

**Section 1
Chapter**

Introduction

Epidemiology of preterm birth

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Introduction

In humans, pregnancy normally lasts nine months, ending with term birth after approximately 40 gestational weeks. Preterm birth is arbitrarily defined as delivery before 37 weeks, and could be further classified as moderately, very or extremely preterm, occurring at 32–36, 28–31, and ≤ 27 weeks, respectively.

Historically, there has been some confusion regarding the diverse concepts of “low birth weight” and “preterm birth.” In 1946, the American obstetrician Raymond D McBurney stated on a congress in San Francisco “... it is extremely annoying to have a pediatrician insist that the baby is premature because it may weigh only ... five pounds” [1]. McBurney correctly emphasized that birth weight is not only a function of gestational age, but also fetal growth.

In research, the definitions of low, very low and extremely low birth weight (birth weights of < 2500 g, < 1500 g, and < 1000 g, respectively) have been widely used as proxies for preterm birth. However, studies defining preterm infants solely on birth weight criteria are limited by some degree of misclassification, i.e. growth restricted infants with more advanced gestational ages are probably over-represented in such studies.

In outcome research including preterm children and adults, it is important to distinguish preterm birth from intrauterine growth retardation, since gestational age and fetal growth may have differential impacts on outcome. One example is the associations between perinatal risk factors and cardiovascular disease. Studies have shown that preterm birth as well as fetal growth restriction is associated with hypertension in adulthood. In adults born very preterm, decreasing gestational age is associated with an increasing risk of high blood pressure regardless of fetal growth. In contrast, intrauterine growth retardation is the principal perinatal risk factor for hypertension in adults born moderately preterm and term [2].

Few fields in medicine have gone through such a rapid and remarkable development as neonatal medicine. Mortality of preterm infants has decreased dramatically during recent decades, and it is now possible to save the lives of extremely immature infants, born just more than half way through a normal pregnancy. Nevertheless, mortality rates increase substantially with decreasing gestational age, and especially extremely preterm infants face a high mortality risk.

Similar to mortality, neonatal morbidity is inversely related to gestational age. The most immature infants commonly suffer from multiple and interacting medical conditions, such as respiratory problems, infections, and brain hemorrhages, which may lead to permanent impairments. Among the new and growing generation of survivors of preterm birth, cognitive and behavioral problems are not uncommon.

Already during childhood, preterm birth has public health implications, related to pediatric healthcare resources, family support, and school education. In addition, if problems emerging in school age persist into adulthood, the need for societal assistance may also be increased later in life.

Researchers in perinatal epidemiology and neonatal medicine face several challenges. Increased knowledge on risk factors and biological mechanisms is needed to develop efficient strategies to prevent preterm birth. Further refinement of neonatal care is necessary to improve short-term mortality and morbidity among preterm infants. Well-designed follow-up studies are essential to learn more about long-term outcomes, in particular for the growing number of children surviving very and extremely preterm birth in the current era of neonatal medicine.

Definitions of preterm birth

Gestational length to non-elective delivery in humans has been estimated as being 282–283 days [3].

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Preterm birth ≤ 36 weeks		Term birth 37–41 weeks	Post-term birth ≥ 42 weeks
extremely preterm ≤ 27 weeks			
	very preterm 28–31 weeks		
		moderately preterm 32–36 weeks	

Fig. 1.1 Categorization of gestational age by completed gestational weeks at birth.

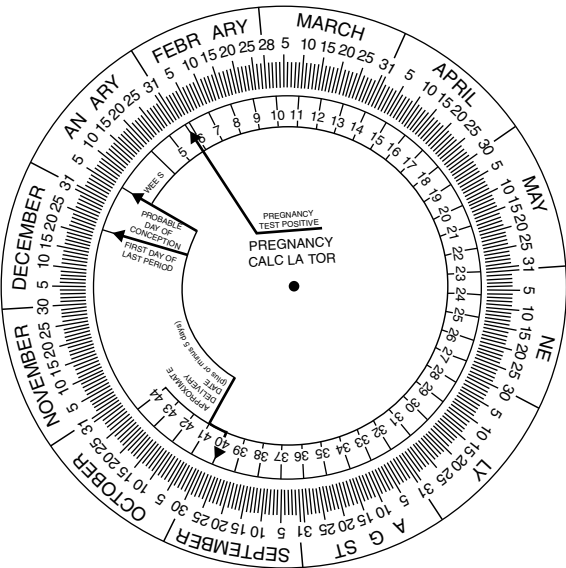


Fig. 1.2 The pregnancy wheel.

Gestational age of a newborn infant is categorized as preterm, term, or post-term (Fig. 1.1), as proposed by the World Health Organization in the 1970s [4]. Preterm birth occurs before 37 completed gestational weeks and could further be subdivided into moderately preterm, very preterm, and extremely preterm. As in this chapter, “very preterm birth” usually refers to all births at ≤ 31 weeks, including also extremely preterm births at ≤ 27 weeks.

To determine gestational age at birth, it is necessary to date the pregnancy and calculate the expected date of delivery (EDD) occurring at 40 completed gestational weeks. One commonly used method is to define EDD as 280 days from the last menstrual period (LMP), using the so-called pregnancy wheel (Fig. 1.2) [5].

The simplicity of this method makes it well suited for low-resource communities. Despite problems of recalling the correct date of LMP [6] the estimations

of gestational age are reasonably good [5,7] and can be used in perinatal epidemiology research when other dating methods are unavailable.

A more accurate way to date the pregnancy is to measure fetal size in early pregnancy, using ultrasound techniques [8]. Fetal growth velocity is constant during early pregnancy [9], and measures such as femoral length and head circumference are proportional to gestational length. Hence, such measures can be used to predict EDD and calculate gestational age in clinical practice [10]. Gestational age derived from LMP typically results in overestimates of about 2–3 days [7]. Importantly, changing the pregnancy dating method from LMP to ultrasound could have an impact on gestational age distribution, leading to an increase in preterm birth rate and a concomitant decrease in post-term birth rate [11]. Hence, rates of preterm birth may not be comparable if these are based on different methods of estimating gestational age.

Rates of preterm birth

Contrary to the general belief, preterm birth is a common pregnancy complication. Internationally, the variation of preterm birth rates is striking. About 6% of all pregnancies end preterm in Sweden (2003) [12], whereas the corresponding figure for the USA is reported to be almost 13% (2005) [13]. In developing countries, rates may be even higher. In a study including ultrasound-dated pregnancies in Malawi, 20% of women delivered preterm [14].

Very preterm births, occurring before 32 completed gestational weeks, account for about 15% of preterm births, which means that 1–2% of all pregnancies end very preterm [12,13].

Rates of preterm birth seem to be constant or even decreasing in the UK and Sweden [15,16], but several countries report increasing rates over recent decades [13,17,18]. This observation has been attributed to a number of factors, such as the introduction of ultrasound pregnancy dating, more frequent medically

Table 1.1 Risk factors for preterm birth

• Ethnicity
• Family history
• Infections
• Maternal characteristics
• Socioeconomic status
• Multiple pregnancies
• Smoking and substance abuse
• Air pollution

induced preterm deliveries, assisted reproduction, and more frequent twin births [17,18]. Increasing preterm birth rates seem to be explained by a greater number of moderately preterm births, since rates of very preterm birth have been stable over time [13,16].

Risk factors for preterm birth

Preterm birth has been associated with a number of risk factors (Table 1.1).

Ethnicity

Epidemiological studies have shown differences in rates of preterm birth among different ethnic groups [19]. In the USA during 2005, 19% of pregnancies ended preterm among black non-Hispanic women, whereas only 12% of white non-Hispanic women delivered preterm [13]. Corresponding rates for very preterm birth were 2.3% and 1.1%, respectively. In addition, black women do not only face an increased risk of preterm birth. Compared to white women, they are also at an increased risk of repeated preterm birth [19]. Although such findings may be explained by environmental or/and/ socioeconomic factors, they could also indicate that some ethnic groups have a genetic predisposition for preterm birth [20].

Family history

One preterm delivery increases the risk of preterm deliveries in subsequent pregnancies [21,22] and the risk of repeating a preterm delivery is especially high for very preterm birth [21]. The heritability of preeclampsia, a common cause of preterm delivery, has been estimated to approximate 31%, and genetic factors may account for one third of all preterm deliveries [23,24]. The mechanisms underlying such genetic influences remain to be determined, but case-control studies

support the idea that inflammatory responses may be influenced by genetic factors [25–27].

Infections

Bacterial vaginosis and intrauterine bacterial infections are well-established risk factors of preterm delivery [28]. Bacterial vaginosis may increase the risk of very preterm delivery more than two fold [29], and intrauterine infection is reported to be associated with even higher risks, especially for extremely preterm birth [30]. Infections localized to organ systems other than the reproductive tract may also be important. Periodontal infections have been reported to more than double the risk of very preterm birth [31].

The uterus and amniotic membranes can become infected in several ways. Bacteria can migrate to the uterus from the vagina or the abdominal cavity, be introduced during invasive procedures such as chorionic villi sampling [32], or through hematogenous spread [33]. If chorioamnionitis develops, the risk of very preterm delivery is increased, especially if an inflammatory response is also elicited in the fetus, when the risk of extremely preterm birth may increase ten fold [30].

A number of bacteria have been cultured from amniotic fluid and chorioamniotic membranes in preterm deliveries; vaginal organisms with low virulence, such as *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Gardnerella vaginalis*, and *Bacteroides* species, and several other bacteria such as *Escherichia coli*, *Enterococcus faecalis*, *Streptococcus* species, and *Chlamydia trachomatis* [28].

While much focus has been on bacteria, less is known about the role of viral infections. The only larger epidemiological study suggested that *Parvovirus B19* may be associated with an increased risk of late spontaneous abortion and stillbirth [34]. The prevalence of immunoglobulin M (IgM) seropositivity for *Parvovirus B19* among women with such pregnancy complications was 13% as compared with 1.5% in the remaining pregnant population [34]. Smaller clinical studies and case-series also report that viral infections may increase the risk of preterm delivery. Levels of antibodies against *Cytomegalovirus* were found to be higher in women with early onset preeclampsia and preterm delivery, compared to women with normal pregnancies ending at term [35]. *Cytomegalovirus* was also more commonly detected in dried neonatal blood

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spots, sampled after birth, in infants born preterm than in term infants (prevalence 33% versus 24%)[36].

Maternal characteristics

Several maternal characteristics have been associated with preterm birth. Firstly, as already described, preterm birth rates differ by ethnicity. Secondly, maternal age is reported to influence pregnancy outcome. Low and high maternal age increase the risk of preterm birth [37,38]. Moreover, maternal age has been shown to interact with parity, i.e., the risk of preterm birth being highest in younger multiparae and older primiparae [39]. Compared with 25- to 29-year-old primiparae, the risk of preterm birth is approximately doubled for multiparae aged less than 18 years and for primiparae aged more than 40 years. One may speculate that teenage mothers with several children are exposed to less favorable socioeconomic conditions [40]. Delayed childbearing at an older age is related to more prevalent assisted reproduction, higher risk of preeclampsia, and more frequent twin pregnancies [41].

Finally, reproductive history may be important. Previous induced abortions may increase the risk of very preterm births with spontaneous onset [42]. Women with a previous second trimester spontaneous abortion or a previous very preterm delivery are at increased risk of very preterm delivery in a subsequent pregnancy [19,21]. A short interval between subsequent pregnancies (< 6 months) has also been reported to be a risk factor, doubling the risk of extremely preterm delivery in subsequent pregnancies [43]. However, the association between a short interpregnancy interval and other adverse pregnancy outcomes including preterm birth may be confounded by socioeconomic factors [44] or adverse outcomes in previous pregnancies [45].

Socioeconomic status

There are marked socioeconomic inequalities in preterm birth rates. The differences in preterm birth rates between countries like Sweden, USA, and Malawi are probably partly explained by different socioeconomic contexts [12–14]. Within developed countries, socioeconomic status is also related to risk of preterm birth. A recent British study demonstrated that very preterm birth was twice as common among women living in the most deprived areas compared to women in the least deprived areas [46]. Similar conclusions were drawn in Norway, where maternal characteristics such as single motherhood and low education were associated

with a 25% and 50% increase in risk of preterm birth, respectively [47].

Multiple pregnancies

An American study reported that 54% of twins were born preterm [48]. In Europe, preterm birth rates in twin pregnancies vary from 42% in Ireland to 68% in Austria, amounting to 20% of all preterm births [49]. Twins resulting from subfertility treatment are more commonly born preterm compared to naturally conceived twins [50]. The majority of preterm births in singletons are due to spontaneous onset of labor, but induced deliveries account for about half of preterm births among twins [49].

In absolute terms, neonatal outcome of multiple pregnancies is generally worse than in singleton pregnancies [51]. However, besides intrauterine growth retardation, prematurity is the principal factor responsible for increased mortality and morbidity rates in twins and triplets. When gestational age is taken into account, risks of neonatal mortality and morbidity are not increased in multiple pregnancies compared to single pregnancies [52].

Smoking and substance abuse

Maternal smoking has a dose-dependent impact on risk of preterm birth [53]. Heavy smoking (≥ 10 cigarettes per day) may increase the risk of very preterm delivery more than two fold. Exposure to environmental tobacco smoke (passive smoking) has also been associated with an increased risk, yet lower than for active smoking [54]. The association between snuff (smokeless tobacco) and preterm birth is less well studied, but an investigation from Sweden found that snuff increased the risk of preterm birth by 79% [55]. A South African study concluded that snuff did not affect the rate of preterm birth, although women using snuff had slightly shorter gestational length in term births compared to women not using snuff [56].

Abuse of other drugs during pregnancy, including narcotics and alcohol, is associated with a number of poor perinatal outcomes, including preterm birth [57]. Prenatal drug exposure to tobacco and cocaine has been estimated to account for 5.7% of preterm births in American settings [58]. Excessive alcohol use is also reported to be more common among women who deliver preterm [59]. However, narcotics and alcohol may be part of a low socioeconomic lifestyle, and it is difficult to disentangle the independent roles

of substance abuse versus deprived socioeconomic circumstances.

Air pollution

Exposure to ambient air pollution, such as particulate matter, ozone, carbon monoxide, and nitric dioxide, has been reported in several studies to increase the risk of preterm birth in a dose-dependent manner [60,61]. However, there are also published studies which reported negative results [62]. Despite attempts to adjust for socioeconomic status in studies reporting positive findings [60,61], one cannot exclude that residual socioeconomic confounders may contribute to explain the association between air pollutants and preterm birth.

Etiologies and biological mechanisms

The variety of identified risk factors could be translated into different etiologies of preterm birth (Table 1.2). Firstly, one needs to consider two principally different etiological concepts; spontaneous preterm birth and medically induced preterm birth [63]. The majority of preterm births have spontaneous onset, initiated by premature labor, rupture of membranes, or vaginal bleeding [49]. The remaining preterm births are medically induced on maternal or fetal indications, typically due to preeclampsia. This heterogeneity of preterm births needs to be considered in research on etiological concepts and biological mechanisms [63]. Neonatal outcome may be more dependent on gestational age at birth than on the etiology of preterm birth [64], but risk factors may have differential impact on spontaneous and induced preterm birth, respectively [65]. Secondly, the various etiologies of preterm birth are related to several biological pathways (Table 1.3).

Genetic mechanisms

Ethnic differences [19], risk of repeated preterm delivery [21,22], and familial aggregation of preeclampsia and preterm birth [23,24] indicate that genetic mechanisms are important for preterm birth. One may speculate about genetic influences on several physiological processes leading to preterm delivery. Polymorphisms of genes involved in the immune system could be related to preterm delivery. One genotype of a promotor gene for interleukin (IL)-6, regulating responses to stressful stimuli, was found in 38% of mothers with very preterm deliveries, and in 29% of mothers

Table 1.2 Main etiologies of preterm birth

• Premature labor
• Preterm premature rupture of membranes
• Placental abruption and vaginal bleeding
• Preeclampsia and other maternal illnesses

Table 1.3 Biological pathways for preterm birth

• Genetic mechanisms
• Inflammation
• Vascular mechanisms
• Neuroendocrine stress responses
• Mechanical stress

with term deliveries [25]. Tandem repeat polymorphism of the gene for the IL-1 receptor antagonist, involved in duration and severity of inflammation, was found in 27% of women with preterm deliveries, compared to 12% of women with term deliveries [26]. Polymorphisms of immunoregulatory genes for IL-10 and mannose-binding protein 2 (MBL2) have also been more commonly found in women with preterm births and may increase the risk of chorioamnionitis [27], a pregnancy complication often preceding spontaneous preterm birth. A low intake of dietary vitamin C may increase the risk of preterm birth [66], and genetic variants of a membrane-bound vitamin C transporter may double the risk of spontaneous preterm delivery [67]. Polymorphisms in folate-metabolizing genes, affecting homocysteine levels, may also play a role for spontaneous preterm delivery, especially in black women with low folate intake [68].

Inflammation

The association between intrauterine infections and preterm birth involves biological pathways related to inflammation [28]. Bacterial colonization and release of toxins activates the production of cytokines, such as tumor necrosis factor α (TNF α) and IL-6. Cytokines stimulate prostaglandin production in the chorioamniotic membranes and placenta and lead to infiltration of neutrophilic white blood cells. Activation of metalloproteases leads to weakening of chorioamniotic membranes and cervical ripening. Prostaglandins also stimulate myometrial contractions. The inflammatory response culminates in preterm labor and rupture of the membranes. An inflammatory response in the fetus also contributes to preterm labor and rupture of membranes.

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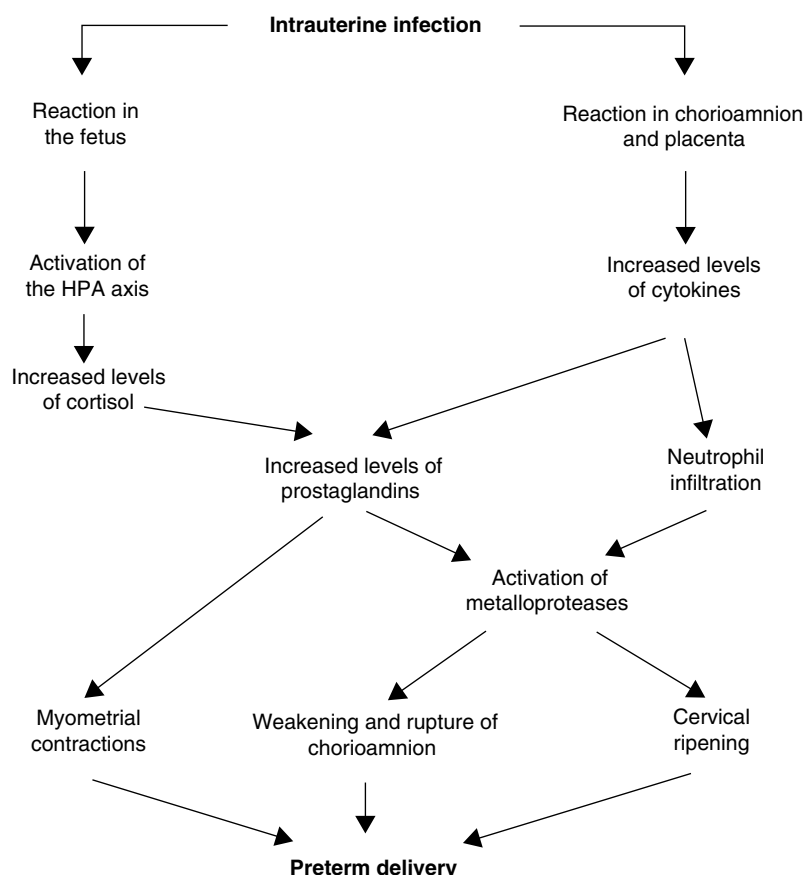


Fig. 1.3 Potential pathways from intrauterine infection to preterm delivery. Adapted from Goldenberg *et al.* [28].

Chorioamnionitis could result in fetal stress involving the hypothalamic–pituitary–adrenal axis (HPA axis). Fetal release of cortisol contributes to increased levels of prostaglandins.

A schematic view of inflammatory pathways leading to preterm delivery is shown in Fig. 1.3.

Vascular mechanisms

Preeclampsia and placental abruption are pregnancy complications often resulting in medically induced preterm delivery. Although principally different, both complications can be attributed to impaired placental vascular function.

Preeclampsia, affecting 3–5% of pregnant women, is a complex disorder initiating already during the critical process of implantation and placenta-tion shortly after conception [69,70]. Inadequate invasion of endovascular cells, placental production of anti-angiogenic factors, and development of endothelial dysfunction leads to small-bore, high-resistant placental vessels that cannot respond to the

increasing demand of blood supply and nutrition to the fetus. Clinical manifestations of preeclampsia, such as hypertension, renal dysfunction, and neurological symptoms, may necessitate preterm delivery on maternal indication. More commonly, delivery is induced on fetal indication, due to signs of fetal stress including abnormal umbilical blood flow and growth restriction.

Placental abruption, complicating 0.5–1% of pregnancies, is a too early separation of the placenta from the uterine wall, diagnosed by a combination of ultrasound findings and clinical signs, such as vaginal bleeding, abdominal pain, and fetal distress [71]. Clinical outcome depends on the degree of placental detachment, the degree of fetal distress, and gestational age at abruption, but the risk of perinatal mortality in very preterm deliveries following abruption is substantially increased [72].

Neuroendocrine stress responses

The association between low socioeconomic status and preterm delivery could be mediated by psychological

distress during pregnancy [73]. Maternal stress activates the HPA axis, illustrated by elevated cortisol levels in gestational week 15 in women who later delivered preterm [74]. Increased secretion of cortisol stimulates placental secretion of corticotropin-releasing hormone (CRH), interacting with prostaglandins and oxytocin, which mediate uterine contractions. Secretion of CRH is reported to be elevated in pregnant women who later deliver preterm [75] and it has been suggested that serum levels of CRH may be a useful marker in the clinical assessment of the risk of parturition in women presenting with preterm contractions [76].

Mechanical stress

Finally, mechanical stress of the uterus and cervix could be associated with preterm delivery. Cesarean section in a first pregnancy increases the risk of preterm birth in a second pregnancy [77]. Uterine overdistension is assumed to increase the risk of preterm delivery, exemplified by shorter gestations in twin pregnancies, especially in those with excessive amniotic fluid (polyhydramnios) [78]. Leiomyomata, benign neoplasms in the uterine wall, are associated with an increased risk of preterm delivery, supposedly due to increased mechanical strain on the uterus [79]. One proposed mechanism is that stretching of fetal membranes increases IL-8 concentrations and collagenase activity, implicated in cervical ripening [80]. Finally, incompetence of the cervix has been regarded to be casually related to preterm delivery, and cervical cerclage (tracheloplasty) has been widely used in attempts to prevent preterm birth. However, cervical cerclage is largely an unsuccessful strategy [81], which suggests that the cervix plays more than just a mechanical role [82].

Relations between risk and biology

There are probably complex relationships between risk factors of preterm birth and biological mechanisms. One risk factor may be important for several pathways and vice versa. In Fig. 1.4 we have made an attempt to summarize these relationships.

Prevention efforts

The ultimate goal of research on risk factors, etiologies, and biological mechanisms of preterm birth is to develop preventive strategies. Especially very preterm infants face substantial risks of mortality or long-term neurological sequels [83,84]. There are also economic implications. Neonatal intensive care is associated with significant costs, which increase exponentially with decreasing gestational age [85]. Preventing preterm deliveries would not only save lives, but also yield large cost savings.

The majority of preterm births have a spontaneous onset [49]. Given the association between preterm delivery and infections [28], antibiotic treatment could provide a potential strategy for prevention. However, large randomized controlled trials have drawn rather disappointing conclusions. Antibiotic treatment of women in preterm labor with intact membranes does not delay or prevent preterm delivery [86]. Similarly, treatment does not prevent preterm birth in pregnant women with bacterial vaginosis [87]. Antibiotic treatment of women with premature rupture of the membranes does not reduce the rate of preterm births, but can to some extent delay preterm delivery [88]. Still, it is possible that antibiotic treatment could be beneficial if offered to high-risk groups, as indicated by a large American study: in black urban women screened for reproductive tract infections, antibiotics reduced

Risk factor	Biological pathway				
	Genes	Inflammation	Vascular	Neuroendocrine	Mechanical
Ethnicity	+++	+		+	
Family history	++	+		+	
Infections	+	+++		+	
Low maternal age		+		+	
High maternal age		+	+	+	
Reproductive history	+	+	+		+
Socioeconomic status	+	+		++	
Multiple pregnancy			+	+	++
Smoking		+	++	+	
Air pollution		+		+	

Fig. 1.4 Relationships between risk factors and biological mechanisms of preterm birth.

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the risk of preterm delivery (relative risk = 0.16, 95% confidence interval [CI] = 0.04–0.66) [89].

Maternal periodontal disease is associated with an increased risk of preterm birth [31]. If bacterial load in the oral cavity contributes to chorioamnionitis, through hematogenous spread or due to increased systemic inflammatory activity, treatment of periodontal disease could be beneficial for pregnancy outcome. One small pilot study showed that treatment of periodontal disease during pregnancy reduced systemic inflammation, measured by levels of IL-6, and reduced the risk of preterm birth (odds ratio = 0.26, 95% CI = 0.08–0.85) [90]. However, in a larger study treatment of periodontitis had no effect on risk of preterm birth, despite improved periodontal health in treated women [91].

Prevention of preeclampsia, as a means to prevent preterm birth, has been extensively studied [92]. Many strategies have been tested, including lifestyle choices (rest or exercise), various nutritional measures, and drugs. However, almost all strategies have been unsuccessful, with the exception of moderate benefits of low-dose aspirin and calcium supplementation [93, 94]. Antioxidants seem to decrease the risk of preeclampsia, but results should be interpreted cautiously, especially since antioxidants may increase the risk of preterm birth [95]. Treatment of preeclamptic women with antihypertensive drugs is widely used, but there are limited data supporting that such treatment may reduce the risk of preterm delivery [96].

Smoking and substance abuse are potentially preventable factors associated with preterm birth. Women who stop smoking from their first to second pregnancy reduce their risk of preterm birth to that of non-smoking women [21]. A recent meta-analysis including randomized controlled trials concluded that smoking cessation during pregnancy was associated with a 16% reduction of risk of preterm delivery [97]. Studies on treatment of substance abuse with regard to infant outcomes are scarce, but two small studies have found that gestational length increases somewhat in women undergoing such treatment [98, 99].

Similarly, social disadvantage may be a target for intervention programs. However, a large randomized trial of psychosocial support and health education during high-risk pregnancies could not find that such interventions reduced the risk of preterm birth [100]. A recent meta-analysis of studies on social support during pregnancy came to the same conclusion [101].

Mortality during the neonatal period and during infancy

Infant mortality (death during the first year of life) has decreased during the last four decades for all infants, as demonstrated by national birth statistics from Sweden (Fig. 1.5, unpublished data from the Medical Birth Register). The reduction in infant mortality over time is mainly explained by decreased neonatal mortality (death during the first four weeks of life), although postneonatal mortality (death after the first four weeks of life but before one year of life) has declined somewhat.

The same pattern of improved survival during the neonatal period is seen among term, moderately preterm and very preterm infants, but in absolute numbers, the improvement is most dramatic for very preterm infants (≤ 31 weeks) (Fig. 1.6). From 1973 to 2002, neonatal mortality rates decreased from 401 to 90 per 1000 live-born very preterm infants, whereas the corresponding rates per 1000 live-born moderately preterm infants (32–36 weeks) and term infants (≥ 37 weeks) decreased from 34 to 8 and from 3 to 1, respectively. This improvement in survival among very preterm infants during the neonatal period has primarily been attributed to improvements of neonatal intensive care, including the introduction of antenatal corticosteroids and surfactant for prevention and treatment of respiratory distress syndrome [102].

Mortality in very preterm infants is inversely related to gestational age. Despite the overall reduction, the most immature infants still face a substantial risk of death, as illustrated by recently reported mortality rates from Sweden, and the Australia and New Zealand Neonatal Network (Fig. 1.7) [103, 104].

Another way to express the relation over time between mortality and gestational age is that the so-called “border-of-viability” has shifted to the left. Today, extremely small and immature infants could be considered as candidates for resuscitation and admission to neonatal intensive care units. However, as demonstrated by data from the Vermont Oxford Network,¹ mortality rates are exceptionally high among the tiniest infants [105]. Of infants born with a birth weight of 401–500 g (mean gestational age of 23 weeks), overall survival was only 17%.

¹ The Vermont Oxford Network is a worldwide network of neonatal intensive care units, which report their outcome data to a central database. Any neonatal intensive care unit can join the Vermont Oxford Network.

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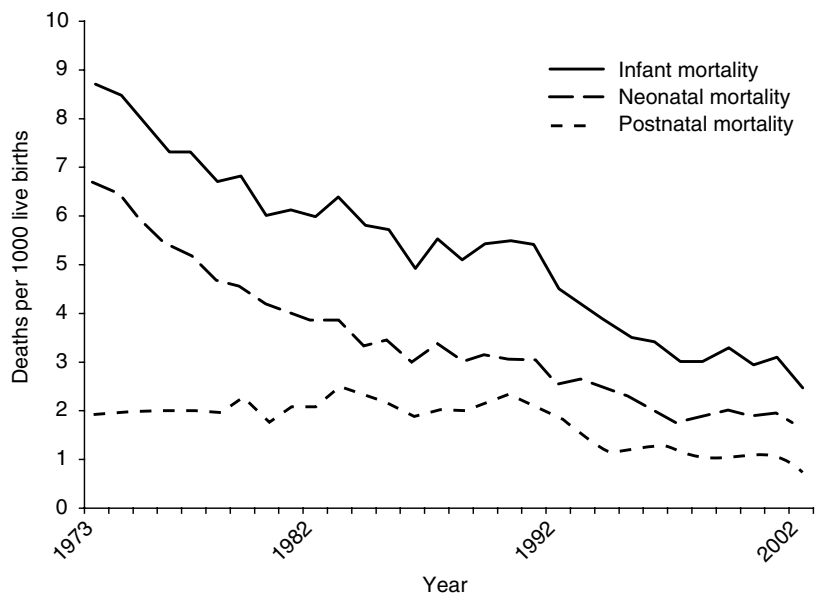


Fig. 1.5 Infant, neonatal, and postnatal mortality in infants born in Sweden 1973 to 2002.

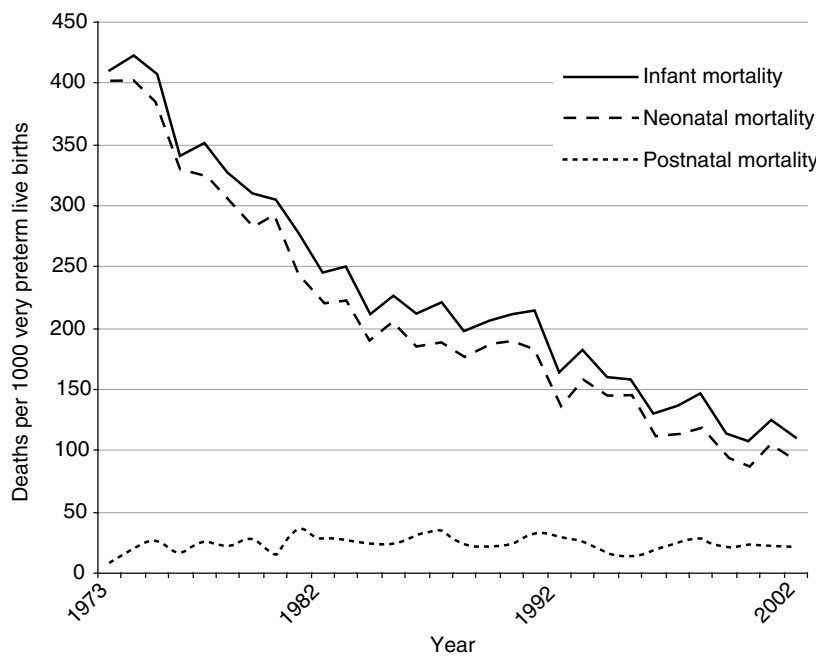


Fig. 1.6 Infant, neonatal and postnatal mortality in very preterm infants born in Sweden 1973 to 2002.

A large proportion of infants born at the “border-of-viability” die because of decisions taken shortly after delivery to limit intensive care and provide only palliative treatment [106]. Therefore, management policies could be important for survival in the most immature infants. Studies from Sweden and Germany support that proactive management promotes survival in infants born at 22–25 gestational weeks [107,108].

To improve survival, the regional and/or national organization of neonatal intensive care also needs to be considered. The complex nature of neonatal intensive care demands highly qualified staffing as well as access to advanced technologies. In several studies from different countries, level-III neonatal intensive care units, i.e. university hospitals, have had lower mortality rates when compared with smaller level-II units. However,

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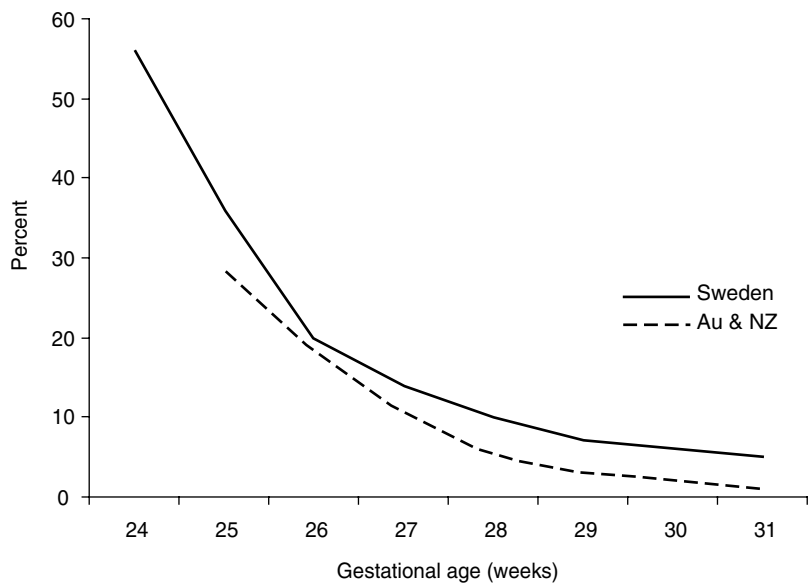


Fig. 1.7 Infant mortality rates in Sweden 1992–8, and mortality rates before discharge from neonatal intensive care in Australia and New Zealand 1998–2001, by gestational week.

the older studies have limitations. They categorized infants according to birth weight instead of gestational age [109,110], were performed before recent improvements of neonatal practice [111,112], or did not adjust for potential confounders such as obstetric complications [109,112]. Still, more recent studies also support that centralization of neonatal intensive care is associated with reduced mortality. A large American study, including 48 237 very low birth weight infants (<1500 g, 75% born at ≤ 31 weeks), found that both volume of care (number of admissions) and level of care were associated with risk of neonatal mortality [113]. According to a report from Finland, 69 of 170 annual deaths could be prevented if all very preterm infants (≤ 31 weeks) were born in university hospitals [114]. A British study investigating variations in standards of neonatal care showed that poor quality of ventilatory support, cardiovascular support, and thermal care increased the risk of mortality two- to threefold for infants born at 27 and 28 weeks [115]. In addition, poor quality of care was especially associated with deaths among infants in good condition at birth (see also Chapter 2).

Neonatal morbidity

Preterm infants face high morbidity risks during the neonatal period, although advances in neonatal care during recent decades have led to reduced rates of some conditions. For instance, the introduction of antenatal corticosteroids has almost halved risks of respiratory distress syndrome and brain hemorrhage [116]. However,

improvements in neonatal care and nursing are not only related to new treatments, but also due to implementation of refined strategies, such as improved nutrition, better infection control, and more gentle ventilatory support. Thus, neonatology has learnt to better deal with the medical problems related to preterm birth.

Similar to mortality, morbidity risks are inversely related to gestational age [107,117]. Compared to term infants, infants born close to term (34–36 weeks) are at risk of developing problems related to immaturity, such as feeding difficulties, temperature instability, infections and respiratory distress, occasionally even necessitating mechanical ventilation [118,119]. Nevertheless, moderately preterm infants are generally spared from complicated morbidity. In contrast, very and extremely preterm infants commonly suffer from multiple and interacting morbidities. Medical problems are especially prevalent among 23–25 week infants [105,107,108], since their extremely immature organs at birth ill-equip them to make the transition from intrauterine to extrauterine life.

A number of different medical conditions may affect preterm infants (Table 1.4) [120]. Although those conditions are separate clinical entities, they are also strongly correlated. For example, acute lung problems shortly after birth (RDS) are correlated with circulatory problems (PDA), brain hemorrhage (IVH) and later lung disease (BPD).

While some studies report relatively low or decreasing morbidity rates among survivors after extremely preterm birth (≤ 27 weeks) [121–123],