delivery, assisted reproduction), maternal socio-demographic and lifestyle characteristics and environmental factors. Exceptions include nulliparity and inflammation which increase risks for preterm, but not early term birth. Birth before 39 weeks GA is associated with adverse child health outcomes across a wide range of settings. International rate variations suggest that reductions in early delivery are achievable; implementation of best practice guidelines for obstetrical interventions and public health policies targeting population risk factors could contribute to prevention of both late preterm and early term births.

1. Introduction

The typical length of pregnancy is between 39 and 41 completed weeks of gestation, but annually 15 million children are born preterm, defined as delivery before 37 weeks [1]. Risks of adverse outcome for preterm infants rise sharply with decreasing gestation, which has led to a focus in research and policy on the 1–2% of the most vulnerable infants born before 32 weeks of gestational age (GA) [2]. Infants born late preterm, between 34 and 36 weeks of GA, have lower risks of infant mortality and morbidity, but their health problems constitute a substantial part of the overall preterm disease burden because of their larger number [3]. Accumulating evidence reveals that infants born early term, at 37 and 38 weeks of GA, also have higher neonatal morbidity, with more frequent neonatal intensive care admissions and respiratory complications at birth than infants born full term at 39–41 weeks [4]. These risks at birth have an influence across the life course and recent studies have documented longer-term morbidities associated with both late preterm and early term birth, including respiratory, infectious, neurocognitive and emotional problems in childhood and adulthood [5–7].

International health comparisons provide benchmarks for public health policy and interventions. There have been cross-country studies on the epidemiology of preterm birth, but few relate specifically to late preterm and early term birth. We therefore aimed to provide an epidemiological overview of late preterm and early term births, and to elucidate outstanding research questions from an international perspective. We used information from the recent scientific literature, national health reports, the European perinatal health surveillance network Euro-Peristat, and other international initiatives. As other articles in this issue focus on morbidity and long-term outcomes after late preterm and early term birth, our focus is primarily on prevalence, risk factors, and neonatal and infant mortality.

2. Definitions, data availability and measurement

2.1. Definitions

Preterm birth is widely defined as birth before 37 completed weeks of gestation (or 259 days). This definition is recommended by the World Health Organisation (WHO) and is used in the International Classification of Diseases [8]. WHO further groups preterm births as follows: 22–27 weeks (extremely preterm), 28–31 weeks (very preterm), and 32–36 weeks (moderately preterm) [9]. However, the relevant gestational age thresholds for defining preterm birth subgroups have been a subject of debate.

Several expert groups have recommended using more refined

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https://doi.org/10.1016/j.siny.2018.09.001

phenotypic classifications for preterm birth, based on clinical presentation, associated medical complications, and risks associated with earlier delivery throughout each week of gestation [10,11]. These initiatives to re-evaluate the terminology used for preterm births reflect more comprehensive efforts to rethink classifications in light of the limited success of research on the causes and prevention of preterm birth [12] as well as concerns with increasing numbers of clinician-initiated deliveries (pre-labour cesarean and labor induction) before full term [3,13].

Initially the terminology of "near term" births emerged to characterize babies born between 34 and 36 weeks; however, this phrasing was replaced by "late preterm" which avoids minimizing the perception of risks for these births by implying that they are "nearly mature" [3,14]. Similarly, to reflect the continuity of risk across the GA spectrum, the terminology "early term" was recommended for births at 37 and 38 weeks of gestation [15].

A final question concerns inclusion of stillbirths. Most studies use rates computed on live births, as recommended in the WHO definition [9]. Including stillbirths has a small impact on preterm birth estimates and country rankings except in low-income countries with higher stillbirth rates [16], and for very preterm birth rates [17].

2.2. Data availability

In the absence of universal first trimester antenatal visits and ultrasounds for pregnancy dating, routinely collected gestational age is often not available or vulnerable to errors in maternal recall, as is the case today in most low- and many middle-income countries [1]. Traditionally, low birthweight < 2500 g was used to delineate infants at risk because of early birth or sub-optimal growth. However, as shown in Fig. 1 based on the Intergrowth 21st newborn birthweight standards [18], a majority of late preterm and most early term infants have birthweights > 2500 g.

Because of the difficulties determining gestational age, preterm birth – unlike low birthweight – is not included in international health databases. This is true even for those containing data from middle- and high-income countries, such as the Organisation for Economic Cooperation and Development's health database (http://stats.oecd.org/index.aspx?DataSetCode=HEALTH_STAT). Data on gestational age were recently added to the EU's statistical system (http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_fweight&lang=en), but fewer than half of countries provide this item. Nonetheless, most high-income and some middle-income countries routinely collect GA data for their own official statistics.

Various international initiatives have collated routine and research data to provide a global view of preterm birth [1]. WHO supported an initiative in 2012 to provide worldwide estimates from 1996 to 2010 and is currently working on more recent estimates for 2014 [1,19]. The WHO Multi-country study is another source for data on preterm births in low- and middle-income countries, although it has a facility-based, as opposed to population-based, design [20]. However, these initiatives have not focused on late preterm or early term births. In Europe, the Euro-Peristat project, which monitors 30 key maternal and newborn health indicators in 31 European countries, has produced several publications on preterm and early term births using routine data [17,21,22]. The PREBIC-Epidemiology working group, sponsored by the March of Dimes, also published international comparisons of late preterm and early term births in Europe, North America, and Asia–Oceania [21,23].

2.3. Measurement

Differences in the recording of births and deaths have been shown to affect perinatal mortality indicators [22,24], but these differences are less problematic for preterm birth rates [1,17,22]. In contrast, the method of determining GA may influence the preterm birth rate [25]. Pregnancy dating can be based on the timing of the last menstrual period (LMP), biometric measures from ultrasound, or a combination of LMP and ultrasound. Compared to reliably recalled LMP dates, ultrasound dating shifts pregnancies towards earlier gestational ages on average, leading to a higher preterm birth rate [25,26]. This is because LMP dating assumes a menstrual cycle length of 28 days, whereas the average cycle is slightly longer [27]. However, the use of ultrasound reduces large errors that have more influence at the extremes of the GA distribution; consequently, in data sources with a high prevalence of GA error, use of ultrasound will lower preterm birth rates.

In Europe, the best obstetric estimate (OE) is the standard for pregnancy dating, although information on how this estimate is derived is often not known [7,22]. The algorithms used to derive gestational age when LMP and scans are both available can affect the preterm birth rate, i.e. always using the ultrasound estimate or only using it when there is a discrepancy between the two measures of two, three or seven days [25]. In the USA, official preterm birth rates changed from using the LMP to the OE in 2014 and this led to a decrease in the rate. In 2013, for instance, the rate was 11.4% using LMP and 9.6% using the OE [28]. Other issues affecting comparability include differences in the

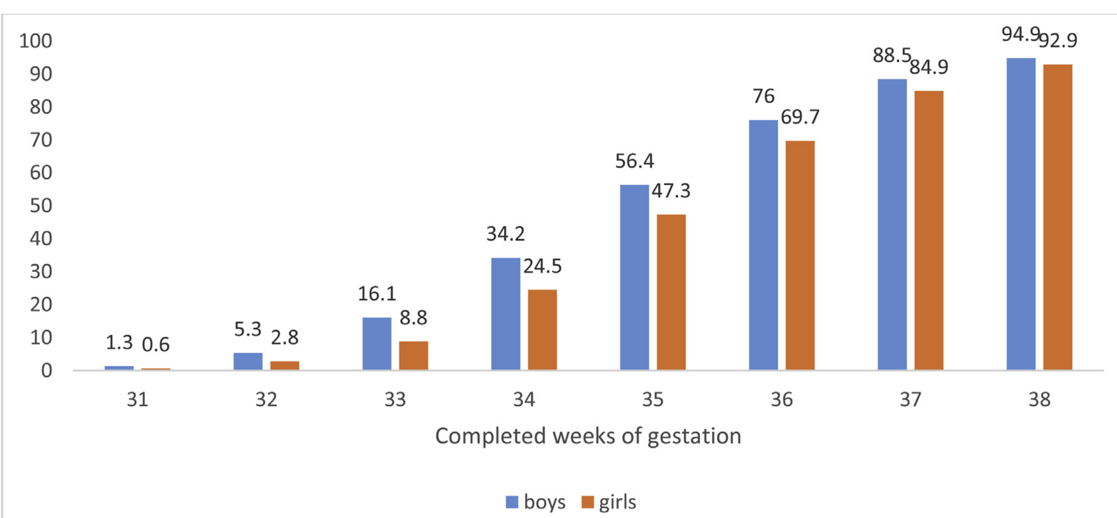

Fig. 1. Percentage of infants estimated to have birthweights of ≥2500 g by gestational age based on Intergrowth 21st newborn birthweight standards. References from the Intergrowth 21st newborn birthweight standards [18], gestational age set at exact weeks + 3 days.

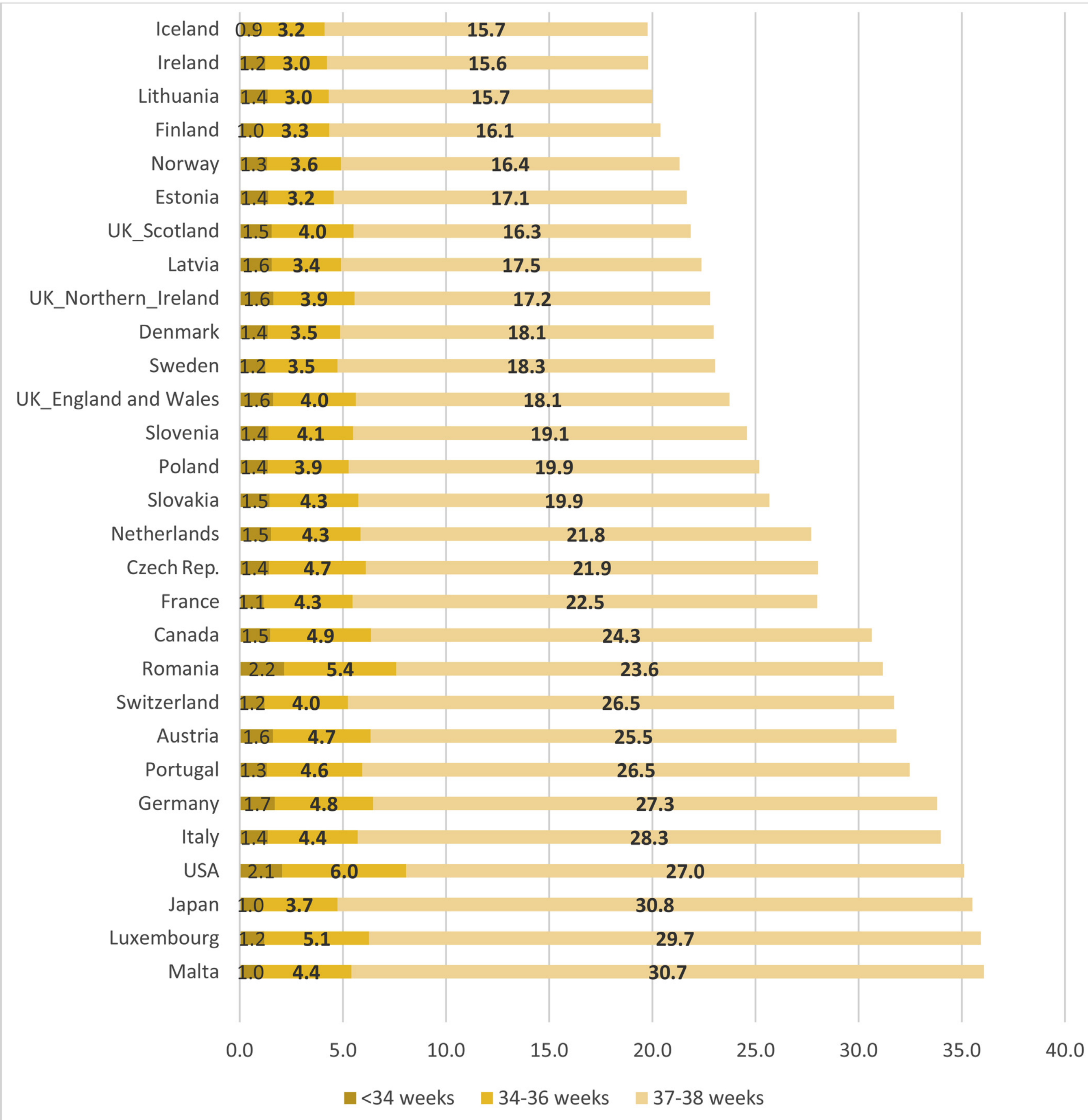

Fig. 2. Prevalence of live singleton preterm and early term births in European and other high-income countries in 2010. Source: Euro-Peristat and PREBIC Projects [21].

references used for ultrasound dating [29] and in access to perinatal care, which could lead to less accurate dates for socially disadvantaged women [30]. Our knowledge about the impact of misclassification errors on comparisons across countries and over time is limited and this is an area where further international studies are warranted.

3. Prevalence of late preterm and early term births

Among live singleton births, late preterm births range from 3.0% to 6.0% and constitute between 65% and 75% of preterm births in high-income countries; as shown using data from 2010 in Fig. 2. Early term births are around five times more common than late preterm births, with international ranges from 15% to 30% [21,23]. Analyses of data on singleton live births from 1996, 2000, 2004 and 2010 in these countries found that those with high preterm birth rates were more likely to have high early term birth rates and experience similar trends in both rates [21]. There were some exceptions, such as Japan, where the preterm birth rate was low, but early term birth rate was high. This study did not carry out analyses specifically for late preterm births, but this group is likely a strong driver of this relationship.

Most analyses are carried out on singleton births, but the population prevalence of late preterm and early term births is impacted by the multiple birth rate [31,32]. Using data from the countries in Figs. 2 and 3 shows that most multiples are born before full term, whereas around

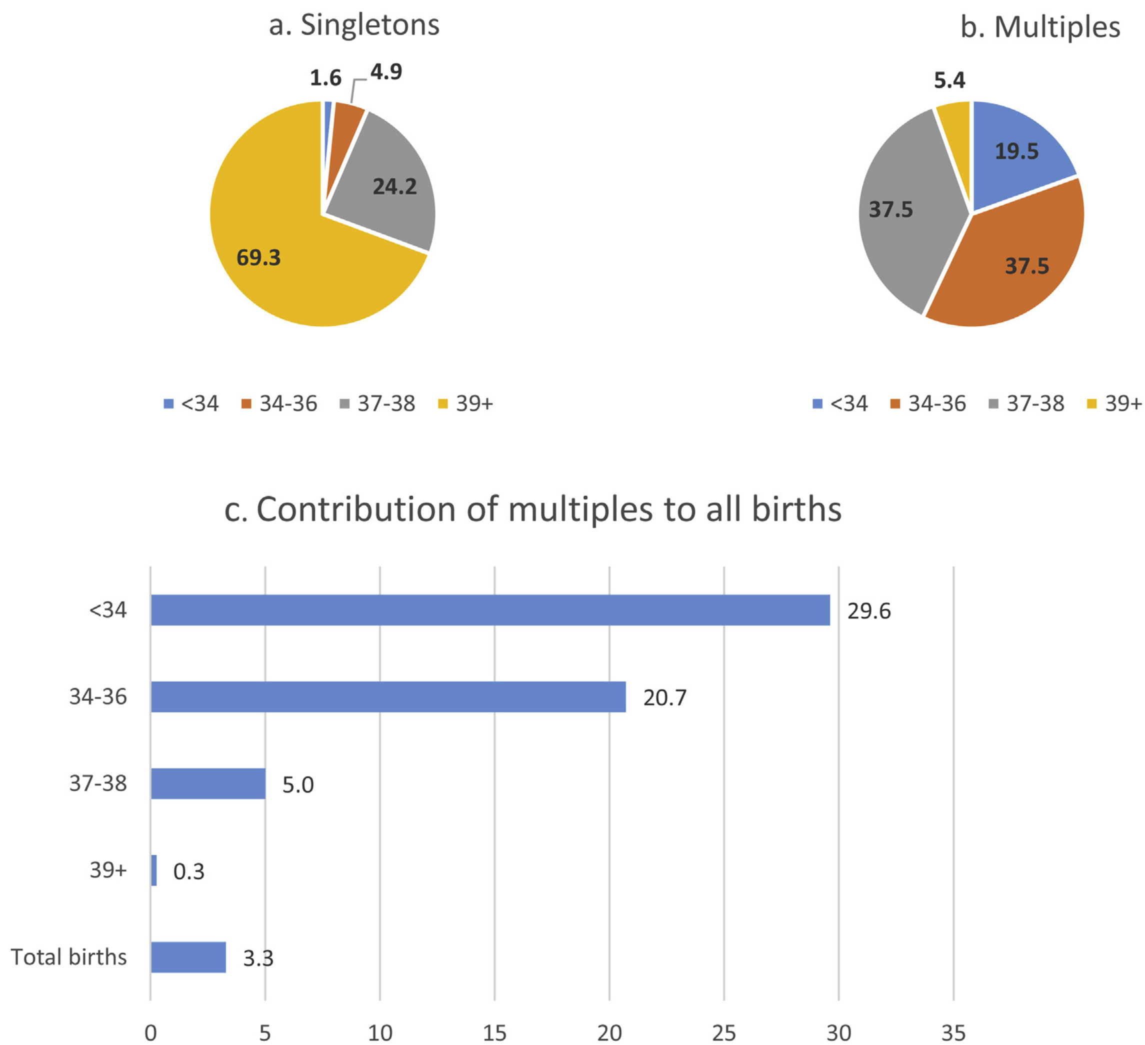

Fig. 3. Distribution of gestational age groups for (a) singleton births and (b) multiple births and (c) contribution of multiples to total number of births overall and by gestational age groups in European countries, North America, and Japan in 2010.

60% are born preterm [31]. Multiples are about 3% of all births, but constitute about 30% of births before 34 weeks, 20% of late preterm births, and 5% of early term births.

Data on the prevalence and trends of late preterm and early term births from developing countries are more difficult to obtain, but available data reveal a similar heterogeneity in preterm birth rates as found in high-income countries [1]. In 2010, an estimated 11.1% of live births worldwide were preterm with rates ranging from 5.0% in Europe to 18.0% in Africa, of which 84% infants were moderate and late preterm, and 60% born in South Asia and Sub-Saharan Africa [1]. Because rates for moderate and late preterm births were combined, we only have partial data on the specific burden of late preterm birth. Only sparse data exist from lower- and middle-income countries on early term birth rates; Brazil reports 35% [33] and China between 23% and 29% among singleton live births [34]. This lack of information on the burden of early term delivery in lower- and middle-income countries constitutes an important limit to our knowledge.

Whereas preterm birth rates have increased globally over the past decades [1], country-specific trends vary overall and by clinical subgroups [22]. In the USA, preterm birth rates increased from 11.2% to 12.8% between 1989 and 2004 [35]. The rise was largely accounted for by increases in late preterm births [6], as well as indicated deliveries [12,35]. Rates in the USA then began to decrease when indicated preterm deliveries declined by 17.2% (from 3.9% to 3.2%) between 2005 and 2012 [36] and overall late preterm singleton live births declined from 6.4% to 5.8% between 2007 and 2015 [37]. In Europe, many European countries maintained or reduced their rate of singleton preterm birth [22]. Rates of non-spontaneous preterm births ranged from 1.1% to 3.0% of all births for singletons in 2008, with differing time trends by mode of onset subtype [22]. Similarly, trends in early term births vary. For instance, between 2006 and 2014, rates decreased in Denmark (19.3% vs 18.1%), Sweden (from 19.5% to 18.5%), Norway (from 17.6% vs 16.8%), and the USA (from 31.2% to 24.4%) and were relatively stable in Canada (24.9% vs 25.3%) and Finland (17.0% vs 17.6%) [23]. By mode of onset, early term rates in high-income countries ranged between 9.8% and 16.6% for spontaneous and 4.3% and 15.5% for provider-initiated early term births [21].

4. Causes and risk factors

4.1. Etiology and pregnancy complications

Two-thirds of preterm births occur spontaneously following preterm labor or premature rupture of membranes [38]. Providers can also induce preterm delivery for fetal (i.e. fetal growth restriction), or maternal (i.e. severe pre-eclampsia) reasons. Several maternal pre-existing conditions as well as pregnancy complications are associated with early delivery and further exacerbate risks tied to low gestational age [4,39]. Clinical risk factors include: a previous preterm/early term birth, multiple pregnancy, infection, inflammation, hypertensive and vascular disorders, diabetes, a shortened cervix, and placentation disorders [38]. Advances in the discovery of genetic and epigenetic predispositions to preterm birth are in line with evidence on recurrence of preterm and early term birth and familial predispositions to early delivery [40]. Nonetheless, in up to about half of all spontaneous preterm births, the biological cause is unknown [41].

Studies have considered whether the etiology of early term birth is similar to preterm birth [39,42]. These suggest that there could be shared mechanisms, with some differences. In spontaneous deliveries, diabetes mellitus was a strong determinant of late preterm and early term birth (aOR > 2), as well polyhydramnios, oligohydramnios, placental ischemia, other hypoxia [39], and a previous preterm birth [39,43]. Infection and inflammation, on the other hand, were risk factors for spontaneous preterm but not early term birth [39]. In indicated deliveries, pre-eclampsia/eclampsia, hypertension, diabetes mellitus, small for gestational age, and placental abruption were strongly associated with preterm and early term deliveries, but not other maternal chronic conditions, including respiratory diseases, anemia, hormonal diseases, and gastrointestinal diseases which were associated with early term deliveries [42].

4.2. Population determinants: socio-demographic, lifestyle and environmental risk factors

Older and younger maternal age, a short inter-pregnancy interval, primiparity and grand multiparity, foreign origin, a low educational level and other measures of social disadvantage have consistently been found to increase risks of preterm birth [44]. Persistently higher rates of preterm birth are found in some migrant groups, such as women from Sub-Saharan Africa, who also have higher risks of maternal medical complications during pregnancy [45]. Racial/ethnic differences in preterm birth risk, with highest risks for non-Hispanic black women, have been widely documented in the USA [46]. These differences may reflect lasting socio-economic status disadvantage and discrimination [45]. The relationship between social disadvantage and preterm birth is observed across diverse contexts, including European countries with strong social welfare systems [47]. The most recent US findings relate national income inequality to preterm birth time trends [48]. Research on associations of sociodemographic risk factors with early term birth are lacking, but a French study found many similar determinants including short stature, a low level of education, and foreign origin (for other European and Sub-Saharan nationals), although the impact of risk factors was greater for preterm than for early term births [43]. Primiparity was a risk factor for preterm birth, but not early term birth [43], as also found by Brown et al. in Canada [39,42].

Associations between sociodemographic characteristics and early delivery may be explained by lifestyle and environmental determinants [49], including maternal body mass index [50], diet and micronutrient intake [51,52], physical activity [53], stress [54], employment conditions [55], active and passive smoking [49], and exposure to environmental pollutants [56]. Most of the research on the social and behavioral determinants of early delivery has focused on preterm birth; however, some studies find similar associations for early term births. For instance, in France, underweight mothers were at greater risk of preterm and early term spontaneous delivery, whereas obese mothers were at greater risk of indicated preterm and early delivery [43]. One study found that women with high anxiety were more likely to deliver late preterm as well as early term [57].

In relation to environmental exposures [56], smoking bans in public places have been shown to affect preterm birth rates [58,59] and this was true for both preterm and early term births in a Swiss study [60]. Poor air quality is associated with preterm birth across multiple settings [61]. Heavy metal pollutants widely found in airborne fine particulate matter, and in food and drinking water, also constitute a risk [62].

4.3. Medical practices and policies

Provider-initiated late preterm and early term deliveries reflect decisions about the balance of risks for the child and the mother related to continuing the pregnancy or inducing delivery. However, evidence on these risks is not straightforward and this results in variations in obstetric intervention across countries [63]. For instance, cesarean rates for singletons 32–36 weeks were between 27% and 52% and for early term between 19% and 47% in 18 high-income countries in 2008 [64]. In one study investigating clinician-initiated deliveries, the USA displayed the highest rates of intervention among late preterm and early births (44% and 42%, respectively); compared to Sweden (24.5% and 36.9%) [23]. In the USA decreases between 2006 and 2014 in provider-initiated deliveries were associated with decreases in late preterm and early term birth [23], but this was not observed in other Nordic countries [23]. In the secondary analysis of the WHO Multi-Country Survey on Maternal and Newborn Health, comprising 29 countries with varying health development index, hospitals with higher labor induction rates had higher risks of late preterm birth [20].

Medical policies and practices related to assisted reproductive technology (ART) affect the incidence of multiple pregnancies, which are more likely to be both preterm and early term [32]. ART is also associated with higher risks of preterm and early term birth, independently of maternal risk factors [65,66]. Kushnir et al. showed an increasing use of subfertility treatments in Australia/New Zealand, Japan, the USA, Canada, European countries, and Latin America between 2004 and 2013. Their study also documented high rates of preterm birth ranging between 9.0% and 16.6% for ART singletons, 53.9% and 67.3% for ART-twins, and 91.4% and 100% for ART triplets and higher-order multiples [66].

5. Infant outcomes associated with late preterm and early term births

Outcomes of late preterm births in comparison with term births have been well documented in the literature [67]. Infant mortality is about four times higher for late preterm births, and about 50% higher for early term births than for full-term births (at 39–41 weeks) as shown by a comparison of gestation-specific infant mortality rates in the USA between 2000 and 2013 (Fig. 4) [68]. Whereas this proportion shows declines over that 13-year span in the USA, a recent study revealed that neonatal mortality increased for singleton late preterm and early term births between 2007 and 2015 after adjustment for population characteristics [37]. The authors' interpretation is that declining preterm and early term birth rates, resulting from policies to stop non-medically indicated deliveries, is leading to higher-risk babies being born at these gestational ages. The contribution of late preterm and early term births to the overall burden of infant mortality is illustrated in Fig. 5 using data from the USA in 2013 and 23 European countries in 2010. Whereas most infant deaths occur at the earliest gestational ages before 34 weeks, about 22% of the total occur among late preterm or early term births in the USA, and 26% in Europe.

Neonatal morbidity rates are higher for late preterm than for term births due to increased risks of respiratory distress syndrome (increased several-fold when they are compared to infants delivered at 39 weeks), sleep apnea, necrotizing enterocolitis, and intraventricular hemorrhage [1,44,69]. Late preterm children not only have increased mortality and in-hospital morbidity, but also later in life, they are more likely to suffer from long term motor and cognitive impairments, chronic disease and premature death [7,70–72]. Early term birth is associated with increased need for hospital care during childhood; a Finnish study which investigated inpatient and outpatient hospital visits and associated healthcare costs, found that children born early term had an increased morbidity by three years of age compared to full-term children (8.6% vs 7.0% for the studied morbidities), mainly due to obstructive airway diseases and ophthalmological and motor problems with €766 more

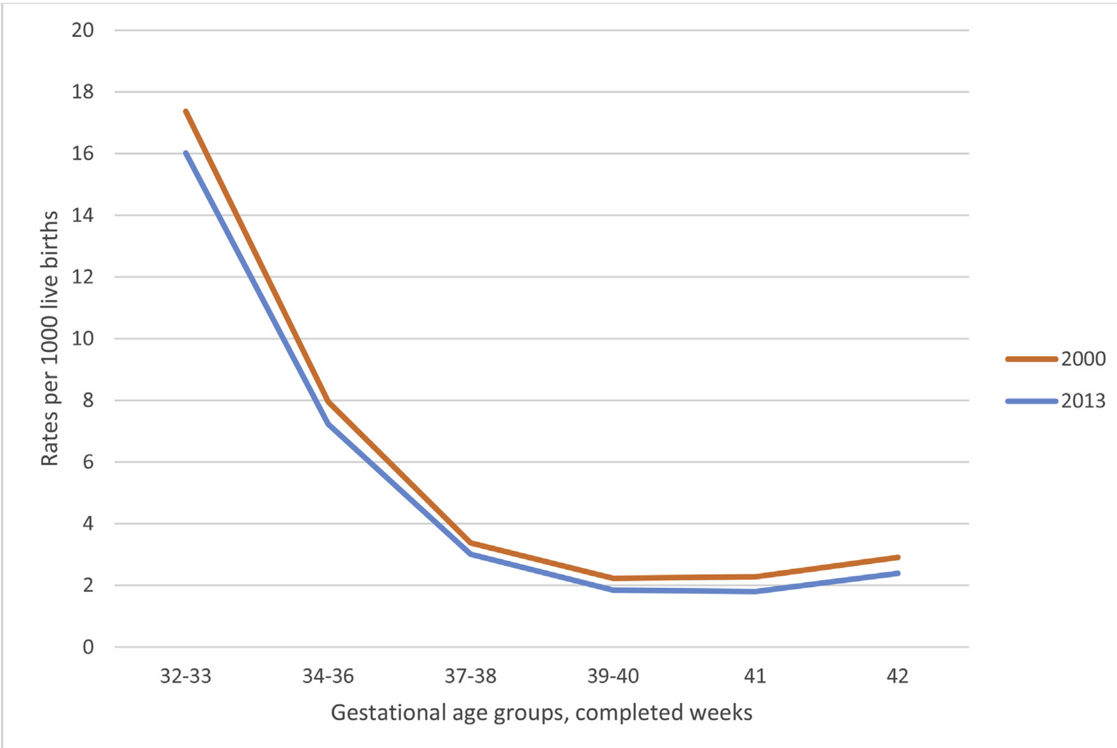

Fig. 4. Gestation-specific risks of infant death in the USA, 2000 and 2013. Data from Infant Mortality Statistics from the 2013 Period Linked Birth/Infant Death Data Set. From Centers for Disease Control and Prevention [68].

spent in healthcare-related costs [73]. In a Norwegian population-based study, girls born late preterm and early term showed an increased risk of emotional problems at 36 months of age, drawing attention to potential gender differences as well [74].

Whereas adverse outcomes associated with earlier delivery are documented across a wide range of countries, an outstanding question is whether the magnitude of the risk is affected by the prevalence of earlier delivery. The recent rises in neonatal mortality for late preterm and early term births in the USA suggest that differences in case-mix may need to be considered when comparing across countries or over time. This constitutes a promising area for further study.

6. Prevention from an international perspective

Variation across countries is striking – nearly two-fold – for countries with higher versus lower rates. When viewed in terms of risk difference, population health implications are more apparent: up to 3% of births for late preterm and 15% for early term births. As an example, applying the Finnish late preterm and early term birth rates to the US population would lead to ~575,000 fewer children before 39 weeks of gestation every year. The wide range of rates observed in countries with similar levels of development suggests that potentially modifiable population and healthcare factors may constitute possible levers for prevention [21].

Our review of the literature shows that differences in indicated early deliveries are likely to explain part of the cross-country variation and that changes in medical practices constitute one lever for lowering preterm and early term birth rates. In countries where there is a relatively high proportion of early term births (> 30%), such as the USA, Portugal and Brazil, there has been a recent push by professional societies to reduce the number of elective obstetric deliveries before 39 weeks [23,33,72], and in the USA financial incentives are used to limit these births based on Medicaid policy [75]. It would be of interest to evaluate management strategies by comparing decision-making and indications for provider-initiated deliveries across countries with high and low rates of early delivery. Further research should also aim to fill the gap in knowledge about early term deliveries in middle- and low-income countries, especially in countries where cesarean delivery rates are high.

Our review also urges reconsideration of the prevention of early delivery through public health policies focused on population risk factors. Existing interventions, targeting in many cases high-risk pregnancies, have shown limited potential for reducing overall preterm birth rates: an estimated 5% relative rate reduction in high-income countries [12]. However, observed differences between countries, as well as decreasing trends in some countries, raise the possibility that change is possible [21]. The existence of shared determinants for late preterm and early term delivery broadens the target population and potential impact of policy initiatives. Our review provides support for stronger public health policies to reduce smoking, including public smoking bans, promoting healthy diets and lifestyles, improving air quality, and focusing on the determinants of social health inequalities. By broadening the research paradigm to include the full spectrum of early deliveries (i.e. preterm and early term births), it may be possible to document the contribution of population risk factors which likely have small but potentially synergistic impacts. Further, targeting the shared population determinants of early delivery < 39 weeks could help steer a greater number of births toward lower levels of risk.

Having international data on the gestational age distribution makes it possible to quantify the global health burden associated with earlier delivery as well as to benchmark early delivery rates across countries and over time. Routine surveillance of international preterm and early term deliveries should be promoted by including gestational age in existing international health databases to inform perinatal health policies and investments in healthcare and research and to encourage efforts to reduce early delivery rates.

Acknowledgments

The authors acknowledge contributors to the European Perinatal

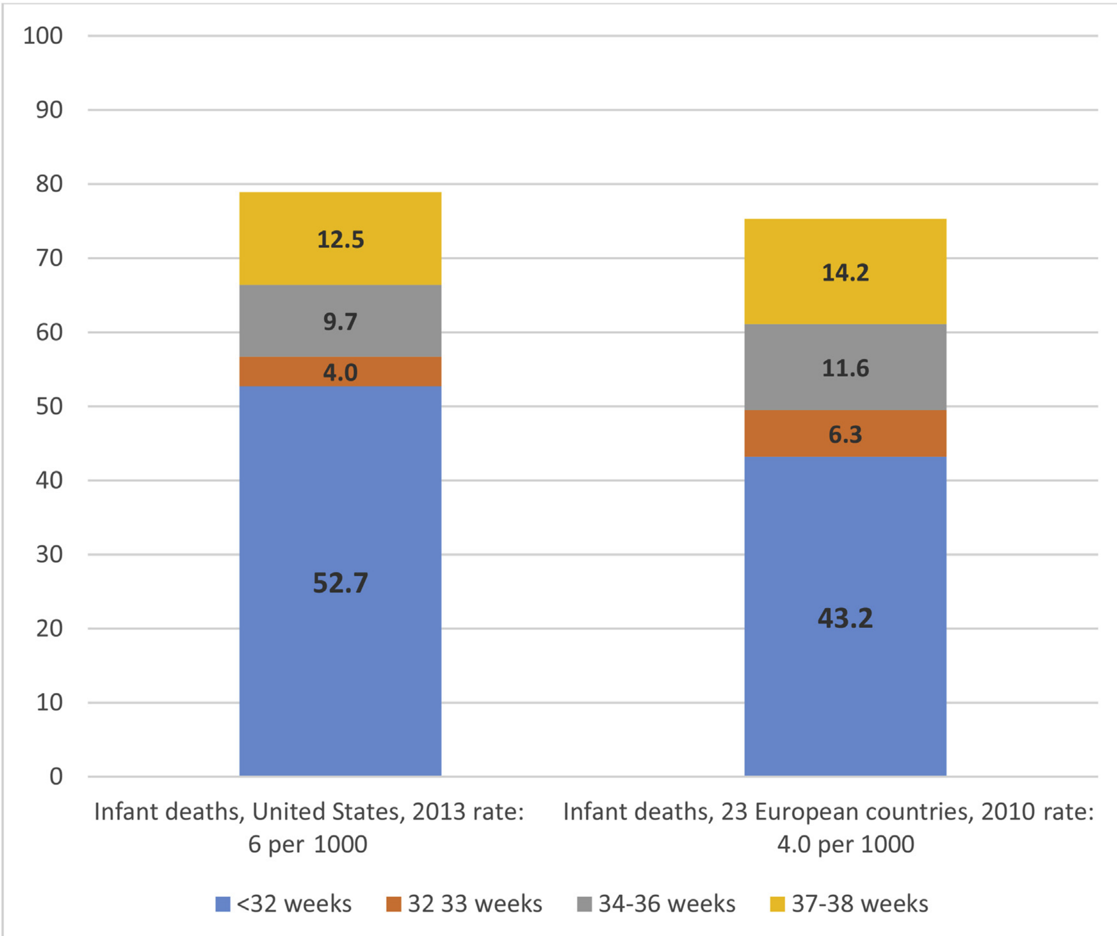

Fig. 5. Proportion of infant deaths delivered preterm and early term in the USA (2013) and in 23 European countries (2010). For Europe: combined data from Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Switzerland, UK. Data for the USA come from Infant Mortality Statistics from the 2013 Period Linked Birth/Infant Death Data Set. From Centers for Disease Control and Prevention [68].

Health Report: Health and Care of Pregnant Women and Babies in Europe in 2010 (see Supplementary Appendix Afor a full list of contributors).

The Euro-Peristat Scientific Committee: Gerald Haidinger (Austria), Sophie Alexander (Belgium), Pavlos Pavlou (Cyprus), Petr Velebil (Czech Republic), Laust Mortensen (Denmark), Luule Sakkeus (Estonia), Mika Gissler (Finland), Béatrice Blondel (France), Nicholas Lack (Germany), Aris Antsaklis (Greece), Istvan Berbik (Hungary), Helga Sol Olafsdottir (Iceland), Sheelagh Bonham (Ireland), Marina Cuttini (Italy), Janis Misins (Latvia), Jone Jaselioniene (Lithuania), Yolande Wagener (Luxembourg), Miriam Gatt (Malta), Jan Nijhuis (Netherlands), Kari Klungsøyr (Norway), Katarzyna Szamotulska (Poland), Henrique Barros (Portugal), Mihai Horga (Romania), Jan Cap (Slovakia), Natasa Tul Mandic (Slovenia), Francisco Bolumar (Spain), Karin Gottvall (Sweden), Sylvan Berrut (Switzerland), Alison Macfarlane (UK). Project coordination: Jennifer Zeitlin, Marie Delnord, Ashna D. Hindori-Mohangoo.

The authors also acknowledge the PREBIC Epidemiology Working group members: Jennifer L. Richards and Michael R. Kramer for contributing data from the USA, Michael S. Kramer from Canada, and Naho Morisaki from Japan.

Appendix A. Supplementary information

Supplementary information on acknowledgements for this article can be found online at https://doi.org/10.1016/j.siny.2018.09.001.

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