Svigerdatteren hans, hun som var gift med Pinha, var med barn og skulle snart føde. Da hun hørte meldingen om at Guds paktkiste var tatt, og at hennes svigerfar og hennes mann var døde, sank hun i kne og fødte, for da kom riene over henne

1. Samuelsbok 4:19

His daughter-in-law, the wife of Phinehas, was pregnant and near the time of delivery. When she heard the news that the ark of God had been captured and that her father-in-law and her husband were dead, she went into labor and gave birth, but was overcome by her labor pains.

1. Samuel 4:19

PUBLIC HEALTH ASPECTS OF PRETERM BIRTH
Studies using Scandinavian population-based data

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ABSTRACT

Morken Nils-Halvdan. 2008. **PUBLIC HEALTH ASPECTS OF PRETERM BIRTH Studies using Scandinavian population-based data**. Institute of Clinical Sciences, Department of Obstetrics and Gynecology at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

Background: Preterm birth is an unresolved serious global health problem, research on which must be multi-disciplinary, with assessment of risk factors and causative agents at many levels of observation, such as the public health level. The general aim of this thesis was to describe, assess and explore public health aspects of preterm birth.

Material and Methods: Scandinavian population-based data from the three Medical Birth Registers in Sweden, Denmark and Norway and the Swedish Hospital Discharge Register were used. Preterm birth in Sweden during the Birth Register era from 1973 to 2001 was studied and subgroups of preterm birth during 1991-2001 were assessed. The association between spontaneous preterm birth and fetal birth weight deviating from the population mean was explored. We propose the use of reference populations as a supplement in international comparison of baseline differences in preterm birth proportions and for time trend surveillance. The respective outcomes in spontaneous and iatrogenic preterm-born infants were examined and compared. Models for prediction of spontaneous preterm birth at <34 and <37 weeks were developed and validated in a test population by combining logistic regression and Bayesian methods.

Results: **(I)** The proportion of preterm birth (<37 weeks) in Sweden decreased from 6.3% in 1984 to 5.6% in 2001 (p<0.0001), a decrease evident among singleton births at 34-36 gestational weeks. The composition of preterm subgroups was similar to that found in populations with higher preterm birth proportions. **(II)** Associations between smaller than the population mean and spontaneous preterm birth were evident in all gestational age groups. The largest risk was found at 28-31 gestational weeks and birth weight <-3SD (OR: 13.3; 95% CI: 10.3-17.2). Spontaneous preterm infants born at 34-36 gestational weeks more often weighed 1-1.9 SD (OR: 1.1; 95% CI: 1.1-1.2) or 2-2.9 SD (OR: 1.6; 95% CI: 1.5-1.7) above the expected mean. **(III)** The national preterm delivery proportion (<37 weeks) increased from 5.3% to 6.1% (p<0.001) in Denmark and from 6.0% to 6.4% (p=0.006) in Norway, but remained unchanged in Sweden, during 1995-2004. In Denmark, the preterm delivery proportion in the reference population increased significantly (5.3% to 6.3%, p<0.001), as did the spontaneous preterm delivery proportion in the reference population (4.4% to 6.8%, p<0.001). No similar increase was evident in Norway. In Sweden, proportions in the reference population remained stable. **(IV)** Spontaneous preterm infants were at increased risk of cerebral palsy at gestational age 28-31 weeks (HR: 1.86; 95% CI: 1.12-3.10) and of sepsis at gestational age 32-33 weeks (HR: 1.58; 95% CI: 1.28-1.96). Other outcome variables were associated with iatrogenic preterm birth, particularly respiratory and gastrointestinal diagnoses. **(V)** Six prediction models were developed. The area under the receiver operator curve in the test population ranged from 0.77 (95% CI: 0.76-0.77) to 0.59 (95% CI: 0.57-0.61) for spontaneous preterm birth at <37 weeks and from 0.80 (95% CI: 0.79-0.81) to 0.64 (95% CI: 0.62-0.67) for spontaneous preterm birth at <34 weeks. For each delivery in the test population, the model that utilized the available information to the greatest extent was used, and total areas under the receiver operator curve for spontaneous preterm birth at <34 weeks (0.74, 95% CI: 0.73-0.75) and <37 weeks (0.71, 95% CI: 0.7-0.71) were calculated.

Conclusions: The proportion of preterm birth in Sweden has decreased since the mid-eighties. Deviation of fetal birth weight from the expected mean is associated with spontaneous preterm delivery. Reference populations may prove to be a valuable supplement in assessments of national preterm delivery proportions in connection with public health surveillance. Spontaneous preterm birth and iatrogenic preterm birth are associated with different pediatric outcomes. Spontaneous preterm birth can be predicted by using the proposed models, which might be applicable in clinical assessment of risk.

Key words: preterm birth; preterm delivery; subgroups; spontaneous preterm birth; iatrogenic preterm birth; birth weight; fetal growth; reference population; outcome; cerebral palsy; prediction

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Morken NH, Källén K, Hagberg H and Jacobsson B, Preterm birth in Sweden 1973-2001: rate, subgroups and effect of changing patterns in multiple births, maternal age and smoking. Acta Obstet Gynecol Scand 2005; 84: 558-65.

II. Morken NH, Källén K and Jacobsson B, Fetal growth and onset of delivery: a nationwide population-based study of preterm infants. Am J Obstet Gynecol 2006; 195: 154-61.

III. Morken NH, Vogel I, Källén K, Skjærven R, Langhoff –Roos J, Kesmodel U, Jacobsson B, Reference population for international comparisons and time trend surveillance of preterm delivery proportions in three countries. Manuscript.

IV. Morken NH, Källén K and Jacobsson B, Outcomes of preterm children according to type of delivery onset: a nationwide population-based study. Paediatric and Perinatal Epidemiology 2007; 21: 458-64.

V. Morken NH, Källén K and Jacobsson B, Prediction of spontaneous preterm delivery by combining logistic and Bayesian methods. Manuscript.

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CONTENTS

ABBREVIATIONS

AA   African-American

ART   Assisted reproductive treatment

BMI   Body mass index

CI   Confidence interval

CP   Cerebral palsy

CRH   Corticotrophin-releasing hormone

DMBR   The Danish Medical Birth Register

E3   Estriol

ELBW   Extremely low birth weight

HPA   Hypothalamic pituitary adrenal

HR   Hazard ratio

ICSI   Intra-cytoplasmatic sperm injection

IL   Interleukin

IUFD   Intrauterine fetal death

IVF   In vitro fertilization

LBW   Low birth weight

LMP   Last menstrual period

LR   Likelihood ratio

NMBR   The Norwegian Medical Birth Register

OR   Odds ratio

pPROM   Preterm prelabor rupture of membranes

PTL   Preterm labor

RR   Relative risk

SGA   Small for gestational age

SHDR   The Swedish Hospital Discharge Register

SMBR   The Swedish Medical Birth Register

TNF   Tumor necrosis factor

VLBW   Very low birth weight

WHO   World Health Organization

INTRODUCTION

Preterm birth is a major health problem and the most important clinical problem in obstetrics. Recent developments in this field have evoked major interest and preoccupation in many researchers in maternal-fetal medicine and obstetrics. Nonetheless, preterm birth remains an unresolved entity; its causes are complex and our current knowledge is fragmented. The use of tocolytics and antibiotics has proved to be rather disappointing and the major causes of iatrogenic preterm birth in the developed world, preeclampsia and severe intrauterine growth restriction, are both unpreventable. A core question is: why have advances not led to reduced incidence? (1).

Progress has been made in elucidating the cascade of events constituting the biological pathways leading to spontaneous preterm delivery, especially in animal models. The relevance of these animal models related to preterm birth and delivery in humans remains an open question and we are still far from understanding the causes of preterm delivery. It is incontrovertible that research on this issue must be multi-disciplinary, with assessment of risk factors and causative agents at many levels of observation, one of which is the public health level. Public health interventions are reported to be the most promising beneficial initiative at present (1), and the best approach to preventing preterm birth is likely to be through socio-economic interventions such as infection control, i.e. improved nutrition; avoiding smoking, alcohol and substance abuse and improving hygiene (2). A comprehensive understanding of the epidemiology of preterm birth is fundamental, since it represents a public health problem for a number of reasons: 1) preterm infants generate substantial emotional and economic costs for their families and communities, 2) preterm infants have a disproportionate impact on health services utilization, 3) disparities in preterm birth exist across populations, 4) disparities in preterm birth exist across ethnic groups (2) and 5) the proportion of preterm birth is increasing in several populations (3, 4).

Increased knowledge of the public health aspects of preterm birth may be helpful in the work towards improving pregnant women's chances of giving birth to full-term babies (5). This thesis investigates public health aspects of preterm birth and presents new nationwide, register-based data from Scandinavia.

Public health and clinical implications of preterm birth

In 2001, the World Health Organization (WHO) established a reference group to work with improving the accuracy of information about the causes of child death. During the period from 2000 to 2003, six causes accounted for 73% of the 10.6 million annual deaths in children under 5 (6). Preterm delivery accounted for 10% and was a greater contributor than asphyxia at birth. In all regions of the world, preterm delivery is the leading cause of death in the neonatal period (6). Other researchers have shown that preterm birth is the most important cause of perinatal mortality and morbidity in the industrialized countries, accounting for 70% of perinatal mortality and nearly half of neurological morbidity (7, 8). There is no doubt that preterm birth is a serious global health problem with great impact on public health worldwide.

One British (9) and one Norwegian (10) study are two examples of recent population-based clinical studies evaluating both short- and long-term outcomes in extremely preterm infants. They showed that recent developments in simple prenatal care have, to some extent, improved short-term outcome, but the longer-term effects are still unsatisfactory. The results of these studies also remind us what this really is about, i.e. a disorder that can affect everyday life for those suffering from severe complications of a very preterm birth. The destiny of the individual infant and family is easy to forget when public health aspects and large datasets are under consideration.

The **EPICure study** included children born at 25 or fewer completed weeks of gestation in the United Kingdom and Ireland in 1995 (11). These children were studied at early school age and 41% of the extremely preterm children had cognitive impairment (defined as test results more than 2 SD below the mean), compared to their classmates. Behavioral problems also seem to occur with high prevalence among these children (9). The rates of severe, moderate, and mild disability were 22%, 24%, and 34%, respectively. Disabling cerebral palsy (CP) was present in 12%. The authors concluded that cognitive and neurological impairment was common at school age among extremely preterm children (11). A recent publication from the EPICure study also concluded that impairment of motor; visuospatial; and sensorimotor function, including planning, self-regulation, inhibition and motor persistence, contributes excess morbidity in addition to cognitive impairment in extremely preterm children and contributes independently to poor classroom performance at age 6 (12). The same dataset was also used to determine survival (314, or 39%, of 811 infants admitted to neonatal units survived until discharge) and complications at discharge from hospital and at 30 months of

age (13, 14). It is, however, noteworthy that between 54% and 75% (depending on the standard used for assessing cognitive function) of the population assessed at the age of 6 were doing well and functioning within normal ranges (9).

In the **Norwegian** prospective observational study, by Markestad and colleagues, of all infants with a gestational age of 22-27 completed weeks or a birth weight of 500 to 999 g who were born in Norway in 1999 and 2000 (10) outcomes were determined in terms of perinatal and early death, need for treatment and morbidity at the time of discharge to home. These researchers concluded that the survival rate was high and that the morbidity rate at discharge to home was low, compared with previous population-based studies, including the EPICure study. There are some major differences between the British and the Norwegian studies. First, the EPICure study included infants at a lower gestational age (<26 weeks versus <28 weeks). Second, the Norwegian infants were born 4-5 years later and a greater proportion had been given prenatal steroids and were born via cesarean section. The improved prognosis found in Norway may partly be due to changes in management and organization of care. Data from a similar **Swedish** national cohort born in 1990-1992 also indicates lower survival rates than that found by Markestad and colleagues (15). Prenatal steroids were not in extensive use and only a few units provided surfactant therapy in Sweden during that period; differences may thus be attributable to improvements in management.

Approximately three-fourths (75-80%) of perinatal deaths occur in babies delivered at < 37 weeks (16-18), and 40% of these deaths occur in those delivered at <32 weeks (19). Preterm infants are also at increased risk of developing cognitive and behavioral abnormalities (20) and of achieving poorly in educational situations (21), problems which persist until adulthood (20, 22). Furthermore, they are at increased risk of chronic lung disease (23-25) and visual abnormalities (26, 27) and they represent approximately half of all pediatric neuro-developmental disabilities (28-30), including CP (31-34) and other severe brain damage (35), as well as long-term morbidity (19, 28, 36). A very recent Norwegian register-based study even showed increased risk of mortality throughout childhood and subsequent reduced reproductive ability, compared to term-born indiviuals (37).

Moderately preterm infants, born at gestational age 32–36 weeks, account for the vast majority of preterm infants (38, 39), while individuals born at <28 weeks of gestation,

contribute 60% of the total infant mortality (38). It has thus been, and remains, a general belief that challenges related to the most extremely preterm-born infants are the most major in perinatal medicine. A modest but steadily increasing body of evidence has recently emerged, indicating that infants born close to term (**34-36 gestational weeks**) also have an increased morbidity and mortality risk, compared with term infants (16, 40-50). Experts have even contended that there is no such thing as a healthy preterm infant (51); this implies that the preterm problem most certainly extends beyond the most extremely preterm births. In addition, efforts to reduce complications among preterm infants at 34-36 gestational weeks will have a major impact on public health as a consequence of the size of this group. The questions of whether benefit is derived from prolonging pregnancy beyond 34 gestational weeks has been raised (46). Investigation into the optimal obstetric and neonatal management of these late preterm infants is thus warranted (52).

Society's **economic** burden from preterm birth is of less importance than the human suffering described above, but it is still far from insignificant. As technology drives medicine's direction and progress, possibilities for new and expensive treatments evolve rapidly. Preterm birth not only results in economic burdens due to initial neonatal treatment, but also in substantial health service costs following discharge from the neonatal unit (53). It imposes an immense burden on health, education and social services and on affected families (53). In the United States, the Institute of Medicine has estimated that preterm birth costs the country at least 26.2 billion US dollars a year or 51 600 US dollars per preterm infant (54). This group of infants accounts for 12% of live US births per year, but its care consumes close to 60%, or 6 billion US dollars, of total spending on initial neonatal care (46, 55). The expenses are clearly related to gestational age (43); an infant born at 38 weeks incurs one tenth the expense of one born at 35 weeks (441 versus 4733 dollars) (55). This means that even a modest reduction in preterm birth will lead to substantially reduced costs (51). The corresponding costs in Scandinavia are most likely similar to those in the US.

An interesting observation is that large registry-based, observational studies have found that women who had delivered a preterm infant had a 2- to 3-fold higher risk of cardiovascular death, compared with those who delivered at term (56, 57). A recent cross-sectional study suggests that vascular and metabolic factors account for a least some of the increased prevalence of cardiovascular disease among women many years after a preterm birth (58).

The authors suggested that a previous preterm delivery may help in identifying women who might benefit from cardiovascular risk screening and intervention (58), indicating that preterm birth may have implications for patients beyond obstetrics and maternal-fetal medicine.

Clearly, the preterm problem has several implications and serious complications and there are medical, societal and financial incentives to further explore both consequences of the problem and the causes resulting in a preterm delivery.

The definition of preterm birth and controversies in defining subgroups

The first serious attempt to come up with an international definition of a "premature" or "immature" infant was proposed by the World Health Assembly in 1948 (59, 60). Since then, definitions have been further developed and refined and preterm birth has finally been defined by the WHO as a birth occurring before **37 completed weeks or 259 days of gestation** (61). This definition has been endorsed by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (62), and is currently the one in common use, although the terms preterm and premature are still used interchangeably. There is thus some confusion, the resolution of which requires international discussion and agreement, but there is as yet no international consensus on any other definition.

The term **preterm is preferable** as the WHO definition is based solely on gestational age and not on degree of infant maturity. Similarly, the terms low birth weight (LBW, <2500g), very low birth weight (VLBW, <1500g) and extremely low birth weight (ELBW, < 1000g) have been used extensively (63-65) but should be avoided in relation to preterm birth, as the latter does not incorporate birth weight. Gestational age may be an imperfect measure, but weight incorporates both the duration of gestation and the adequacy of fetal growth. There is reasonable agreement that the WHO definition should be used despite the confusion in the literature regarding the terms preterm and premature.

When it comes to the **subgroups** of preterm birth, far more ambiguity exists. Categorizing preterm infants into precisely defined subgroups is valuable in a number of contexts, i.e. risk assessment, reporting for surveillance/research purposes, generating health policy guidelines, research, patient care and counselling. It is possible that preterm birth is not a single entity,

but rather a cluster of conditions with different etiologies ultimately resulting in the delivery of an infant before 37 gestational weeks (66). It is also important to be aware that obstetric intervention and practice will influence the relationship between spontaneous and iatrogenic preterm births. One possible scenario is that increased fetal surveillance with ultrasound might detect growth restrictions that, if undetected, would have ended in spontaneous onset of preterm delivery. Despite the convenience of categorizing and sub-grouping, there is no consensus in the literature that the subcategories of preterm birth represent etiologically different entities and this assumption has indeed been contradicted (67). Whether the distinction between spontaneous and iatrogenic preterm births should be used when studying etiology has been questioned in a recent report (68), but the authors concluded that the complexity of the etiological pathways in preterm birth justifies both aggregation and disaggregation. An alternative classification, based upon understanding of the causal mechanisms, rather than on clinical presentation, has also been suggested (69).

The most important sub-grouping is based on **gestational age** (Table 1), as prognosis depends on gestational age at birth (7). Preterm infants born at gestational age 32-36 weeks are classified as moderately preterm, while infants born at gestational age 28-31 weeks and <28 weeks are designated very and extremely preterm, respectively. About 10% of preterm births are extremely preterm, another 10% are very preterm and 80% are moderately preterm (38). The designation "near-term" has been used for those infants born closest to term at 34-36 gestational weeks and 34 gestational weeks is an obstetrical milestone in many respects. Prenatal corticosteroids and tocolytic treatment are no longer administered in cases exceeding 34 weeks. "Near-term" implies that these infants are not preterm, but close to term, despite their being at much higher risk of both mortality and morbidity than term infants. It has therefore recently been recommended that "near-term" should be replaced by "late preterm" (59, 70).

Gestational age and birth weight categories	Definition
	weeks+days
Late preterm birth	34 to 36+6
Moderately preterm birth	32 to 36+6
Very preterm birth	28 to 31+6
Extremely preterm birth	<28
	grams
Low birth weight	<2500
Very low birth weight	<1500
Extremely low birth weight	<1000

Table 1 Gestational age categories and birth weight categories

Preterm birth is further categorized according to three different modes of **clinical presentation** or to the nature of the preterm delivery: preterm labor (PTL), preterm prelabor rupture of membranes (pPROM) and medically indicated (iatrogenic) preterm birth. PTL and pPROM are often combined and called spontaneous preterm birth. The distinction between PTL and pPROM became more interesting during the early 1990s, as it appeared that these subgroups had different antecedents (71-74). Furthermore, multiple births, fetal malformations and intrauterine fetal deaths (IUFD) contribute (Figure 1) to preterm birth and can be regarded as distinct subgroups (75). The contribution of each of the subgroups-iatrogenic, PTL and pPROM-to the total preterm birth proportion in Scandinavia is not known. It has been assumed, based on studies from other parts of the world, that each subgroup contributes 1/3 in a Scandinavian population as well (75). Previous studies on preterm subgroups are either hospital- or regional-based and are thus not performed on population-based data (76-81).
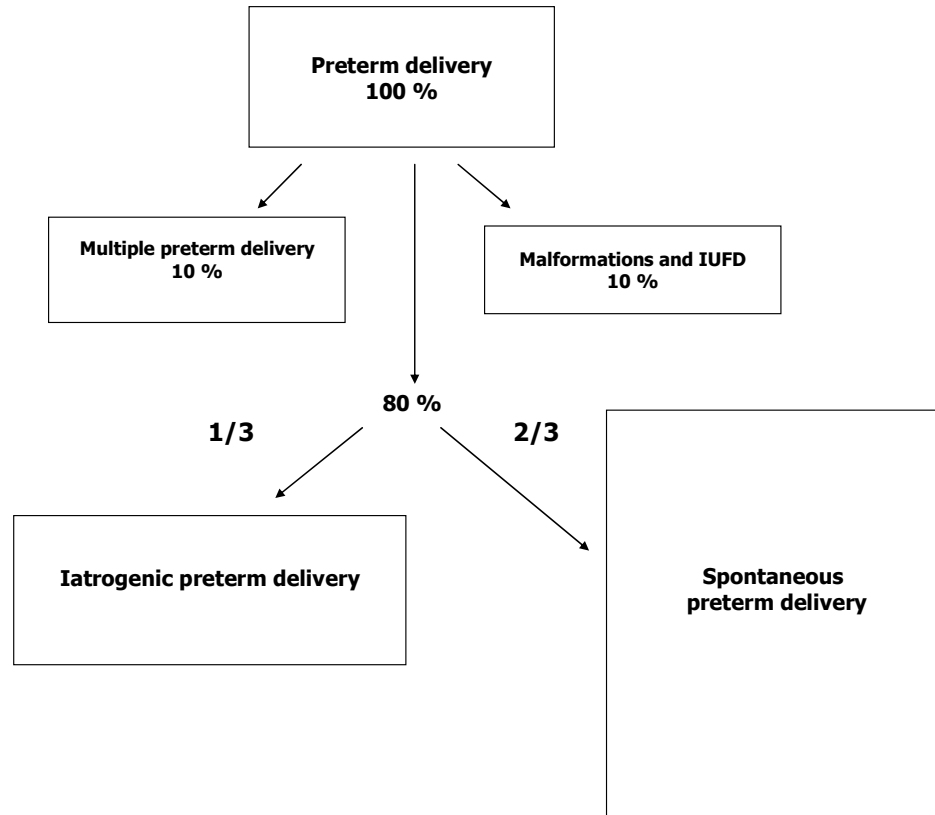
Figure 1 Subgroups of preterm birth

Due to the heterogeneity of preterm birth and as a result of rather disappointing findings in fields such as genetics (82, 83), **further sub-grouping** of preterm birth and introduction of the endophenotype concept into preterm birth research may prove useful in the future. The term endophenotype, as created by Gottesman, Shield, John and Lewis(84), can be defined as a heritable characteristic normally associated with a condition but not a direct symptom of that condition. The idea that some phenotypes bear a closer relationship to the biological processes giving rise to illness than do diagnostic categories has attracted considerable interest, especially in the field of psychiatry (85). It is believed that the exact nature of endophenotypes will be easier to analyze than that of the genetic basis of psychiatric disease (85). Measuring cytokine levels is one possible way of determining endophenotypes in preterm birth.

Preterm birth is a heterogeneous group in terms of different gestational ages, different subgroups and possible ways of sub-grouping (38). So far, no uniform international set of definitions conserning all aspects of the phenomenon has been agreed upon.

Determination of gestational age

The definition of preterm birth is based on gestational age assessment which is thus the key feature of this entity. It is not possible to establish the "real" normal length of gestation, but 280 days seems to be a realistic working figure and is that most widely used, at least in Caucasian populations (86). The implications of gestational age depend on the method chosen to determine it. One such definition has been proposed by the American Academy of Pediatrics (Figure 2), i.e.time elapsed between the first day of the **last menstrual period** (LMP) and the day of delivery (87).
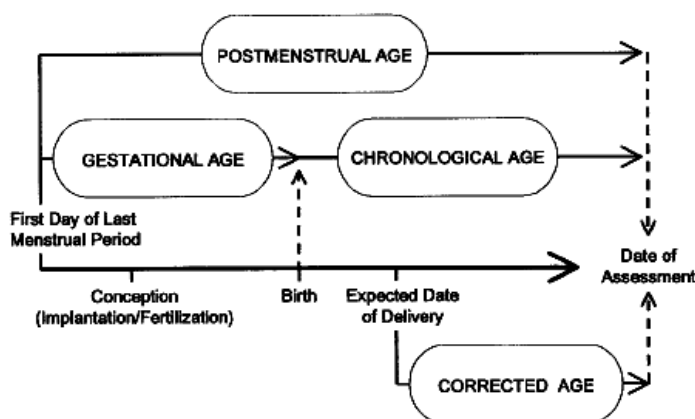
Figure 2 Age terminology during the perinatal period, according to the American Academy of Pediatrics (Reproduced with permission from The American Academy of Pediatrics. Engle WA. Age terminology during the perinatal period. Pediatrics 2004;114(5):1362-4)

What the obstetrician really wants to know is the time elapsed from conception but this is rarely feasible except in the case of births after assisted reproductive treatment (ART); thus, several methods determining a substitute for this interval are used. An accurate assessment of gestational age is fundamental in a number of situations, such as categorization into risk groups (7), timing and planning of elective delivery in case of complications, estimation of

likelihood of survival if delivery occurs preterm and assessment of fetal growth, as well as for research purposes (86).

Gestational age has traditionally been determined by calculating the interval from the first day of the LMP to the date of delivery. This variable is the cornerstone of gestational age determination in US vital statistics. LMP was the only gestational age variable in the Norwegian Medical Birth Register (NMBR) until as late as 1998. It has been shown in numerous studies during the last 40 years that this method has its **limitations** in establishing the duration of pregnancy (88-98). Uncertain LMP is more common among women with low socioeconomic status and is associated with higher proportions of preterm birth and other adverse pregnancy outcomes. The method is more uncertain in the extremes, i.e. preterm and, especially post-term gestations (97). Furthermore, irregular menstrual cycles, forgotten dates, early bleeding in pregnancy and conception before menstruation returns after an abortion or birth complicates its use. As a result, other methods, such as ultrasound gestational age determination and antenatal and postnatal estimations of gestational age, have been developed (99-106).

Ultrasound measurement of the fetus as a method of determining gestational age started in the 1970s and is currently offered as a routine examination in many countries, including in Scandinavia. The examination is performed between the 17th and 20th gestational week and estimates or corrects the date of delivery, diagnoses plurality and identifies placenta location. The main differences between LMP and ultrasound gestational age determination are found in preterm and postterm gestations, while differences are smaller for infants born at term (97, 107). Ultrasound gestational age assessment lowers gestational age across the entire gestational age range resulting in a left-hand skewness that leads to reduced proportion of postterm births, with a concomitant increase in the proportion of preterm births (108). The fact that late ovulation is more common than early ovulation is one explanation for this (108). It has been shown in several (104, 109-112) studies that ultrasound gestational age determination predicts the day of delivery more accurately than LMP. Despite quite widespread agreement on the superiority of ultrasound compared to LMP, there are **limitations** to this method. The basic assumption underlying ultrasound gestational age determination in the second trimester is that all fetal crania are equal in size at any given gestational age; variations in fetal size at a given stage in pregnancy are thus converted into differences in gestational age (113). However, other factors influencing fetal size, such as

gender and maternal smoking (early growth restriction), may introduce systematic bias into gestational age determination (114). In a Danish study comparing female and male infants, a 13% excess of preterm birth in female infants was found based on ultrasound assessment, but not based on LMP (113). A similar bias was found for smokers versus non-smokers. The authors concluded that factors reducing fetal size in early pregnancy inflate the risk of preterm, and deflate the risk of postterm delivery when gestational age determination is based on ultrasound and that this bias can distort the relative risk of preterm or postterm delivery by 10-20% (113).

The determination of gestational age is at best an imperfect science (97, 108, 115, 116). Factors such as heterogeneity in menstrual cycle duration, implantation bleeding misinterpreted as menstruation, recall error, preconception amenorrhea due to oral contraceptive use, examiner's skill and the choice of technology can introduce additional errors into the assessment (59, 97, 110, 111). Therefore, **no golden standard** for gestational age determination is agreed upon and different methods are used in different studies. In Scandinavia, gestational age determination by LMP and ultrasound are the main methods; the latter is the most common and has been considered the most reliable since the mid-1990s.

The proportion of preterm delivery will change depending on the method of gestational age determination but the time trends will not be affected as long as the criteria for the different methods of gestational age determination are kept constant. The importance of national trend monitoring is probably the reason LMP still continues to be the basis for national surveillance of preterm birth in the United States (117). It is important to be aware of which method is used for gestational age determination when comparing different preterm birth frequencies, as studies indicate that substituting or combining different methods has consequences, especially concerning preterm gestations (118, 119).

Proportions of preterm delivery and difficulties in international comparison
Since the 1980s several industrialized countries, such as the United States (51), Canada (120) and Australia (121), have reported increasing proportions of preterm delivery. There has been a 31% increase in the United States, from 9.4% of total births in 1981 to 12.3% in 2003. During this period, late preterm births (34-36 gestational weeks) increased by 40% while very preterm births rose by only 11% (51). In light of the increasing evidence of adverse effects of

these late preterm births, this current tendency is troublesome, despite the increase having occurred in the gestational subgroup traditionally considered to be of the least importance. The steady increase in preterm births in the United States has continued into 2004 (12.5%) (122) and further into 2005 (12.7%) (3).

A Swedish study showed an increasing proportion of preterm deliveries, from 5.7% to 6.8% during the 1980s in hospitals practicing early age determination by ultrasound (123). Postterm births were simultaneously reduced; these findings were in accordance with findings from other parts of the world (124-129). A Danish study reported a 22% increase in the crude national proportion of preterm delivery during the period 1995-2004 (4). The spontaneous preterm birth proportion increased by 51% in a group of low-risk women during the same period (4). In Norway, there was a steady decline in the preterm birth proportion from the late 1960s until 1980 (124), after which the proportion surged from 5.5% to 7%, representing a 27% rise (124). Earlier intervention and induced delivery in high-risk pregnancies (124) and more frequent use of ultrasound to determine gestational age (128) have been put forward as explanations for this increase. The perhaps most striking example of the impact of changing intervention practice on the preterm birth proportion comes from Brazil, where an eight-fold rise in cesarean sections over the past 20 years was associated with a three-fold rise in the preterm delivery proportion (130).

With the exception of the Norwegian decline during the 1960s, there have been few documented reductions in preterm birth proportions and these were reported more than 20 years ago. The oldest described reduction was in Aberdeen, Scotland, where the proportion fell from 9.3% of all births in 1951-1955 to 6.8% in 1976-1980 (131). Other improvements have been interpreted as positive results of intervention and prevention programs either at the national (132) or institutional level (133). The most quoted reduction was reported from France, where the preterm birth proportion declined from 8.2% in 1972 to 5.4% in 1981 (134). This reduction reflected the results of a national preterm birth reduction program that was started in 1971 and implemented in most institutions (135). As part of this effort, a 12-year intervention study including a program for prevention of preterm deliveries was conducted in a district hospital in Haguenau in northeastern France, to evaluate and measure the effects of the national program (136, 137). Between 1971 and 1982, a reduction from 5.4% to 3.7% (134) occurred in Haguenau. What was so striking about these French results was that the total reduction was related to a reduction in births at ≤34 weeks of gestation.

There was a reduction by one-third at gestational age 33-34 weeks, and a more than 50% decrease at gestational age 28-32 weeks (134). The national French preterm birth proportion seems to have continued to decline during the 1980s but this was not attributed to the improved accuracy of gestational age determination by ultrasound (138). A more recent report comparing two samples, both including all stillbirths and live births during one week in France in 1995 and 1998, found that the proportion of live births before 37 gestational weeks had increased from 5.4% to 6.2% (139). This indicates that two decades of continuous reduction in the French preterm birth proportion may have come to an end.

A Finnish study also reported a historic reduction in preterm birth (140). Two population-based birth cohorts from northern Finland in 1966 and 1985-1986 were compared. The overall preterm birth proportion fell from 9.1% to 4.8%, including a reduction from 8.8% to 3.4% in spontaneous preterm births. Iatrogenic preterm births increased from 0.3% to 1.4%. Several maternal determinants were evaluated, most of which underwent favorable changes during the 20 years. The authors concluded that only a small part of the decrease in the total preterm birth proportion could be attributed to these changes. However, it was speculated, since the overall standard of living had increased tremendously in all social classes during the period that better living conditions and increased social well-being had significantly contributed to the reduced spontaneous preterm birth proportion. A very recent report from Finland claims that the positive tendency seems to have continued, at least in extremely preterm deliveries (<28 gestational weeks), with a 12% reduction from the period 1987-90 (0.39%) to 2001-05 (0.34%) (141). Decreasing iatrogenic preterm deliveries among early gestations, increasing smoking cessation during pregnancy and prevention of multiple pregnancies after in vitro fertilization (IVF) were suggested as contributors to this favorable trend in Finland (141).

The official crude national preterm birth proportion varies considerably between different nations and rather wide variation is evident among industrialized countries (Table 2). This variation may reflect differences in the examined populations, national differences in the definition and reporting of stillbirths and neonatal mortality (142) as well as different practices in terms of intervention.

Reference	Regions	Country	Year	Proportion of preterm birth <37 weeks
	Nordic countries			
Gissler et al [147]		Sweden	2004	5.4%
Langhoff-Roos et al [4]		Denmark	2004	6.3%
Gissler et al [147]		Norway	2006	6.0%
Gissler et al [147]		Island	2004	5.2%
Gissler et al [147]		Finland	2006	5.0%
	United Kingdom			
Buitendijk et al [145]		Scotland	2000	7.3%
Buitendijk et al [145]		Wales	2000	7.9%
Buitendijk et al [145]		Northern Ireland	2000	7.1%
	Central Europe			
Buitendijk et al [145]		Germany	2000	7.6%
Buitendijk et al [145]		Netherlands	1999	7.4%
Buitendijk et al [145]		Belgium Flanders	2000	7.8%
Buitendijk et al [145]		Belgium French	2000	8.5%
Buitendijk et al [145]		Luxembourg	2000	5.0%
Buitendijk et al [145]		France	1999	6.2%
	South Europe			
Buitendijk et al [145]		Italy	1998	6.2%
Buitendijk et al [145]		Spain	1999	7.7%
Buitendijk et al [145]		Greece	1998	5.8%
Buitendijk et al [145]		Portugal	1999	5.9%
	North-America			
Hamilton et al [3]		USA	2005	12.7%
Health Canada [120]		Canada	2000	7.6%
	Australia			
Laws et al [144]		Australia	2003	7.9%
Craig et al [146]		New Zealand	2001	6-7%

Table 2 Reported proportion of preterm birth from different countries during the last decade

The preterm birth proportion in the United States was reported to be 12.7% in 2005 (3), exceeding that in other western countries such as Canada (143), Australia (144), France (145), the Netherlands (145), New Zealand (146) and Scotland (145). The recent national crude preterm birth proportions reported from Sweden, Denmark, Norway, Finland and Iceland are also less than that in the United States (147). The reason that preterm birth is apparently a more common problem in the United States is not known, but a recent study has pointed out that LMP in the US data misclassifies gestational duration and overestimates both preterm and postterm birth proportions (143). The authors concluded that gestational age in the United

States should be based on the clinical estimate for international comparisons, as in the Scandinavian countries and Canada. LMP probably continues to be the basis for national surveillance of preterm birth in the United States because monitoring national trends has been given higher priority than making international comparisons (117). The latter will most certainly become a much more important aspect in the future, as international collaboration and comparison will be fundamental for successful elucidation of the mechanisms behind this complex problem. International collaboration and pooling of samples have proven successful in other fields of medical research (148, 149) and would be timely in preterm birth research at this time.

International comparisons of preterm delivery proportions are complex for a number of reasons. Core questions, such as "Does the baseline preterm birth proportion differ across populations?" and "Does the preterm birth proportion increase over time?", are difficult to answer due to the number of influential factors. Different methods of registering and calculating gestational age, the use of either pregnancies or children as the observational unit (38) and diverse obstetric practices concerning induction of labor, influence numbers and make comparisons challenging (73). Ethnic diversity and socio-demographic factors are also important and influence the proportion of preterm birth. The frequency of several of these risk factors, well known for their association with preterm delivery, also changes over time and differs between countries. ART, high maternal age, primiparity and elective delivery before term have changed in recent years, changes that have been offered as explanations for the increase in preterm delivery proportions seen in several countries (125, 126, 150). Better living conditions, reduced smoking and specific prevention programs may have contributed to the decreased preterm delivery proportion seen in a few other countries (134, 140). Methods that facilitate and simplify comparison of preterm birth proportions are needed.

Risk factors, clinical diagnoses and complications associated with preterm birth
Numerous risk factors, clinical diagnoses and pregnancy complications have been found to be associated with an increased risk of preterm birth. Most of these factors can be divided into three main groups: 1) maternal and constitutional risk factors, 2) pregnancy history and 3) index pregnancy risk factors. Some more curious associations have also been found, e.g. a possible seasonal pattern in preterm birth (151-157), although there is conflicting evidence, as

one study of spontaneous preterm birth did not find any seasonal variation in this preterm subgroup (158).

Maternal and constitutional risk factors	Pregnancy history	Index pregnancy risk factors
o Ethnicity	o History of prior preterm birth	o Polyhydramnios/oligohydramnios and placental disorders
o Socioeconomic status	o History of prior abortion	o Elective and complicated preterm birth (maternal and/or fetal complications that indicate preterm delivery)
o Marital status	o History of prior cervical incompetence	o Antepartum hemorrhage
o Maternal age		o pPROM
o Parity		o Fetal malformations
o Maternal size (weight and height)		o Fetal male gender
o Maternal diet		o Lack of antenatal care
o Smoking		o Abdominal surgery
o Drug and alcohol abuse		o Multiple pregnancy
o Coffee		o ART
o Physically demanding work and other occupational exposures		o Maternal infection: systemic, genital, asymptomatic bacteriuria
o Maternal genital abnormality		o Fetal growth disturbances
o Periodontal disease		o Preeclampsia
o Maternal stress		o Maternal medical disorders: thyroid disease, asthma, diabetes, hypertension, etc.
o Short interpregnancy interval		o Cervical procedures

Table 3 Risk factors, clinical diagnoses and pregnancy complications divided into three main groups: maternal and constitutional risk factors, pregnancy history and index pregnancy risk factors.

Maternal and constitutional risk factors

Disparity in preterm birth between **ethnic** groups persists after stratification for educational level and social class (159, 160), and indicates a genetic predisposition. In a recent report, the proportion of births <28 weeks was found to be 0.35%, 0.45%, and 1.39% for Caucasians, Hispanics, and African-Americans (AA), respectively (50). AA undergo preterm birth at <37 gestational weeks twice as often as women of other races, and three times as often at <32 weeks as Caucasian women (161). At the same time, AA infants are at lower risk of neonatal

mortality (number of deaths in infants 0-27 days of age per 1000 live births) related to preterm birth (50), which could indicate an ethnic disparity in the normal length of pregnancy.

Mothers with low **socioeconomic status** have an increased risk of preterm birth (162-168) and factors such as **single marital status** have also been found to be associated with an increased risk of preterm birth, although this is considered to reflect other social factors (38).

Delayed childbearing has an impact on several adverse obstetric outcomes, of which preterm birth is one (169). The mother's **age** at childbirth contributes increased risk among younger and older women (51). Women younger than 16 and older than 35 years of age have been found to have a 2-4% higher rate of preterm birth, compared to women aged 21-24 (54). There are indications of an interaction between maternal age and ethnicity, with the risk of preterm birth starting to rise at a younger age (27-29) among AA than among Caucasians (33-35) (54). First teenage birth is not associated with an increased risk of preterm birth, whereas second teenage birth is associated with a highly increased risk, compared to women aged 20-29 (170). In all other age groups, **primiparity** is associated with a higher rate of preterm birth than second or third births, with a slightly increased risk for fourth births (38).

Maternal size seems to influence the risk of preterm birth, but conflicting data exist for both maternal weight (171-175) and height (176-178), probably because these factors interact with other risk factors such as smoking, parity and stress (179). There is reasonable agreement that low pre-pregnancy body mass index (BMI)(177, 179, 180), as well as a slow weight gain rate, especially in the latter part of pregnancy (181), increase the risk of preterm birth. Both maternal **dietary habits** and supplement intake have been found to be associated with the occurrence of preterm birth (182) and a recent interesting finding requiring further attention is that a cholesterol-lowering diet reduced the occurrence of preterm birth significantly (relative risk (RR): 0.10; 95% confidence interval (CI): 0.01-0.77) in a Norwegian randomized clinical trial (183). Two very recent studies on the Norwegian and Danish pregnancy cohorts resulted in conflicting findings concerning the effects of cholesterol-lowering and Mediterranean diet on preterm birth risk (184, 185).

Intervention aimed at prevention of maternal **smoking** in pregnancy may be the most obvious public health challenge, as smoking is definitely a modifiable risk factor for preterm birth. It has been shown that women who quit smoking during the first trimester have a reduced rate

of preterm deliveries (6.7% vs 9.1%), compared to women who smoked beyond the first trimester (186). The association between smoking and preterm birth has been recognized since the 1950s (187) and later confirmed in several other studies (188-193). A Swedish study examining 300 000 live singleton births found a dose-related impact of smoking on preterm delivery; furthermore, the smoking-related risk of spontaneous preterm birth was more pronounced than that of iatrogenic preterm birth (194). The adjusted odds ratio (OR) for spontaneous preterm birth at <32 gestational weeks was 1.4 (95% CI: 1.2-1.6) among women smoking 1-9 cigarettes daily and 1.7 (95% CI: 1.4-2.0) among women smoking > 10 cigarettes daily (194). There has been a reduction in the proportion of women who smoke in many industrialized countries, including Scandinavia (4, 195). This has resulted in social inequality related to smoking, which now is strongly associated with lower socioeconomic status (196). The most recent Cochrane review assessing the effects of smoking cessation programs implemented during pregnancy found a significant reduction in smoking in the intervention groups of 48 included trials (RR: 0.94, 95% CI: 0.93-0.95) and that smoking cessation interventions reduced preterm birth with a RR of 0.84 (95% CI: 0.72-0.98) (197).

There is conflicting evidence regarding the abuse of **other substances** such as cocaine, marijuana, caffeine and alcohol related to the risk of preterm birth, and there are no clear conclusions regarding whether a possible increased risk is due to the actual substance or related to adverse socioeconomic factors (19).

The association between **physically demanding work** and preterm birth was presented by Mamelle et al in 1984. They found a significant relationship between the preterm birth proportion and the number of high fatigue scores observed on the job (198). This has later been confirmed by others (199-201) and a recent meta-analysis of 29 included studies found a significant association between preterm birth and physically demanding work (OR: 1.22, 95% CI: 1.16-1.29) (202).**Other occupational exposures,** such as prolonged standing (>6 hours/day), shift and night work, high cumulative work fatigue and long working hours (>42 hours/weeks), were also significantly associated with preterm birth (202, 203).

Preterm deliveries were found to be rather common among women with **Mullerian duct anomalie**s in a Spanish study (204). The preterm prediction study found Mullerian duct abnormalities to be one of the most important risk factors for an iatrogenic preterm delivery, with an OR of 7.02 (205). **T-shaped uterus**, another uterine abnormality, that may be found

in women exposed in utero to diethylstilbestrol, has also been associated with an increased risk of preterm birth (206).

Several recent studies suggest that **periodontal disease**, a source of sub-clinical and persistent infection, may induce a systemic inflammatory response that increases the risk of adverse pregnancy outcomes such as preterm birth (207-212), but conflicting evidence exists (213, 214). A recent systematic review on the issue concluded that periodontal disease may be associated with an increased risk of several adverse pregnancy outcomes, but more methodologically rigorous studies are needed for confirmation (215).

Preterm birth is more common among women reporting increased **stress and anxiety** during pregnancy (216) and, as mentioned above, several socio-demographic factors associated with maternal stress are also linked to preterm birth. Corticotrophin-releasing hormone (CRH) plays an important role in the etiology of preterm birth associated with maternal and fetal stress and is the biological link for this risk factor (217, 218). It has also been shown that high maternal stress during gestational weeks 25-29 was significantly associated with spontaneous preterm birth, the largest preterm subgroup (OR:1.16, 95% CI: 1.05-1.29) (219).

Short interpregnancy interval is a risk factor for preterm birth (220-222). The mechanism is unknown, but could be related to maternal depletion of nutritional agents or the time required for resolution of the inflammatory status associated with the previous pregnancy (223). An interval of at least 12 months between pregnancies has been recommended (221).

Pregnancy history
One of the leading risk factors for preterm birth is a **previous preterm birth** (224-226); the relative risk increases with the number of previous preterm births: 2.2 for one, 3.7 for two and 4.9 for three or more. In addition, the earlier the previous preterm birth, the earlier the subsequent birth. This effect is most pronounced if the previous birth was an extremely preterm birth (227). There is also evidence of an association between previous spontaneous and induced **abortion** and preterm birth (38). The threshold between spontaneous preterm birth and late spontaneous abortions in the second trimester is a grey zone, indicating that these two entities might be part of the same causal axis.

True **cervical incompetence** is most certainly a risk factor for preterm birth and a shortened cervix on transvaginal ultrasound is often considered to be diagnostic (209). Cervical cerclage is the treatment option for an incompetent cervix. A recent meta-analysis revealed that cervical cerclage did not prevent preterm birth in the total population of women studied (RR: 0.84; 95% CI: 0.67-1.06). However, there was a significant reduction of preterm birth at <35 gestational weeks in women with singleton pregnancies (RR: 0.74; 95% CI: 0.57-0.96), a singleton pregnancy and previous preterm delivery (RR: 0.61; 95% CI: 0.40-0.92) and a singleton pregnancy and a previous mid-trimester loss (RR: 0.57 95% CI: 0.33-0.99). On the other hand, a significant increase in preterm birth at <35 gestational weeks was found in twin gestations (RR: 2.15; 95% CI: 1.15-4.01) (228). We may not be good enough at differentiating between true cervical incompetence and other causes of preterm birth (209) and further studies are required in order to elucidate its role.

Index pregnancy risk factors

Several **pregnancy complications,** such as polyhydramnios, oligohydramnios, abruption of the placenta, placenta previa, preeclampsia and eclampsia in the index pregnancy, may result in an increased risk of either iatrogenic or spontaneous preterm labor and delivery (38). **Antepartum hemorrhage** (17%), hypertension (19%) and **pPROM** (30%) were the principal complications leading to spontaneous preterm delivery, according to an Australian study (229). The same study also showed that **fetal anomaly** is a risk factor for spontaneous preterm birth (229); this has later been confirmed by several other authors (230-232).

Gender aspects of preterm birth seem to be of importance, as an excess of male fetuses is constant across the whole gestational age spectrum from 20 to 37 gestational weeks (233). Swedish Medical Birth Register (SMBR) data from 1999-2000 have also shown that boys are more likely to be born preterm, accounting for 55-60% of all newborns between 23 and 32 gestational weeks (234). It has been proposed that male fetuses may promote the onset of preterm birth either through androgen precursors or interleukin (IL)-1 effects (234). In a study of low risk singleton pregnancies, male gender was found to be one of two major determinants of PTL, together with nulliparity, the former with a population-attributable risk of 13.6% (235). Furthermore, outcome in the perinatal period is better in female infants (234).

Lack of or late presentation for **antenatal care** is related to low socioeconomic status and has been consistently associated with preterm delivery in older studies (38). These aspects are

most certainly not a very big problem in the Scandinavian countries as poverty is rare and our health services are very well developed and well attended.

Abdominal surgery is an uncommon event during pregnancy; only 0.5-2.2% of the obstetric population will undergo surgical procedures unrelated to an obstetric indication (236-239). The preterm birth proportion after abdominal surgery varies between 8.8% and 16% in different studies (239, 240). A Swedish study reported an increased proportion of VLBW and LBW infants due to prematurity and intrauterine growth restriction after abdominal surgery (241). However, a more recent American study concluded that non-obstetric surgery appears to be relatively safe during pregnancy, despite a preterm birth proportion of 21% (242). General anesthesia, longer surgery duration and intra-abdominal procedures were associated with lower birth weights (242).

Multiple pregnancies comprise just 1-3% of all births (38, 243-245), but account for 12-25% of all preterm births (243, 245). Slightly below half of all multiple pregnancies will end in delivery prior to gestational week 37 (38). During the last 25 years there has been a great increase in the incidence of multiple births in the developed world, mainly as a result of increased use of ART (246-248). In Scandinavia, the twin live birth rate increased from 10 per 1000 in the early 1980s to 15.7, 22.2 and 19.6 per 1000 in 2002 in Sweden, Denmark and Norway, respectively (147). The preterm birth proportion among multiple pregnancies has also increased substantially and contributed to an increased preterm delivery proportion in developed countries (125, 126), but a contemporary increase in labor induction in twin pregnancies may also have played a central role (249). Multiple births definitely have major public health impact and influence on trends in central perinatal health indicators such as the preterm birth proportion (250).

As noted above, **ART** has had a major impact on preterm birth proportions during the last 20-25 years through the increased occurrence of multiple births. However, Perri et al. determined that the occurrence of singleton preterm birth was significantly increased after IVF but not among intra-cytoplasmatic sperm injection (ICSI) patients (251). This indicates that infertility per se can predispose to preterm birth. After ART, singleton pregnancies are also believed to be at a higher risk of preterm birth and other obstetric complications. These risks may be related to pre-existing medical conditions such as uterine anomalies and pelvic infection, or to infertility management-associated diagnostic and operative procedures. This latter possibility

is hinted at by the finding that ICSI patients-who usually undergo the ART procedure due to male-related infertility rather than abnormalities of the female reproductive tract—were not found to be at increased risk of preterm birth, compared with controls (251). However, these findings were recently contradicted in a Swedish register-based study (252). The proportion of preterm births among singleton infants born after IVF was nearly twice that among all singleton infants, but this increase was, to a large extent, due to characteristics of the women undergoing IVF: mainly maternal age and parity distribution but also duration of involuntary childlessness. On the other hand, preterm birth seemed to occur less often after frozen than after fresh standard IVF. Thus, current evidence in the literature is conflicting.

The risk of obstetric complications is not the same in all ART patients and may vary depending on the technique. Wang et al. determined that the occurrence of preterm birth (<37 weeks) was progressively increased when controls were compared with women who had undergone low-tech procedures (intrauterine insemination and ovulation induction) and high-tech techniques such as IVF, ICSI or gamete intrafallopian transfer (253). No difference in deliveries at <32 weeks of gestation was found between controls and the low-tech procedure group, while the occurrence of this complication was significantly increased in women who had undergone high-tech procedures.

Infection and/or inflammation is the only pathological process for which both a firm causal link with preterm birth has been established and a molecular pathophysiology defined (254). The observations associating **systemic maternal infections** such as pyelonephritis (255-259), pneumonia (260-262) and malaria (263-266) with preterm birth are one important component in this line of reasoning. The association between **genital tract infection**, intrauterine infection, inflammation and spontaneous preterm birth has been widely examined. Increased risk of preterm birth in women with intra-amniotic infection (267-269) or inflammation (270, 271) in mid-trimester has been taken as important evidence of causality for infection (272). The frequency of preterm birth accounted for by infection varies from 25-40% (273, 274) and the specific organisms involved are not well known (19). Other important proof of evidence is that antibiotic treatment of ascending intrauterine infections can prevent preterm birth in experimental models of chorioamnionitis (275) and that treatment of **asymptomatic bacteriuria** prevents preterm birth (276, 277).

According to previous studies, infants born preterm (<37 weeks of gestation) are small for gestational age (SGA) or growth-restricted to a greater extent than infants born at term (278, 279). This is not sensational if all preterm infants are taken into consideration since a considerable proportion of preterm births are iatrogenic and indicated by maternal or fetal problems. The preterm population has been considered to be homogeneous, in several previous studies, when the association between SGA and preterm birth was evaluated (278, 279). In order to be able to study whether deviations in fetal growth are related to spontaneous preterm birth, it is necessary to study spontaneous and iatrogenic preterm birth separately. The issue of whether deviations from a normal fetal growth pattern are associated with spontaneous onset of preterm birth is not clear (280-282). When it comes to **fetal growth** in preterm infants, several studies during the last decade have resulted in convincing data indicating that intrauterine-derived growth standards should be used, since birth weight-derived growth standards are not representative of normal-weight infants born preterm (281-283).

In addition to intrauterine growth restriction, serious hypertensive disorders in pregnancy such as **preeclampsia** are the most common indications for iatrogenic preterm birth. Preeclampsia can be classified according to the gestational age at onset (284). Term preeclampsia is considered to be a mixture of conditions, whereas preterm preeclampsia is characterized by abnormal implantation and reduced utero-placental blood flow, causing fetal hypoxia and suboptimal nutrition, linking this condition to intrauterine growth restriction (284-287). Maternal and perinatal outcome are favorable in women developing mild preeclampsia after 36 gestational weeks, but less favorable in women developing the disorder before 33 gestational weeks (288).

Various maternal medical disorders, such as thyroid disease, asthma, diabetes, cardiac/cardiovascular disease, nephritis and chronic hypertension, are associated with increased risk of preterm birth, many resulting in iatrogenic delivery due to maternal complications during pregnancy (38, 223). An association with clinical depression has also been found, although results are inconsistent (223).

Cervical procedures such as cone biopsy or loop electrocautery excision, secondary to premalignant cervical disorders, have been associated with preterm delivery, an important

association to bear in mind when treating young women for cervical intraepithelial neoplasia (289, 290).

The problem of predicting preterm birth

Identification and management of high-risk patients and avoiding overtreatment of low-risk patients is an ultimate goal for all doctors working in clinical medicine. A high-quality risk predicting system can help in providing optimal management, in putting the right amount of effort and resources into treatment of the right patients and in facilitating counselling of patients and relatives. What is most needed in the field of preterm birth is a tool that makes it possible to detect a preterm delivery process in progress or assess a woman's risk given certain historical risk factors early in pregnancy (from gestational week 23-24, as this is the threshold of fetal viability). The early detection of preterm birth is difficult for a number of reasons. Most women who deliver preterm have no obvious risk factors and more than half of preterm births occur in low-risk pregnancies (291, 292). Only half of the women exhibiting signs of preterm birth actually deliver early. In other cases, the initial contractions stop without any intervention from the obstetrician, i.e. they are "false" contractions that do not affect the cervix. Furthermore, the initial symptoms and signs of preterm birth are often mild and are easily mistaken for signs and symptoms also occurring in uncomplicated, normal pregnancies. The clinical diagnosis is difficult and both risk assessment systems and diagnostic tests are needed to aid in the daily clinical care of these patients.

Huge efforts have been put into the development of both diagnostic tests and risk-scoring systems, but the results have been rather disappointing, so far. In general, predictive tests can be divided into two groups applicable in different clinical situations. Screening tests can be used to detect asymptomatic disease and diagnostic tests can be used in patients with symptoms. The former require high sensitivity and high negative predictive value and sufficiently low cost to be an option. Furthermore, an established intervention or treatment should be developed and available to patients that test positive. No such appropriate screening tool has been developed for the detection of preterm birth.

Risk-scoring systems

The numerous developed risk-scoring systems are the closest thing to a screening tool (293-301). According to a recent systematic review, a total of twelve risk-scoring systems for preterm birth have been created (302).These systems aim at identifying women at risk of preterm birth, based on obstetric history factors known to be associated with preterm birth. They are not as useful for nulliparas as for multiparas and substantial numbers of women considered to be at low risk actually give birth to preterm infants. No scoring system has been shown to be superior to clinical assessment (292). In otherwise asymptomatic women, the risk- scoring systems currently used in early pregnancy have a wide range of accuracy for predicting spontaneous preterm birth, lack evidence of good quality and cannot be recommended in clinical practice (302).

Home uterine activity monitoring

Home monitoring of uterine activity does not improve pregnancy outcome and does not reduce preterm birth proportions in high- or in low-risk women (303, 304).

Maternal salivary estriol

The serum level of estriol (E3) increases gradually during the second and third trimesters, with a typical surge preceding the onset of labor by 3 to 4 weeks in term, preterm and postterm pregnancies (305-307). These findings have been shown by both direct serum measurement of E3 and by measuring the salivary E3/progesterone ratio (308). The maternal salivary E3 level seems to correlate well with the serum level and it has been shown that elevated maternal serum E3 levels are associated with increased risk of preterm birth in asymptomatic and symptomatic women presenting for symptoms of preterm labor (308). E3's role in parturition is further strengthened by the findings that women with pregnancies prolonged beyond 42 gestational weeks, who had an increase in salivary E3, went into spontaneous labor to a greater extent than those who did not (309). It has been hoped that salivary E3 would prove to be a useful marker for preterm birth and delivery (304) and a diagnostic test has been developed and approved for clinical use (310); a positive test is associated with late preterm birth, which limits its clinical use (310). It also has low sensitivity and is currently mainly used in clinical settings due to its negative predictive value (i.e. women who test negative are at very low risk of preterm birth and no interventions are necessary) (310). This test is thus currently more useful for research than for clinical practice (310).

Fetal fibronectin and cervical assessment with sonography

These two tests are currently the most commonly used in clinical situations to determine the risk of preterm birth and they are, together with IL-6 testing in amniotic fluid, those with the best scientific evidence (311). Fetal fibronectin and vaginal sonography of the cervix have proven effective, by their high negative predictive values, in predicting which symptomatic women are actually at low risk of preterm birth (312-314). A negative test in a high-risk woman can prevent overtreatment and be reassuring, thus helping the clinician counsel the patient, but neither fetal fibronectin nor cervical sonography play a role in routine screening of women for preterm birth risk (315).

Fetal fibronectin is a glycoprotein produced by many cell types; it forms a part of and functions in maintaining the extracellular matrix by binding cells together (304). In the feto-maternal unit, it is produced by the trophoblasts (316) and is a normal finding in the placenta, fetal membranes and cervico-vaginal secretion during the first 20 weeks of gestation (317). It disappears and then reappears days before labor (304) and its presence in the cervico-vaginal secretion after 20 weeks of gestation has been identified as a predictor of spontaneous preterm birth (318). The mechanism linking fetal fibronectin to spontaneous preterm birth is unknown (304), but strong evidence has been found for a close link between upper genital tract infection and cervical and/or vaginal fetal fibronectin (319). This may imply that fetal fibronectin is secreted in states of disruption of gestational tissues. It has been shown that the test significantly reduces the preterm labor admissions, length of stay in hospital and prescriptions for tocolytic agents (320). A recent update of an older meta-analysis concluded that fetal fibronectin is an effective short-term marker of preterm delivery, especially in women with symptoms of preterm labor (321).

The old understanding of the cervical condition as a dichotomous variable-competence or incompetence-has changed as endovaginal sonography has advanced our understanding of the preterm birth syndrome (322). Funneling comprising 40-50% of the total cervical length or a persistently shortened cervix (<25-30 mm) have, in several studies, been associated with an increased risk of preterm birth (304, 312, 323-326). At present, there is growing consensus that the cervix functions along a continuum of competence (304), and that the safety, availability, patient acceptance and reproducibility of endovaginal sonography has made it an important investigational tool (322). A systematic review and meta-analysis concluded that endovaginal cervical ultrasonography appears to be an effective predictor of preterm birth in

patients with symptoms of preterm labor (327). There is agreement that the best time to examine patients with this method to estimate their preterm birth risk is between 18 and 28 gestational weeks (304). Before 18 weeks the cervix is difficult to differentiate from the rest of the uterus, and in the third trimester some degree of funneling at the internal cervical os is probably normal (326).

None of the above-mentioned risk classification systems or diagnostic tests can presently be used to screen for preterm birth early in pregnancy in asymptomatic women. Although this is rather disappointing, there are some hopes for the future. Promising risk-scoring systems for other adverse obstetric outcomes have been developed (328, 329) and there is also interest in developing multiple-marker tests for preterm birth by combining historic risk-scoring data with both old and new biological markers, thus increasing our ability to predict spontaneous preterm birth (330-332).

Models for understanding the mechanisms of spontaneous preterm birth

Our present understanding of etiological factors, pathogenetic mechanisms and their relationships to clinical signs and symptoms in spontaneous preterm birth can be summarized as in the figure presented by Buhimschi et al (Figure 3). The etiological factors (white) are incomplete and we have an idea about the different pathogenetic mechanisms (grey), but it is the signs and symptoms (black) that we see in the clinical setting.

Spontaneous preterm birth, inflammation and infection

It has been suggested that microbial invasion of the amniotic cavity is one of the most important factors associated with preterm birth (333-335). Cytokine concentrations in the amniotic fluid are significantly higher in preterm delivery than in term labor. IL-1, IL-6, and tumor necrosis factor (TNF)- α are capable of inducing COX-2 gene expression, leading to elevated prostaglandin concentrations and uterine contractions (336, 337). The importance of TNF-α is enhanced by its dual role in pPROM, a condition predisposing to preterm delivery and associated with 30-40% of all preterm deliveries. AA have a more than two-fold higher risk of preterm birth than Caucasians, and pPROM is more likely to precede spontaneous preterm birth in AA (159, 160). These observations suggest that, in addition to known environmental and medical risk factors, as yet unidentified biological factors may contribute to the risk of preterm birth.
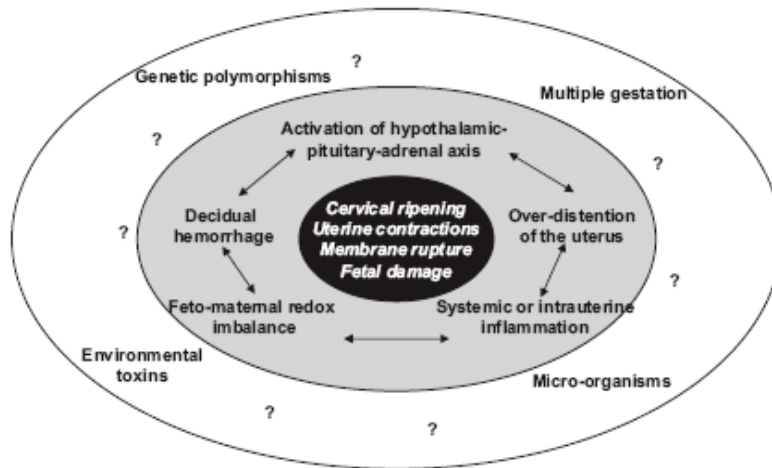
Figure 3 Schematic model of the etiological factors (white) that, through activation of pathogenetic mechanisms (gray), induce signs and symptoms (black) that together characterize the clinical entity known as preterm birth. (Reproduced with permission from Lippincott Williams & Wilkins. Buhimschi et al, Obstet Gynecol Surv 2006, 61: 543-553)

Other pathophysiological pathways

The most investigated of the suggested pathways to spontaneous preterm birth is the inflammatory axis, very briefly described above: the hypothalamic pituitary adrenal (HPA) pathway, the pathological uterine distension pathway and the decidual bleeding pathway are others.

It is hypothesized that parturition starts from activation of the maternal or fetal **HPA axis**. CRH is the principal regulator of the HPA axis. CRH is synthesized by the adrenal medulla, testes, ovaries, gastrointestinal tract and pancreas. It has been suggested that this pathway is activated by maternal stress, intrauterine growth restriction and elevated maternal cortisol levels. During human pregnancy, the CRH gene is also expressed in the placenta and membranes, and results in exponentially increased production and release of placental CRH into both maternal and fetal compartments during the course of gestation (338). There is no information regarding polymorphisms in the estrogen, progesterone or CRH genes in relation to spontaneous preterm birth. However, there are changes in the mRNA and protein levels related to the parturition process.

Pathological **uterine distension** is associated with PTL and pPROM. It is the result of either an abnormal increase in intrauterine volume, as in multifetal gestations and polyhydramnios, or of limited uterine expansible capacity, as seen in women with T-shaped uteri. One suggested mechanism is that acute stretching of myometrial cells is associated with increased expression of myometrial gap junctions (mediated by connexin 43) and cellular contact zones that are required for propagation and synchronization of uterine contractions (339, 340). Polymorphism in this region may affect its affinity to bind to regulatory proteins and, hence, expression of connexin 43, which may in turn affect an individual's susceptibility to develop PTL in the presence of pathological uterine distension.

Disruption of placental **vascular flow and decidual hemorrhage** have been proposed as a possible pathophysiological pathway leading to the activation of uterine contractility before term and, possibly, preterm birth (341).

The link between intrauterine infection, neonatal brain damage and cerebral palsy
It has previously been hypothesized that proinflammatory cytokines, such as IL-1, IL-6 and TNF–α, might be the biological substances linking prenatal intrauterine infection and neonatal brain damage through a fetal inflammatory response (342). The infectious and inflammatory axis of the preterm birth mechanisms is the most explored and the only mechanism for which a causal role has been established (254). The two subgroups of spontaneous preterm birth, PTL and pPROM, are both associated with a higher risk of intra-ventricular hemorrhage, peri-ventricular leukomalacia (343) and CP (344). It has also been suggested, based on previous smaller studies, that infants born after spontaneous preterm delivery are at increased risk of developing CP or neurological impairment, compared to infants born after iatrogenic preterm delivery (35, 345-348). There is, however, no documentation for such an association in a population-based setting. Authorities in the field are reluctant to unequivocally state that inflammation causes brain damage, despite rather consistent epidemiological observations that support the contention that infection, inflammation and neonatal brain damage are associated (349). The main reason for this reluctance is the lack of convincing evidence that inflammation actually precedes the brain damage (349). Clarification of these essential connections in the causal axis might open up the possibility for the creation of drugs that modify the inflammatory response as a strategy to reduce brain damage and disabilities (350).

Treatment and prevention strategies

The precise mechanisms underlying normal human labor are unclear, as is the pathophysiology of preterm labor and delivery (19). Current management of this problem is symptomatic rather than causal and the previously described limited prediction possibilities complicate further the generation of prevention and treatment strategies. Treatment and prevention strategies are possible at three levels: 1) primary prevention/public health prevention, directed at all women of reproductive age, 2) secondary prevention, aimed at reducing existing risk and 3) tertiary prevention, aimed at treating women at immediate risk (351). The ultimate goal for all these treatment strategies is to reduce both morbidity and mortality in preterm-born infants.

1) Primary prevention/public health prevention directed at all women of reproductive age
Primary prevention can be implemented both before and during pregnancy and may include public education programs; public and professional policies, such as reducing the number of high-order multiple pregnancies; smoking cessation programs; reducing pregnant women's workloads and increasing services to improve access to prenatal care (351). Many of these issues have already been addressed in the Scandinavian countries. The most successful example of this type of effort is the French national policy from the 1970s that resulted in a significant reduction of preterm birth, including those at <32 weeks, during 1971-1981 (135). As previously mentioned, authorities in the field have stated that public health interventions have so far proven to be the most beneficial initiative in the prevention and treatment of preterm birth (1).

2) Secondary prevention aimed at reducing existing risk
Methods of prevention and treatment include antibiotics, progesterone and cervical cerclage. Conflicting evidence exists for preventing preterm birth by treating abnormal vaginal flora with **antibiotics**, despite the infectious and inflammatory mechanism for spontaneous preterm birth being the only pathophysiological pathway for which proof of evidence exists (272). Bacterial vaginosis has attracted the most interest among infectious conditions contributing to preterm delivery. A recent Cochrane review (352) found that treatment of bacterial vaginosis in women with a previous preterm birth may reduce the risk of pPROM and LBW while another contemporary systematic review (353) failed to show any benefit. There seems to be

no evidence that treating all pregnant women with asymptomatic bacterial vaginosis will prevent preterm birth and its consequences (352). It is uncertain whether treatment of other vaginal infections yields any benefit; antibiotics do not seem to have the desired effect (354). However, the ORACLE I study indicated favorable outcomes, including a significant prolongation of pregnancy and improved neonatal outcome, in women treated with erythromycin after pPROM (355). In contrast, the ORACLE II found no benefit to administering antibiotics to women in spontaneous PTL without evidence of clinical infection (356).

Progesterone's role in the treatment and prevention of preterm birth is still uncertain. It has been advocated for the last 50 years for the prevention of preterm birth because of its role in maintaining pregnancy (357), but interest vanished as evidence accumulated for the infectious and inflammatory mechanisms, according to which preterm labor is more likely to be caused by infection than by hormone deficiency, at least in singleton pregnancies (254). A Cochrane meta-analysis from 2005 showed that intramuscular progesterone is associated with a reduction in risk of preterm birth before 37 gestational weeks (358). This meta-analysis is, however, based on few studies with very few patients. The focus of current research on progesterone has been its efficiency in high-risk, asymptomatic patients. Two recent studies yielded conflicting results, i.e. no effect on preterm birth in twin gestations (359) but a reduced rate of spontaneous early preterm delivery in women with short cervices (360). Further research is necessary and several randomized trials are underway to clarify the efficacy and fetal safety of progesterone treatment (361).

Cervical cerclage is an old, easily performed procedure for treatment of true cervical incompetence. Diagnosis of cervical incompetence is difficult and may be one reason that this procedure remains one of the more controversial surgical interventions in obstetrics (362). Despite its long history, sparse evidence for its efficiency has been produced (362). There is, however, apparently agreement that high-risk patients with previous risk factors or short cervices might benefit from the procedure (19, 362, 363). Cerclage is not indicated in low-risk patients (363). It is, however, promising that some small recent studies suggest that emergency cerclage in combination with antibiotics, tocolysis and bed rest may be more effective than was previously thought; neonatal survival of up to 96% with cerclage, compared to 57% without, was reported (364, 365).

3) Tertiary prevention aimed at treating women at immediate risk

Acute prevention includes administration of tocolytic agents and corticosteroids to patients presenting at delivery units for symptoms of preterm labor. The tocolytic agents are administered in order to delay labor, thus granting the physician time to determine if preterm labor is related to a specific medical condition or if it is idiopathic. Additional benefits of delaying delivery may be derived from administration of corticosteroids that may enhance fetal lung maturity and/or from transfer to a tertiary center better equipped to care for a preterm infant. Delaying delivery also allows time for initiation of, and benefit from, other necessary treatments, such as antibiotics, and for additional examinations, such as amniocentesis. However, the strategy of delaying delivery has never been shown to improve outcome more than that of exclusively administering steroids (357).

Historically, **β2-adrenerigic agonists**, such as terbutaline and ritodrine, have been the most widely used tocolytic agents in clinical practice (366). They are effective in delaying delivery for 48 hours, but this short period of time has no proven effect on perinatal mortality or morbidity (367). Long-term tocolysis with oral terbutaline for maintenance therapy after intravenous treatment for threatening preterm labor has not proven effective either (368). The major drawback of β2-adrenerigic agonists in the clinical setting is their unpleasant and potentially serious cardiovascular, metabolic and neuromuscular side effects (19). Recently, atosiban became the first **oxytocin antagonist** approved for treatment of threatening preterm labor. It has been shown to be at least as effective as the betamimetics, with a much lower frequency of side effects (369, 370). Several other substances, such as nifedipine, indomethacin and magnesium sulphate have been used (19), but less frequently than those described above.

Routine administration of **corticosteroids** (betamethasone or dexamethasone) to women presenting with threatening preterm labor at gestational age <34 weeks has reduced mortality, respiratory distress syndrome and intra-ventricular hemorrhage in preterm infants (371) and may be one of the most important factors contributing to the improved results in preterm birth management reported from Scandinavia (10).

Corticosteroids and public health efforts are definitely the most beneficial interventions thus far. However, options are limited and increased interest in understanding the mechanisms of

preterm labor will hopefully elucidate new strategies for treatment and prevention, helping to direct the right treatment to the patients at the highest risk.

AIMS OF THE STUDY

The general aim of these studies was to describe, assess and explore public health aspects of preterm birth by using Scandinavian population-based data from the Swedish, Danish and Norwegian Medical Birth Registers and the Swedish Hospital Discharge Register.

The specific aims were:

- to report the proportion of preterm birth in Sweden between 1973 and 2001, to estimate the contribution of each subgroup of preterm birth to the total preterm birth proportion between 1991 and 2001 and to assess possible risk factors related to each subgroup.

- to evaluate the association between spontaneous preterm birth and deviations from expected fetal weight by using an intrauterine-derived growth standard, to describe the incidence of small for gestational age among all preterm infants in Sweden and to present differences in the occurrence of this diagnosis between the spontaneous and iatrogenic preterm birth groups.

- to test the concept of a defined reference population and to evaluate if this simple model could be used for international comparison of preterm delivery proportions.

- to assess whether an association between spontaneous preterm birth and cerebral palsy could be demonstrated in a population-based setting by testing the hypothesis that infants born after spontaneous and iatrogenic onset of preterm birth differ in terms of perinatal, neonatal and long-term neurological outcome.

- to identify the most important clinically available predictive variables for spontaneous preterm delivery from high-quality, register-based data, to apply a previously tested model developed for other obstetric outcomes, to assess whether spontaneous preterm delivery can be predicted and to validate the final models in a test sample.

MATERIAL AND METHODS

Data sources

The Swedish Medical Birth Register

The SMBR was the main data source for all five papers in this thesis. The SMBR was established after an act of the Swedish parliament and has been maintained by the National Board of Health and Welfare since 1973. The basic structure of the register has remained unchanged since 1973, but content and methods of data collection have undergone some modifications. From 1973 until 1982, the register was based on Medical Birth Reports (MFM=Medicinskt Födelsemeddelande in Swedish), written by secretaries at the departments of obstetrics, summarizing information from medical records on a standardized form. After an evaluation of the SMBR in 1976, major changes in data collection were proposed and implemented, beginning in 1982. Medical records were abandoned as a basis for register data. Instead, three standardized record forms used at all antenatal clinics (MHV1), all delivery units (FV1) and at all pediatric examinations of the newborn infant (FV2) were and are still used. Data collection is undertaken prospectively by the staff responsible for patient care; it is started at the first antenatal appointment, forwarded to the National Board of Health and Welfare and computerized. Furthermore, the use of these documents eliminates uncertainty in data transfer to the SMBR. Some minor changes in register content were made in 1990, 1994 and 1998. A flowchart for the SMBR is outlined in Figure 4.

The SMBR is validated annually against the National Population Register, using the mother's and infant's unique personal identification numbers, and contains data on more than 99% of all births. Several quality analyses of the register have been performed (372, 373).
The SMBR contains information on birth weight, gestational age, smoking habits, socio-demographic factors and complications during pregnancy, delivery and the neonatal period. Information on maternal smoking in early pregnancy is available from 1983 and onwards.
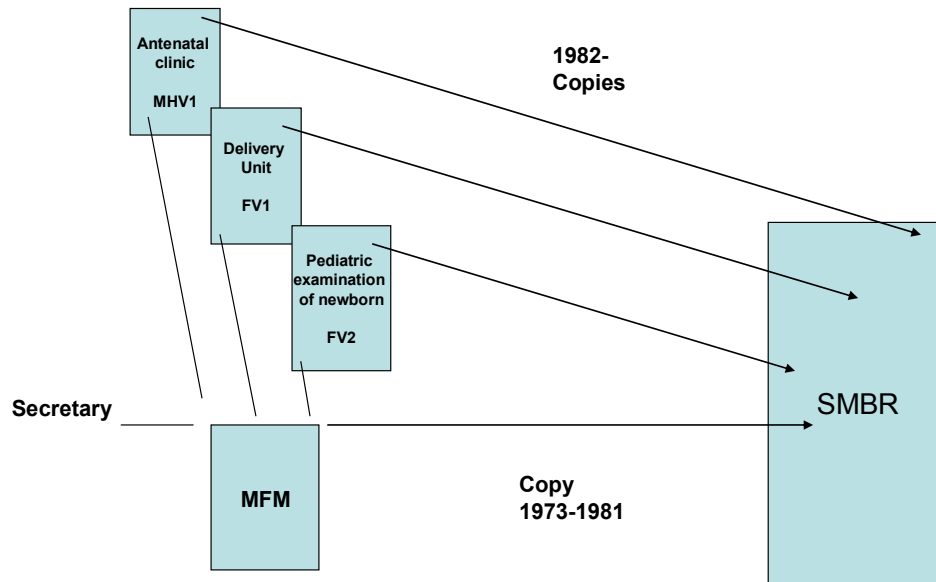
Figure 4 Flowchart for the SMBR (Reproduced with permission from Informa Healthcare, Taylor and Francis. Cnattingius et al, Scand J Soc Med 1990, 2: 143-148)

The Swedish Hospital Discharge Register

Data from The Swedish Hospital Discharge Register (SHDR) was used in Paper IV. The personal identification number given to every Swedish resident at birth made it possible to link the SHDR to the SMBR. The SHDR is maintained by the National Board of Health and Welfare and contains information concerning all in-patients treated in public health care institutions in all of Sweden, since 1987. Public health care comprises the vast majority of all health care in Sweden. The SHDR database contains detailed information about the patient (personal identification number, sex, age and county of residence), institution (hospital, department), administrative data (date of admission, date of discharge, treatment duration) and medical data (main diagnosis, other diagnoses, operation codes and accidents or intoxications) registered as ICD, Procedure or E-codes. The SHDR has been validated and found to be reliable (374).

The Danish Medical Birth Register

Data from the Danish Medical Birth Register (DMBR) was used in Paper III. The DMBR was established in 1968 and is maintained by the Danish Board of Health. Today, data on pregnancy, delivery and complications during pregnancy and delivery are available from

1973. From 1973 to 1995 the collection of data was based on submission of written forms to the Board of Health. Since 1995, all births in hospitals are electronically reported to the DMBR through the National Patient Register. Stillbirths and home deliveries are still reported on written forms. The DMBR is created by linkage of four national registers (the National Patient Register, the Civil Registration System Register, the IVF Register and the Cause of Death Register), using the mother's personal identification number. A quality analysis of all births registered during one day has been conducted (375).

The Norwegian Medical Birth Register

Data from the NMBR was used in Paper III. The register was established in 1967 by the Directorate of Health and was the first national medical birth register. The NMBR is based on compulsory notification of all live births and stillbirths from 16 weeks of gestation. A standardized notification form is used to collect data on demographic variables, maternal health before and during pregnancy, previous reproductive history, complications during pregnancy and delivery and pregnancy outcomes. This form was almost unchanged from 1967 until 1999, with the exception of addition of the Apgar score in 1978. Beginning in 1999, a completely new and more detailed form was introduced in which smoking and ultrasound gestational age determination were included. All records in the NMBR are matched with the files of the Central Person Register, ensuring medical notification of every newborn in Norway (376). The NMBR contains information on almost all births in Norway.

Material

The study populations in the individual studies in this thesis differ.

In the first part of **Paper I,** focusing on the proportion of preterm births in Sweden**,** all births occurring in Sweden from 1973 to 2001 and registered in the SMBR were included. The total population was 2 902 738 deliveries. Cases of unknown gestational age were excluded, leaving 2 891 811 (99.6%) and 2 620 242 (90.3%) deliveries for analysis, according to the two methods of gestational age determination, best estimate and LMP, respectively.
In the second part of **Paper I,** in which subgroups of preterm birth, including multiple births, unknown type of onset, IUFD and congenital malformations, were assessed, inclusion was restricted to 1991-2001 as type of onset of delivery-spontaneous or indicated- has been

registered in the SMBR since late 1990. The population consisted of 1 076 851 singleton births and 16 355 multiple births.

In **Paper II,** the included population consisted of all singleton births in Sweden occurring during the period 1991-2001 and registered in the SMBR. Cases of IUFD and congenital malformations were excluded as well as those with unknown type of birth onset and unknown gestational age. The total population consisted of 1 076 851 singleton births and 1 007 648 singleton births remained in the population for analysis after the exclusions. During the study period, 46 726 preterm infants were born and 501 infants were excluded due to missing information on birth weight, leaving 46 225 preterm infants for the final analysis.

In **Paper III,** all live births and stillbirths ($\geq$ 28 weeks) registered in the Medical Birth Registers of Sweden, Denmark, and Norway from 1995 to 2004 were included. The total population undergoing analysis constituted 2 111 014 deliveries, of which 912 227 (43.2%) were Swedish, 648 388 (30.7%) were Danish and 550 399 (26.1%) were Norwegian. Less than 1.5% of the total registered deliveries from 1995 to 2004 in the three Scandinavian countries were excluded due to missing gestational age or obvious misclassification.

In **Paper IV,** singleton births occurring in Sweden in 1991-2001 and registered in the SMBR were included. IUFD, congenital malformations and unknown type of delivery onset were excluded. The total population consisted of 1 076 851 singleton births. After exclusions, 1 010 487 singleton births, of which 46 726 were preterm, remained in the population for analysis. The preterm population consisted of 34 215 (73.2%) spontaneous preterm infants and 12 511 (26.8%) iatrogenic preterm infants.

In **Paper V,** and during the study period from 1992 to 2005, a total of 1 294 014 deliveries were registered in the SMBR after the initial exclusion of 15 121 iatrogenic preterm deliveries (<37 gestational weeks) and 1 861 deliveries at unknown gestational age. There were 17 130 twin deliveries and 53 531 spontaneous preterm deliveries at <37 gestational weeks, yielding a total spontaneous preterm delivery proportion of 4.1%. The corresponding proportion for spontaneous preterm delivery at <34 gestational weeks was 1.0%. The development (n=663 538) and test (n=630 476) samples had the same proportion of spontaneous preterm delivery at <34 and <37 gestational weeks, i. e. 1.0% and 4.1%, respectively. Information on some of the various explanatory variables were missing, which left us with a final

development sample of 429 733 singleton deliveries and a final test sample of 408 182 deliveries. The corresponding numbers for twin deliveries were 5 378 and 5 157, respectively. The proportions of spontaneous preterm delivery at <34 and <37 weeks were similar in the two samples: 0.9% and 3.8%, respectively.

Variables and methods

<u>*Definitions and general variables used in this thesis*</u>

Preterm birth

The definition of preterm birth used in this thesis is related to gestational age and defined by WHO as birth before 37 completed weeks or 259 days of gestation (377). In **Paper III**, this definition was further specified for standardization purposes as delivery occurring between 22 weeks + 0 days and 36 weeks + 6 days of gestation, as the three Scandinavian databases register the lower gestational ages to different extents.

Gestational age categories

The preterm population was divided into several gestational age strata. In **Papers I, II and IV,** data were categorized according to gestational age: <28, 28-31, 32-33 and 34-36 weeks. In **Paper I,** data concerning preterm deliveries at <34 and <37 weeks were presented as well, which was similar to the prediction of spontaneous preterm delivery in **Paper V**. In **Paper III**, data were presented according to gestational age: 22-27, 28-31, 32-36 and <37 weeks.

Gestational age determination

In the SMBR, the following sources are available for estimation of gestational age: (1) LMP, (2) corrected expected date of parturition according to LMP (the estimate made by the midwife at the antenatal care center, essentially based on LMP and menstrual cycle length), (3) expected date of parturition according to ultrasound and (4) estimated gestational age at birth reported by the delivery unit. By using these sources in hierarchical order, the best available estimate of gestational age for each infant is determined and designated best estimate. The available sources for estimating gestational age are presented in hierarchical order in Table 4.

Gestational age determination methods in hierarchical order

Code	Description
1	Expected date of parturition according to ultrasound supported by estimated gestational age at birth reported by the delivery unit. Expected date of parturition according to ultrasound is used.
2	Corrected expected date of parturition: the estimate made by the the antenatal care center midwife, essentially based on LMP and menstrual cycle length and supported by estimated gestational age at birth reported by the delivery unit. Gestational age determined by corrected expected date of parturition is used.
3	Gestational age determined by LMP and supported by estimated gestational age at birth reported by the delivery unit. Gestational age determined by LMP is used.
4	Only the estimated gestational age at birth reported by the delivery unit is registered. Gestational age estimated by the delivery unit is used.
5	Expected date of parturition according to ultrasound is in accordance with corrected expected date of parturition. Expected date of parturition according to ultrasound is used.
6	Expected date of parturition according to ultrasound is in accordance with gestational age determined by LMP. Expected date of parturition according to ultrasound is used.
7	Only expected date of parturition according to ultrasound is registered. Expected date of parturition according to ultrasound is used.
8	Only corrected expected date of parturition is registered. Corrected expected date of parturition is used.
9	Only gestational age determined by LMP is registered. Gestational age determined by LMP is used.
10	Only corrected expected date of parturition and gestational age determined by LMP are registered. If these two variables differ by no more than 7 days, then corrected expected date of parturition is used.

Several variables for gestational age determination are registered, but do not agree:

11	If information on gender or birth weight are missing or multiple gestation or cleaned malformation is registered, then gestational age is determined in the following hierarchical order: a) Expected date of parturition according to ultrasound b) Corrected expected date of parturition c) Gestational age determined by LMP d) Estimated gestational age at birth reported by the delivery unit
12	Least number of standard deviations between birth weight and expected birth weight, according to respective method of gestational age determination.

Table 4 Gestational age determination based on registered information in the SMBR. Only gestational age determinations of more than 139 days and less than 316 days are accepted as reasonable. Gestational age determinations based on code 12 require registered gestational ages of more than 181 days and less than 301 days. Estimated gestational age at birth reported by the delivery unit is to be regarded as supporting the other gestational age determinations if the respective ages differ by no more than 14 days. The other registered variables are to be regarded as supporting each other if the respective ages differ by no more than 7 days. (Reproduced with permission from Elsevier Limited. Morken et al, Am J Obstet Gynecol 2006; 195: 154-61)

In **Paper I,** LMP alone was also used to determine gestational age. In **Papers II-V**, when data from the SMBR was used and according to this method, the gestational age determined by ultrasound was preferred when available and not too incongruous with the other sources. The limits of incongruity are presented in Table 4. Cases with unknown gestational age were

excluded. To avoid erroneous estimates of gestational age, infants were excluded if their weight and length were $\geq$ 4 SD above the expected at the reported gestational age.

The method described above was used also in **Paper III**, for the Swedish data. In Denmark, the designated best clinical estimate of gestational age is based on information from obstetric records (including LMP and ultrasound data) and is reported to the National Patient Register immediately after delivery. In Norway, gestational age determination was based on LMP through 1998. Beginning in 1999, ultrasound-based estimation of gestational age has also been registered. In the case of Norway, we decided to use LMP only in the absence of gestational age determination by ultrasound. We decided to let best estimates for each individual country determine gestational age in this study and cases with unknown gestational age were excluded. In order to avoid obvious misclassifications of gestational age, deliveries were excluded in **Paper III** if the infants' birth weight and length exceeded 4 SD, according to national growth curves (283, 378).

Type of delivery onset and subgroups of preterm birth

Type of delivery onset has been registered in the SMBR since 1990, as spontaneous or induced labor or as cesarean section prior to contractions. The two latter groups were regarded as iatrogenic preterm births. In the presence of pPROM (ICD 9: 6581; ICD 10: O42), births were regarded as spontaneous preterm, regardless of the reported onset of labor. Mistakes in the distinction between PTL and pPROM are possible in a register-based setting and this distinction was therefore avoided in all these studies. The same variable was also registered in the Danish and Norwegian dataset during the study period from 1995 to 2004, and the above definitions were used in **Paper III** as well.

The onset of labor variable in the SMBR was validated using parts of a previously published dataset (379) in a small pilot study. We identified 52 patients from this dataset, of which six lacked the variable in the CP study. That left 46 patients for the pilot, 35 were identified as spontaneous onset and 11 patients had an iatrogenic onset, according to the SMBR. One of the 35 spontaneous onset deliveries, according to the register, was classified as iatrogenic onset in the CP study. Four of the 11 iatrogenic onset deliveries, according to the register, were classified as spontaneous in the CP study. Despite the fact that a small dataset was used to validate this variable, and that cases in the CP study were recruited from only one region of Sweden, we consider the onset of labor variable to be fairly reliable and feasible for use in these studies. Furthermore, it makes relying exclusively on ICD-codes avoidable. The fact

that onset of labor is registered by check box makes it more reliable than if only diagnoses had been used.

The onset of labor variable was used to distinguish between the two main subgroups of preterm birth, i. e. the spontaneous and iatrogenic subgroups. The other subgroups of preterm birth considered were multiple gestations, IUFD and congenital malformations.

Intrauterine fetal deaths

The SMBR does not register IUFD at < 28 weeks, so we had to use this threshold, as data in this thesis is primarily based on the register. Registered cases in which IUFD occurred at <28 weeks are clearly misregistrations.

Congenital malformations

In this study, congenital malformations were defined as cleaned malformations, i.e. excluding unimportant and banal diagnoses. The ICD 9 and 10 codes included in this definition are listed in Table 5.

Cleaned malformations	
Codes **ICD-9**	**Codes** **ICD-10**
740A - 743D;	Q000 - Q129;
743F - 744A;	Q140 - Q169;
744C - 744D;	Q171 - Q179;
744F - 747E;	Q183 - Q269;
747G - 752E;	Q271 - Q529;
752G - 754C;	Q540 - Q649;
754E - 754W;	Q657 - Q689;
755B - 759X;	Q691;
	Q700 - Q999;

Table 5 ICD-9, ICD-10 codes and diagnoses included in the definition of cleaned malformations.

Methods and variables used in each paper

Paper I

This paper describes the proportion of preterm birth in Sweden from the establishment of the SMBR in 1973 until 2001. In this study we used both best estimate and LMP as methods for gestational age determination. The proportion of multiple births occurring preterm during the same period of time is reported. We compared the risk of preterm birth during certain four-year periods with all other periods during 1983-2001 and reported the respective risks for gestational age <37 and <34 weeks. It was possible to stratify for parity, maternal age and smoking during these years, as smoking during pregnancy has been registered in the SMBR since 1983.

As a complement to the stratified analyses described above, logistic regression analyses were performed to evaluate a possible time trend as well as other risk factors for spontaneous preterm and medically indicated preterm birth, respectively. Cases with unknown smoking status were excluded.

Paper II

This paper assesses the association between spontaneous preterm birth and deviant fetal weight, by comparing spontaneous preterm infants to infants born after spontaneous labor at term. The gestational age used to define term for spontaneous-born infants was 37-42 weeks. Fetal weight was estimated using an **intrauterine-derived growth standard** with sex-specific growth curves, developed by Marsal and co-workers, based on ultrasonically estimated fetal weight (283). This growth standard is better suited for studying preterm infants than growth standards based on birth weight data. Birth weight-derived growth standards underestimate normal fetal weight during the preterm period, since preterm-born infants are SGA more often than term-born infants. Marsal and colleagues stated that the intrauterine-derived growth standard is better at revealing the true distribution of SGA fetuses and neonates, and they suggested its use in perinatological practice. This concept has been supported by a recent Canadian hospital-based cohort study of spontaneous preterm deliveries (281). Lackman and colleagues concluded that fetal growth curves are more appropriate for predicting the impact of birth weight category on the risk of spontaneous preterm delivery than neonatal growth standards.

Fetal weight was divided into **six classes** according to SD from expected birth weight (SD classes: **1)** <-3SD **2)** -3 to -2.1 SD **3)** -2 to -1.1 SD **4)** -1 to 0.9 SD, **5)** 1 to 1.9 SD and **6)** 2 to 2.9 SD). Infants with birth weight in SD class 4 were considered to be appropriate for gestational age and to have reached a birth weight corresponding to the expected population mean. Birth weight in one of the five other SD classes was considered to be deviant from expected fetal weight. Only SD classes 1, 2 and 6 have clinical implications in this Scandinavian population. We wanted to describe the whole distribution of deviant growth among spontaneous preterm infants and therefore considered SD classes 3 and 5 to be deviant growth as well. ORs with 95% CI for deviant fetal growth versus appropriate for gestational age in infants born after spontaneous preterm labor, compared to term infants, were obtained using multiple logistic regression analysis.

The following efforts were made in order to investigate possible erroneous estimates of gestational age in the subgroup of women giving birth to a **large for gestational age** child at 34-36 weeks. Infants were excluded if the expected date of birth according to ultrasound was more than one week later than the expected date of birth according to LMP. This exclusion was undertaken to clean the group when the two methods of gestational age determination diverged, and has no clinical implications. Infants were also excluded if information on LMP was lacking or if they were born before 37 weeks according to ultrasound but at term according to LMP. Furthermore, all cases with a maternal diagnosis of diabetes or gestational diabetes (ICD9: 6480, 6488; ICD10: O24) were excluded.

SGA was defined as birth weight below 2SD from the mean, in accordance with Marsal's curve (283). The occurrence of SGA in the two main subgroups of preterm birth, spontaneous and iatrogenic was compared with the occurrence of SGA in term infants born after spontaneous labor onset. Large for gestational age was defined as birth weight above 2SD from the mean, in accordance with Marsal's curve (283).

Paper III
This paper presents a new and very simple model for international comparison of preterm delivery proportions, i.e. defining a reference population. This model cleans the population of the most substantial risk factors and makes it possible to compare reference populations directly.

The proportion of preterm deliveries for each year in the three Scandinavian countries is presented according to above-mentioned gestational age groups and selected **risk factors**. The latter included the proportion of women not born in the respective country, IVF or ICSI, multiple gestations, primiparity, iatrogenic delivery and maternal age <20 and >35. Time trends were tested.

A **reference population** of pregnant women for each of the three countries was designed using the following criteria: 1) maternal age 20-35 at delivery; 2) primiparity; 3) spontaneously conceived pregnancy, i. e. excluding ART; 4) singleton pregnancy and 5) woman born in the respective country (citizenship at childbirth was used when country of birth was not available). The latter criterion was included to account for differences over time caused by immigration. The proportion of preterm deliveries according to gestational age in the reference population and the proportion of spontaneous preterm deliveries of the total number of deliveries in the reference population were presented for each country. Time trends for each of the different gestational age strata were tested for each country. Homogeneity of trends in the reference population's preterm delivery rate across the three countries was also tested.

Paper IV

In this study, spontaneous preterm births were compared to iatrogenic preterm births in terms of perinatal, neonatal and long-term neurological outcome. The personal identification numbers made it possible to link the SMBR to the SHDR. The linkage of these two registers was carried out for better assessment of long-term neurological outcome, as CP is often diagnosed after several years of life. The diagnoses were identified in the register using ICD 9 and ICD 10 codes.

The investigated **outcome variables** were: early neonatal death (0-6 days), neonatal death (0-27 days), infant death (0-364 days), sepsis, CNS disorders (including intra-ventricular hemorrhage, peri-ventricular leukomalacia and seizures or convulsions), infant respiratory distress syndrome, necrotizing enterocolitis, broncopulmonary dysplasia, retinopathy of the premature and CP.

ORs for early neonatal death, neonatal death and infant death, when spontaneous preterm birth was compared to iatrogenic preterm birth, were obtained by stratified analyses. ORs were controlled for gestational age at birth, maternal age, parity and smoking. For the remaining outcome variables, the possibility of confounding due to different survival rates in the study groups was suspected. Therefore, Hazard Ratios (HR) with 95% CI were computed using Cox analyses and adjustments were made for the same possible confounders as above. If data from the SMBR were used, date of discharge from hospital is registered and was used as date of diagnosis. When diagnoses stored in the SHDR were used, date of admission to the hospital the first time a particular diagnosis occurs was available and was used as date of diagnosis.

Paper V

In this paper, we use a statistical technique previously published by Smith and colleagues and developed for prediction of cesarean risk. It is applied to prediction of spontaneous preterm delivery at <34 and <37 gestational weeks. The singleton and twin pregnancies were randomly assigned to the development sample (mother's birth day odd) or the test sample (mother's birth day even).

Numerous combinations of predicting variables were tested. Each model was designed in the development sample and the predictive ability was validated by testing the model in the test sample. For obvious reasons, information utilizing details from previous pregnancies could not be evaluated in a model including primiparas. Also, information on infant gender could not be used in a model including twin pregnancies, in which case information on the gender distribution in the twin pair could be used instead (male-male, female-female, or male-female). Thus, in order to optimize prediction of spontaneous preterm delivery, we developed 6 different models: **Model 1** utilizes information available for all women, regardless of parity and plurality; **Model 2** utilizes information available for all multiparas, regardless of plurality; **Model 3** utilizes information available for all singleton pregnancies, regardless of parity; **Model 4** utilizes information available for all singleton pregnancies in multiparas; **Model 5** utilizes information available for all twin pregnancies, regardless of parity and **Model 6** utilizes information available for twin pregnancies in multiparas. Spontaneous preterm delivery at <34 and <37 gestational weeks constituted the dependent variables when fitting the multiple logistic regression models using data from the development samples. Twenty-

nine variables were considered and evaluated for inclusion as independent variables; twenty qualified in any of the final models and are listed in Table 6.

Table 6 Variables that qualified in any of the six developed prediction models.

Variable
Maternal age at delivery
Maternal smoking
Maternal BMI
Maternal height
Discrepancy between expected date of parturition according to LMP and ultrasound (days)
Duration of infertility (years)
Fetal Downs syndrome
Fetal major heart anomalies
Fetal neural tube defects
Fetal major kidney anomalies
Vaginal bleeding in early pregnancy
Maternal diabetes
Fetal gender
Gender distribution in twin pair
Previous spontaneous abortion
Maternal chronic hypertension
Interval since last delivery (years)
Parity one
Gestational age at last delivery
Twin pregnancy

Maternal urinary tract infection and *type of delivery onset* were not associated with spontaneous preterm delivery and were not included. Similarly, 5-minute *Apgar score at last delivery* and *plurality (singleton or twins)* were either not used or not significantly associated with the outcomes. *ART* was significant in the univariate analyses but not in the multivariate settings. In univariate analyses, women from the Middle East or Far East Asia, respectively, appeared to be at increased risk of spontaneous preterm birth. This risk increase disappeared when maternal height was added to the model and *ethnicity* was not included. *Mother not living with father* seemed to be negatively associated with spontaneous preterm delivery. As this relationship was unlikely to be causal, the variable was not included in the final models. *Maternal gestational age* and *maternal birth weight* were also considered, but data was only available for a minor subset of the population, resulting in the exclusion of these variables as well.

The included continuous variables in the multivariate logistic regression models were assessed for linearity in the log odds scale and higher order terms were added when appropriate (maternal age, BMI and interval since last delivery). Each model was tested for goodness-of-fit with the Hosmer-Lemeshow test.

The output of the final fitted multiple logistic regression models was used as previously described in detail by Smith and colleagues in their prediction model for cesarean section risk (328). Using this statistical technique, the output of the multiple logistic regression models was converted into likelihood ratios (LR), briefly summarized as follows: 1) an optimal replacement constant was estimated for the included independent variables in the logistic

regression model, to be used when information on the variable was lacking (x1, x2 etc is lacking); 2) The LRs were adjusted by assessing the difference between the replacement constant and the actual "overall log odds" for the outcome in the development sample; 3) the above steps were repeated for each included independent variable and the output was used to calculate adjusted LRs for the outcomes (spontaneous preterm delivery at <34 and <37 gestational weeks) for every woman in the development sample. The final models were then validated by calculating the area under the receiver operator characteristic (AU-ROC) curve with 95% CI for assessment of predictive ability in the test sample.

Finally, for every delivery in the test population, the model that utilized the available information from each individual to the greatest extent was used to calculate a total AU-ROC curve for spontaneous preterm delivery at <34 and <37 gestational weeks.

Study design
In general terms, the studies in this thesis could be described as **historical cohorts,** as the cohorts were identified from recorded information stored in national registers and the time during which they were at risk occurred before the beginning of the studies.

Nevertheless, the designs of the respective studies can also be described as follows:

Paper I: Nationwide population-based register study.
Paper II: Nationwide population-based register study.
Paper III: Multinational population-based register study.
Paper IV: Nationwide population-based register study.
Paper V: Nationwide population-based register study.

The national birth registers in Sweden, Denmark and Norway are population-based, as all births from a given time period are intended to be included. It is intention rather than performance that defines the term population-based (380).

Ethical considerations and approvals

All the studies in this thesis were considered for ethical approval by the requisite ethics committees prior to start. The data were registered in national databases and raw data files were used so that no single person was identified.

The local ethics committee at Sahlgrenska University Hospital/Östra, Göteborg, Sweden, approved the studies presented in **Papers I, II and IV** (Reference number Ø 562-02 and Ø 632-02). The study presented in **Paper III** was approved by the ethics committee in Göteborg (Reference number: Göteborg 091-06). In Denmark and Norway, this study was exempt from such approval. The ethics committee in Göteborg also approved the study presented in **Paper V** (Reference number: Göteborg 258-07). The Swedish National Board of Health and Welfare approved the use of data from the SMBR and the SHDR.

Statistics

The statistical methods used in this thesis were either based on frequentistic (stratified, regression and survival analyses) or Bayesian theory.

Stratified analyses

The stratified analyses were performed and ORs calculated using Mantel–Haenszel's technique (381). Ninety-five percent CIs were estimated with Miettinen's method (382). In **Paper I**, ORs were stratified for maternal age, parity, and smoking. In **Paper IV**, ORs were stratified for gestational age at birth, maternal age, parity, and smoking.

Regression analyses

Multiple logistic regression analysis was performed in **Paper I** as a complement to the stratified analyses. Several multiple logistic regression models were tested to determine the simplest model with the best available fit. In the final models, year of birth (1-year classes were entered: the results are shown as 18-year increase or 5-year increase, respectively), maternal age (5-year increase) and maternal smoking (1=nonsmoking, 2=1–10 cigarettes/day and 3=more than 10 cigarettes/day) were entered as continuous variables, whereas parity (parity 2 or 3, and parity 4+) were entered as class variables and compared to parity 1.

In **Paper II,** multiple logistic regression analysis was performed. One SD class was used as the dependent variable, with gestational age as the independent variable, in each analysis. Adjustments were made for year of birth (continuous independent variable), maternal age and maternal age^2 (continuous 5-year classes), parity (class variables 1, 2, 3, 4+) and maternal smoking (0, 1-10, or ≥ 10 – as a continuous independent variable).

In **Paper III,** the reported p-values for trend were obtained from simple logistic regression analysis with the dichotomized variables specified as outcome variables and year of birth as the only independent variable. P-values <0.05 were considered to be statistically significant. To test for homogeneity of the ORs across the three local estimates (OR_i), the log (OR_i^*):s were weighted according to precision to compute a pooled estimate (OR_m): $OR_m^* = \exp(\Sigma \, (w_i \, (\log(OR_i^*)) \, / \, \Sigma w_i \,)$, $w_i = 1/V(\log(OR_i^*))$, and the test statistics used were $X_i = (\Sigma \, (w_i \, (\log(OR_i^*) - \log(OR_m^*))^2$, which was compared to the $\chi^2(2)$ – distribution.

In **Paper V**, we fitted six final multiple logistic regression models. P-value for significance after univariate assessment and for inclusion of variables into the multivariate model was set at <0.20. Significance level for acceptance of variables in the multivariate setting was 0.10, unless clinical arguments for acceptance were obvious.

Survival analyses
For the remaining outcome variables in **Paper IV**, the possibility of confounding due to different survival rates between the study groups was suspected. Therefore, HRs with 95% CI were computed using Cox analyses and adjustments were made for gestational age at birth, maternal age, parity and smoking.

Bayesian methods
The output of the logistic regression models in **Paper V** were converted into adjusted LRs, using a novel method of Bayesian modeling, previously described by Smith and colleagues (328), and applied on a different obstetric outcomes. The adjusted LRs were then used to estimate the risk of spontaneous preterm delivery in the test sample.

REVIEW OF PAPERS

Paper I

Preterm birth in Sweden 1973-2001: rate, subgroups and effect of changing patterns in multiple births, maternal age and smoking

Background: The objectives of this report are to evaluate changes in the preterm birth proportion in Sweden in1973-2001 and to report on the proportion of spontaneous and indicated preterm births and assess risk factors for these preterm birth subgroups during the period from 1991 to 2001.

Methods: A population-based register study of all births occurring in Sweden from 1973 to 2001 registered in the Swedish Medical Birth Register was designed. The analysis of subgroups was restricted to the period 1991-2001. Gestational age was calculated using last menstrual period and best estimate. The odds ratio for preterm birth related to risk factors was calculated for the subgroups spontaneous and indicated preterm birth.

Results: After an increase in the beginning of the eighties, the preterm birth proportion decreased from 6.3% in 1984 to 5.6% in 2001 (p<0.0001). The proportion of preterm multiple births of the total birth proportion increased from 0.34% in 1973 to 0.71% in 2001 (p<0.0001). Spontaneous preterm births account for 55.2% and iatrogenic preterm births for 20.2% of all preterm births. The strongest association with maternal smoking in early pregnancy was found for gestational age <28 weeks and spontaneous preterm birth (OR smoking versus no smoking: 1.55, 95% CI: 1.42-1.69). The strongest association with maternal age was found between gestational age <28 weeks and indicated preterm birth (OR five-year-increase: 1.34, 95% CI: 1.21-1.47).

Conclusions: The preterm birth proportion in Sweden has decreased since the mid-eighties. The proportions of different subtypes of preterm birth in a Scandinavian low-risk population seem to be similar to those in populations with higher incidences of preterm birth and perinatal infections.

Paper II

Fetal growth and onset of delivery: a nationwide population-based study of preterm infants

Morken NH, Källén K and Jacobsson B. Am J Obstet Gynecol 2006; 195: 154-61.

Background: The objective was to assess whether deviations from normal fetal growth are associated with spontaneous preterm delivery.

Methods: A population-based study was performed, using Swedish Medical Birth Register data from 1991-2001. The total population comprised 1 007 648 singleton births. Intrauterine-derived growth standards were used to identify individual standard deviations from expected birth weight. Spontaneous preterm infants were compared to infants born after spontaneous labor at term. Results were obtained using multiple logistic regression analysis.

Results: Associations between smaller than population mean and spontaneous preterm birth were evident for all gestational age groups. The largest risk was found at 28-31 gestational weeks and birth weight <-3SD (OR: 13.3; 95% CI: 10.3-17.2). Spontaneous preterm infants born at 34-36 gestational weeks weighed 1-1.9 SD (OR: 1.1; 95% CI: 1.1-1.2) or 2-2.9 SD (OR: 1.6; 95% CI: 1.5-1.7) above the expected mean more often.

Conclusion: Deviation of fetal growth from the expected mean is associated with spontaneous preterm delivery.

Paper III

Reference population for international comparisons and time trend surveillance of preterm delivery proportions in three countries

Morken NH, Vogel I, Källén K, Skjærven R, Langhoff –Roos J, Kesmodel U, Jacobsson B. In manuscript.

Background: International comparison and time trend surveillance of preterm delivery proportions is complex. New techniques that might facilitate interpretation of these proportions are needed.

Methods: We studied all live births and stillbirths (≥ 28 weeks gestation) registered in the medical birth registers in Sweden, Denmark and Norway from 1995 through 2004. Gestational age was determined by best estimate. A reference population of pregnant women was designed using the following criteria: 1) maternal age 20-35, 2) primiparity, 3) spontaneously conceived pregnancy, 4) singleton pregnancy and 5) mother born in the respective country. National preterm delivery proportion, preterm delivery proportion in the reference population and spontaneous preterm delivery proportion in the reference population were calculated for each country.

Results: The total national preterm delivery proportion (<37 completed gestational weeks), increased in both Denmark (5.3% to 6.1%, p<0.001) and Norway (6.0% to 6.4%, p=0.006), but remained unchanged in Sweden, during 1995-2004. In Denmark, the preterm delivery proportion increased significantly in the reference population (5.3% to 6.3%, p<0.001) and the spontaneous preterm delivery proportion in the reference population (4.4% to 6.8%, p<0.001). No similar increase was evident in Norway. In Sweden, proportions in the reference population remained stable.

Conclusions: Reference populations can increase perspectives and thus contribute to explanations for changing preterm delivery proportions. The model also permits comparisons over time. This model may prove, in its simplicity, to be a valuable supplement to assessments of national preterm delivery proportions for public health surveillance purposes.

Paper IV

Outcomes of preterm children according to type of delivery onset: a nationwide population-based study.

Background: The objective of the study was to investigate whether spontaneous and iatrogenic preterm births are associated with different pediatric outcome.

Methods: A nationwide population-based study comprising 1 010 487 singletons was designed. Swedish Medical Birth Register and Swedish Hospital Discharge Register data from 1991-2001 were used. Intrauterine fetal deaths, unknown type of delivery onset and congenital malformations were excluded. Neonatal, perinatal and long-term neurological outcome were studied. Spontaneous preterm births were compared to iatrogenic preterm births. Odds ratios and hazard ratios for outcome variables were obtained using the Mantel-Haenszels technique and Cox-analyses, respectively. Adjustments were made for gestational age at birth, maternal age, parity and smoking.

Results: Spontaneous preterm infants and iatrogenic preterm infants constituted 73.2 % (34 215) and 26.8 % (12 511) of the preterm population, respectively. Spontaneous preterm infants were at increased risk of cerebral palsy at gestational age 28-31 weeks (HR: 1.86; 95% CI: 1.12-3.10) and of sepsis at gestational age 32-33 weeks (HR: 1.58; 95% CI: 1.28-1.96). Other outcome variables were associated with iatrogenic preterm birth, particularly respiratory and gastrointestinal diagnoses.

Conclusion: Spontaneous preterm birth and iatrogenic preterm birth are associated with different pediatric outcomes.

Paper V

Prediction of spontaneous preterm delivery by combining logistic and Bayesian methods

Morken NH, Källén K and Jacobsson B. In manuscript.

Background: The objectives were to develop prediction models for spontaneous preterm delivery, to assess if spontaneous preterm delivery can be predicted by combining logistic regression and Bayesian methods and to validate the models in a test sample.

Methods: Singleton and twin pregnancies with spontaneous onset of delivery during 1992-2005 in Sweden, registered in the Swedish Medical Birth Register, were included and randomly assigned to a development or a test sample. Predictive variables were identified by using multiple logistic regression analysis and outputs were used to calculate adjusted likelihood ratios. The predictive ability was validated in the test population.

Results: The development and test samples were similar in terms of the outcome and the independent variables. Six final models were developed and the area under the receiver operator curve in the test population ranged from 0.77 (95% CI: 0.76-0.77) to 0.59 (95% CI: 0.57-0.61) for spontaneous preterm delivery at <37 gestational weeks and from 0.80 (95% CI: 0.79-0.81) to 0.64 (95% CI: 0.62-0.67) for spontaneous preterm delivery at <34 weeks. For each delivery in the test population, the model that utilized the available information to the greatest extent was used, and total area under the receiver operator curve for spontaneous preterm delivery at <34 weeks (0.74, 95% CI: 0.73-0.75) and <37 weeks (0.71, 95% CI: 0.7-0.71) was calculated.

Conclusion: Spontaneous preterm delivery can be predicted by using the proposed models, which might be applicable in clinical assessment of risk.

DISCUSSION

The aim of this section is to summarize the methodological limitations and advantages of these studies, and to discuss to what extent the limitations may have influenced the findings in this thesis. The results will also be discussed in relation to and compared with previous and similar findings in the literature.

Methodological considerations

Assessing methodological quality is important when considering any kind of research and methods have been developed for judging scientific quality in general (383). Precision and validity are central terms in this evaluation. **Precision** means the abscence of random errors. **Validity** means the abscence of systematic errors. Validity can be further divided into internal and external validity. Different combinations of precision and validity are visualized as in Figure 5, below. Both high precision and high validity are necessary if the results of a study are to be regarded as trustworthy findings and generalized to the population that the study sample is meant to reflect. Precision and validity issues affect any kind of study design, both case-control and cohort studies, be they retrospective or prospective. There is no reason to disregard any study simply on the basis of design (384). Both precision and validity aspects are discussed separately below by evaluating the random and systematic errors influencing the quality of the current study. Initially, aspects related to study design are discussed.

Figure 5 Possible combinations of precision and validity. (Reproduced with permission from Ahlbom and Norell, Grunderna i epidemiologi, Studentlitteratur AB, 1987)
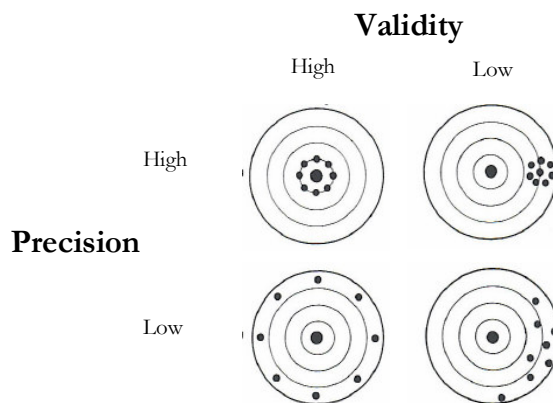
Study design

The first studies assessing the association between pregnancy and the perinatal period and the subsequent outcome in child were performed in the British birth cohorts from 1946 (385), 1958 (386) and 1970 (386). Such large-scale cohort studies have been tremendously important and of high quality, but they are time-consuming to recruit and follow up and tend to be very expensive to perform. The main advantage of register data is that they already exist (380). The use of the existing nationwide medical birth registers **cuts research costs** and enables studies and analyses of time trends in much **less time** than is usually possible in cohort studies (387). The lack of biological material is a disadvantage in ordinary register-based research but new ongoing national birth cohorts studies do collect biological material and will permit linkage of register-based data, questionnaire data and biological data (388-390). These studies will add new dimensions to the nationwide population-based medical birth registers. Another limitation in using register-based data is that analyses are **restricted to the already collected variables** and that researchers cannot influence data collection, at least not in the short term.

The enormous amount of study objects available from large registers is an unequivocal strength of such secondary data, enabling the **detection of moderate risk factors** (391). Power simulations have shown that even with the assumption of no misclassification in studies using small study populations, only detection of exposures causing extremely increased risks can be expected (Figure 6). Use of nationwide medical birth register data also provides a unique opportunity to elucidate possible weak associations between preterm birth and risk factors for this condition, for which very few new risk factors have been described in recent years.
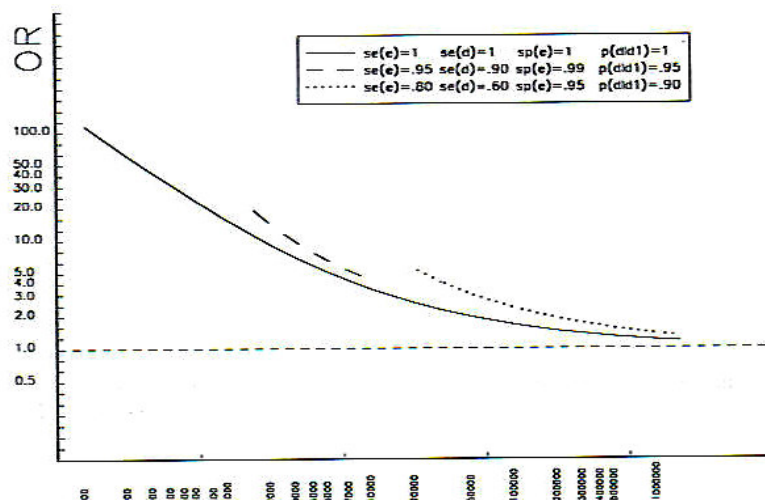
Figure 6 The association between study population size and detectable risk. The solid line shows, by hypothetical study population size, the magnitude, detectable with a probability of 80%, of an association between a certain event (with an incidence of 0.0013) and an exposure present in 25% of the population. The broken and dotted lines show the corresponding magnitude after adjustment for a putative low sensitivity and specificity (non-differential) among larger register. The following denotations were used in the figure box: se(e) = sensitivity of exposure, se(d) = sensitivity of the diagnosis, sp(e) = specificity of exposure, p (d │ d1) = percentage of truly diseased among all classified as diseased. (From: Maternal smoking and congenital malformations, thesis, Lund University 1999, Karin Källen. Used with author's permission).

Evaluation of random errors

Consideration of possible random errors is important in all kinds of studies, including in large settings as in the studies presented here, as these errors may reduce the accuracy of reported measurements. The typical epidemiological method of increasing precision is to enlarge sample size. The birth register data that were the basis for this thesis included almost all pregnancies in Sweden, Denmark and Norway. Therefore, enlarging sample size was impossible; furthermore, the number of study objects was more than enough to generate accurate data for the vast majority of analyses. However, in some subgroups (Paper IV), the number of infants was small and we were forced to merge some diagnoses to obtain a number of cases that was meaningful for analysis. Increasing sample size was impossible as these data were obtained from a nationwide register. Nevertheless, one of the main **advantages** of these large historic population-based datasets is the fact that random errors can be considered to be minor due to the large number of included study objects.

Evaluation of systematic errors

Consideration of possible systematic errors may be of greater importance than random errors in this population-based setting. Two concepts are important related to systematic errors, i.e. internal and external validity. They are described and considered separately below.

Internal validity

Internal validity of a study implies validity of inference for the study subjects within the study. This type of validity may be reduced by systematic errors, commonly divided into three major classes of bias: selection bias, information bias and confounding (384, 392). This is the

most common classification of systematic errors in study design, but there are other published ways of describing bias (393, 394).

Selection bias

Selection bias comes from the procedures used to select subjects and from factors that influence participation in a study. If the association between exposure and disease differs between those who participate and those who do not, resulting in a different estimate of the effect measure compared to the case if the entire population had been studied, then selection bias has been introduced into a study.

Selection bias is most certainly not a major problem in the studies in this thesis, as data are collected from Scandinavian nationwide registers that are based on mandatory notification of births and that have low drop-out rates. The entire parturient population was in fact the population of interest and nearly all births in each Scandinavian country were registered in the respective birth registers. An important advantage of these studies is the low probability of selection bias which thus does not seem to threaten the internal validity of the results and conclusions.

Information bias

Information bias arises in a study if the collected information about or from the study subjects is erroneous. Systematic errors in classification of subjects create information bias. Misclassification is either differential (misclassification in exposure or outcome is dependent on a subject's category for the other variable) or non-differential (misclassification in exposure or outcome is not dependent on a subject's category for the other variable) and criticism of the reliability of population-based register data most often pertains to the possibility of misclassification. In general, skepticism towards all findings and questions about valid conclusions are legitimate, but as long as the collected data is gathered prospectively, as in the case of the Scandinavian register data used in this thesis, any putative misclassification can be expected to be non-differential (391). This means that the possible misclassification is independent of whether or not an outcome indeed occurs in an individual. Furthermore, non-differential misclassification bias will always bias the estimated risk measurements towards unity (395), whereas the bias can be in either direction if the misclassification is differential. Non-differential misclassification will therefore always mask an existing association towards the "null effect". Huge differences in power are seen between studies using large and small study populations (Figure 4, above), but the decreased power

due to **misclassification bias seems to be of less importance** if non-differential misclassification is assumed (391). The reduced likelihood of differential misclassification and the comprehensive population coverage, resulting in minor selection bias problems, might in fact be considered to be the main advantages of using secondary data such as those from the Scandinavian birth registers (396).

In this thesis, there may be sources of information bias associated with the quality of the registered data. These register-based data come from large computerized systems in three different nations, so registration errors are probably inevitable despite regular quality controls and validations. Errors are inevitable, possibly affecting both outcome and exposure variables. Nonetheless, as long as misclassifications are non-differential, which is the most likely situation, the results and conclusions in this thesis are not seriously biased.

Gestational age is the key variable in all preterm birth research, including in this thesis. The validity of gestational age registered in the three birth registers in Sweden, Denmark and Norway has been assessed and considered to be 90 to 98 % satisfactory in all three countries (387). It is therefore appropriate for studies such as those presented here. However, it is important to bear in mind the limitations of the two most important methods of gestational age dating (ultrasound and LMP) and that changing from one method to another has major implications, especially when time trends are studied (108).

Type of delivery onset is another key variable in this thesis; it was registered in all three birth registers during the study periods. Some aspects are important when the quality of this variable is under consideration. First, it is registered in check boxes, which is generally considered to be superior to other methods of register data registration (372). Second, the division of the preterm population into subgroups is similar to that found in later Scandinavian data, both hospital based (397) and from a recent large cohort (398). Third, we have performed a minor pilot assessment of this variable as described above, and found it reliable. These arguments strengthen the reliability of this variable, but do not change the fact that a major validation assessment would have been beneficial.

Birth weight has been registered since the foundation of the SMBR and it is considered one of the most reliable variables in the database (372, 399).

The most serious data loss in the SMBR is that related to **infant diagnoses** (373), which is the reason we included data from the SHDR, also enabling us to study long-term neurological outcome. A recent validation of the diagnoses in this register revealed that gynecology and pediatrics actually had the lowest misclassification rates of all examined specialties (400). Furthermore, the proportion of misclassification was low among younger patients (400). This confirms that the SHDR is useful for research (374, 401).

Confounding

Confounding is defined by Rothman as confusion or mixing of effects, implying that the effect of the exposure variable is mixed with the effect of another variable, leading to bias (384). An alternative definition is that a confounder is a variable that affects results by being associated to both the exposure and outcome variables. The variables consistently considered as possible confounders in most of these studies were parity, maternal age and smoking.

The validity of the **parity** variable has been assessed on several occasions and found to be of acceptable quality (372). In a later validation, it is pointed out that there is a difference in validity depending on the plurality of the reported pregnancy, with poor quality for multiple births (373). Thus, great care must be taken when parity information from multiple births is used (373).

Calculation of **maternal age** is based on the mother's personal identification number, which contains the date of birth. This variable is regularly validated and of high quality. The personal identification number is missing in as few as 0.03 percent, according to the latest validation study (373).

Information on maternal **smoking,** reported at the first antenatal appointment, is available since 1983 and information on maternal smoking during week 30-32 was introduced as a variable in 1990. The latter is incompletely registered and not useful (373). We therefore used the former, for which only a small proportion is missing (4-9%) (373). The variable has recently been validated in a medical record sample, and it was found that the available smoking data had not been computer-recorded in about 2%, and that the information had been misrepresented in about 1% (373). These figures are acceptable in large datasets such as those in this thesis.

Residual confounding is of course possible as long as the entire body of preterm birth, a coplex entity with syndromic characteristics, is far from well understood. The use of register data limits the possibility to select variables for this research and might have influenced findings. We obviously gained huge data sets, but may have lost some variables that could easily have been collected in a well-controlled clinical setting. Nevertheless, it is most likely that we have taken the major confounding factors, with the greatest impact on our assessments, into consideration.

External validity

External validity refers to whether the results and conclusions of a study can be generalized to other populations than the study population. Internal validity, discussed above, is of course a premise and prerequisite for external validity.

The data that make up the basis for this thesis all come from nationwide, compulsory, population-based reporting systems. The registers are considered to be of high quality and very close to 100 % of all births are registered. The results in this thesis are doubtless applicable to the Scandinavian population. This population is described as low-risk in terms of the reported proportion of preterm birth. The Scandinavian countries have a rather low proportion of preterm birth compared to several other countries, the most striking difference being with the US, in which the preterm birth proportion is twice that in Scandinavia. Whether our results are applicable to populations with a high risk of preterm birth is a relevant question when assessing this thesis. In Paper I, we showed that the composition of the preterm population in Scandinavia is similar to that reported in high-risk populations, indicating similarity between countries and populations despite different risks. Also interesting is the finding in Paper II that SGA, in this Scandinavian population with its well-developed antenatal care system, is also associated with spontaneous preterm birth, possibly indicating a biological or mechanistic relation to preterm birth. These findings strengthen our belief that our results are applicable to preterm populations from different parts of the world, despite the fact that all data in this thesis were collected from low-risk populations.

Discussion of results in Papers I-V in relation to other studies in the literature

Paper I

Declining proportion of preterm birth in Sweden

The decline in the proportion of preterm birth found in this study has few parallels in the international literature. A striking decline in the incidence of preterm birth was reported from France after implementation of a regional prevention program (134) in the eighties and a reduction was later reported from Finland (140). The French study reported a reduced proportion among preterm births at <34 weeks of gestation as well, which contrasts with our data. This decrease in France has later been followed by an increase from 1989 to 1995 (138). No specific gestational age is prominent in the Finnish study. It was speculated whether changes in living conditions and increased social well-being could have been the main contributors to the reduced incidence seen in the spontaneous group. We find a striking decrease in the total proportion of preterm birth (<37 gestational weeks), despite an increasing contribution from multiple births and increasing maternal age.

The significant reduction in OR for preterm birth is evident for singletons at <37 weeks during 1983-2001. This reduction is not evident in infants at <34 weeks, indicating that the reduction in the total preterm birth proportion can be explained by reduced occurrence of late preterm birth (34-36 gestational weeks) among singleton preterm infants. The reduction in the total singleton preterm birth proportion (<37 weeks) is not altered after stratification for maternal age, parity or smoking. On the other hand, smoking among pregnant women in Sweden has decreased from 31.4 % in 1983 to 11.3 % in 2001, according to the SMBR, and it is likely that this reduction has had an impact which is, however, not visible in our data.

We identified smoking as a risk factor for singleton preterm birth in Sweden during the study period 1991-2001, and smoking is more strongly associated with spontaneous than with iatrogenic preterm birth at all preterm gestational ages. The strongest association between maternal smoking in early pregnancy and preterm birth was found for gestational age <28 weeks and spontaneous preterm birth (OR: 1.55). The significance of smoking as a modifiable risk factor (127, 402) for preterm birth has been a subject of research and debate for several decades. A recently published study, based on the same data sources as the current study but conducted during a limited time period (1991-93), did point out the contribution of smoking

to preterm birth in Sweden (194); smoking was associated with increased risk of both spontaneous and indicated preterm birth at both <32 weeks and 33-36 weeks, which is in accordance with our findings. The strongest association in this study was found between smoking and spontaneous preterm birth as well as very preterm birth (<32 weeks of gestation).

Our data do not confirm any significant reduction in the proportion of preterm birth at gestational ages below 34 weeks. This contrasts with a recently published report from Finland (141), in which researchers claim to have found a significant reduction (12%) in extremely preterm deliveries (<28 weeks). When looking more closely at these Finnish data, it seems more like an increase in the denominator than a reduction in the numerator. Nonetheless, the significance of this finding is incontrovertible, but the researchers' unequivocal interpretation is difficult to understand. When our figures are scrutinized, there was an apparent increase in preterm births at below 28 weeks from 1984 to 2001 (0.19% to 0.26%) in Sweden. These figures are very small and difficult to interpret.

We are not able to come up with any single explanation for the decreasing proportion of preterm births in Sweden from 1983 to 2001. It is, however, tempting to suggest that the decline in smoking among pregnant women in Sweden from 1983 to 2001 has had a major impact on the reduction of the preterm birth proportion seen in Sweden since the mid-eighties, although our figures show that smoking alone can not explain the reduction. The difficulty in explaining this decline may be related to the fact that preterm delivery is a complex entity with syndromic characteristics and associated with a number of known, and probably also unknown, risk factors. Changes in preterm birth proportions would be influenced by simultaneous changes in several risk factors, changes influencing the proportion in different directions. Another fascinating aspect, in the light of our findings and in relation to the public health issue, is the recent recognition that infants born late preterm at 34-36 gestational weeks are at increased risk of morbidity and mortality, compared to term infants (51, 403). Perhaps the reduced proportion of preterm birth at gestational age 34-36 weeks had a greater impact on outcome in the Swedish population than was previously believed.

Subgroups of preterm birth
According to previous studies, the size of each preterm subgroup varies and is influenced by population characteristics and inconsistency in terminology (73, 78, 80, 229, 404-406). These

studies are either hospital- or region-based. However, having excluded IUFD, congenital malformations and unknown type of onset and looking exclusively at the relative relationship between spontaneous and indicated preterm birth, we find that nearly 75% are spontaneous and 25% are iatrogenic. Spontaneous preterm birth is the largest preterm subgroup in this Scandinavian population. This finding is interesting as it indicates no difference in the subgroup composition of the preterm population when a country with low risk of preterm birth such as Sweden, is compared with a country with high risk such as the US (73). It has been suggested that the lower prevalence of maternal and perinatal infections in the Scandinavian countries might result in a lower proportion of spontaneous preterm births. Our findings do not support this hypothesis.

Paper II

Deviant fetal weight is associated with spontaneous preterm delivery
The preterm delivery proportion in Scandinavia is low, compared to other countries, as we have shown in Paper I. This may raise questions about whether our findings concerning fetal weight deviation can be generalized to diverse obstetric populations. We have also shown in Paper I that the composition of the preterm population in Sweden is similar to that in populations with higher genital and perinatal infection rates and higher preterm birth proportions. It is our opinion that preterm populations may be more similar than is believed, despite differences in preterm birth proportions. The findings in this study reveal that there is a strong association between spontaneous preterm delivery and lower birth weight than the population mean in Sweden, where pregnant women receive extensive and qualified care. Our findings are in accordance with both previous (407, 408) and more recent studies (280, 282, 409) from other countries. The novelty is that these findings are based on data from a nationwide register and that a population with low rates of preterm birth and perinatal infections has been investigated for the first time.
The causal mechanisms underlying the association between spontaneous preterm birth and SGA are not well understood. Several possible pathways have been discussed. Speculations concerning changes in cortisol production and levels of CRH in cases of fetal sub-nutrition have been presented as possible explanations for the link between SGA and spontaneous preterm birth (338). Fetal sub-nutrition results in decreased levels of growth-promoting hormones and increased levels of cortisol. The cortisol/CRH axis has been theoretically linked

to both term and preterm labor (217, 218, 410, 411). It has previously been shown that this neuroendocrine axis is functional and capable of exerting biological action in growth-retarded fetuses (412). Another theory involves intrauterine infections. There are some infections related to both SGA and preterm labor (413). Fetal immunodeficiency as a result of placental insufficiency may also increase vulnerability to infections (414). Furthermore, undernourishment may affect the tensile strength of the amnion and chorion as it affects the fetus, resulting in fragile membranes and increased incidence of pPROM (63).

The question of whether spontaneous and iatrogenic preterm births should be separated to enable studies of the respective etiology has been addressed in a recent report (68). We have found a large discrepancy in the occurrence of SGA between the two preterm birth subgroups indicating that it is indeed necessary to distinguish these two etiologies when studying the association between SGA and preterm birth.

The finding of an increased risk of spontaneous preterm birth at gestational age 34-36 weeks in infants weighing more than one SD above expected birth weight is very interesting. The association remains after sub-analysis, indicating that it is true and not caused by erroneous estimates of gestational age. The fact that the risk increased with increasing deviation from expected birth weight may indicate that the bigger the infant, the greater the risk of spontaneous preterm birth. This connection has recently been described in a smaller data set (281). Pathological uterine distension is associated with both PTL and pPROM. It is the result of an abnormal increase in intrauterine volume, as in the case of multiple gestations and polyhydramnios or of limited uterine expandability, as seen in women with T-shaped uteri due to intrauterine diethylstilbestrol exposure or Müllerian duct anomalies. Therefore, our findings concerning increased fetal growth and spontaneous preterm delivery may suggest that overstretching of the myometrium is a mechanism of labor in general, not only at term, but also among preterm singletons.

Small for gestational age among preterm singleton infants
The majority of preterm SGA singletons were born preterm due to medical interventions, but infants born after spontaneous preterm labor were SGA to a greater extent than infants born after spontaneous onset of delivery at term. Antenatal care is highly developed and has a longstanding tradition in Sweden. This implies that deviation in fetal growth from population standards is probably more easily diagnosed in Sweden than in populations with less

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developed antenatal care. This is reflected in our data by the fact that 72% of all SGA infants in the preterm population are found in the iatrogenic subgroup. It is likely that this proportion would have been smaller and that the corresponding proportion found in the spontaneous preterm group would have been higher in a different antenatal care setting.

Paper III

Reference population

The design and use of reference populations when analyzing Scandinavian birth register data show that changes in maternal age, parity, ART, multiple births and immigration can explain the increase in preterm birth in countries such as Norway. However, these factors cannot explain the increase in Denmark and no trend was found in the Swedish data.

The increased use of rigorous population-sampling methods and the analysis of these samples in diverse study designs have highlighted the need to create links between populations and samples in epidemiology (415). Kalsbeek and colleagues propose the definition and design of a reference population as a solution to all problems related to sampling, and suggest that sample results and design features be understood in relation to that reference population (415).

The model using a reference population was applied to control for detectable confounding from major risk factors that vary over time and between countries. The factors used to identify the reference population were selected from a combination of clinical experience, availability and literature reviews of risk factors for preterm delivery. It might, for instance, be argued that smokers should be eliminated from the reference population as smoking is relatively common and increases the risk of preterm delivery. However, reports of smoking are often not valid or even omitted. Inclusion of such factors would decrease the validity of data and the number of countries from which data could be obtained and was thus rejected. Calculation of the national proportions as well as the proportion in the reference population can provide answers to several questions that would otherwise require complex statistics, i.e. "Is there a basic proportion of preterm delivery?" "Has it changed over time?" "Can the factors eliminated in the reference population explain changes across populations or over time?" The suggested model can thus facilitate meaningful international comparison of baseline differences between countries. The omission of smoking clearly illustrates that this model

cannot replace more complex analyses such as logistic regression analysis which it is clearly meant to supplement.

Increasing ethnic diversity, increasing contribution from ART, increasing number of multiple births, increasing maternal age and increasing relative number of iatrogenic preterm deliveries have all previously served as explanations for increasing preterm delivery proportions (125, 126, 150, 416). Primiparity was reduced in Denmark which should have contributed to a decreasing preterm delivery proportion. Multiple pregnancies increased in both Denmark and Norway, while remaining unaltered in Sweden. Despite rather consistent changes in risk factors among the Scandinavian countries, clear differences were evident in terms of time trends for the proportion of spontaneous preterm deliveries in the reference population. In our opinion, this indicates that current understanding of different risk factors and their respective contributions to the changing preterm delivery proportion is incomplete.

The recent temporal increase in the overall preterm delivery proportion in both the United States and France is said to be driven by an impressive concomitant increase in medically indicated preterm deliveries (18, 150). Our data show an increasing number of iatrogenic preterm deliveries in all three Scandinavian countries which should contribute to an increased total preterm delivery proportion. Furthermore, according to the literature, the increasing incidence of multiple pregnancies associated with ART is another main cause of increased preterm delivery proportions (1, 150, 249, 417). The availability and use of these techniques have increased in all three countries. However, neither medically indicated nor multiple preterm deliveries can be the only explanation for the increased proportion of spontaneous preterm delivery found in the Danish reference population, as was argued in previous reports, which illustrates the benefit of using this method.

It is well known that gestational age determination by ultrasound increases the incidence of preterm delivery (125). Might not the increase in preterm delivery proportions in Denmark and Norway just be the result of an increased use of ultrasound? Gestational age has, however, been extensively determined by ultrasound during the whole study period and there has been no recent change in clinical guidelines in any of the three countries. A Danish study of a cohort from 1990-1999 reported that the reduction in gestational age during the study period occurred regardless of whether the calculation was based on LMP or ultrasound (418). It thus seems that there has been a true decrease in gestational age over the study period.

A factor not accounted for in the current study is smoking. Smoking during pregnancy is a well known, and reducible, risk factor for preterm delivery. Smoking was not registered in the NMBR until 1999. There has been a substantial decrease in smoking during pregnancy in all three countries during the study period (4, 195). These figures are similar in the three Scandinavian countries and should most likely have contributed to a decreased preterm delivery proportion; they can therefore not explain the diversities found.

Another aspect of this study that may invite criticism is the fact that we did not include stillbirths at gestations below 28 weeks. Inclusion of stillbirths at lower gestational ages would have been advantageous but the SMBR did not, and still does not register them; we were thus obliged to limit our samples from the other two countries as well. This old convention is a major disadvantage in our research. Initially, we did include stillbirths at <28 weeks in the Danish data, but they did not affect conclusions.

The increased spontaneous preterm delivery proportion found in the Danish reference population is a cause for concern and most likely a true and reliable finding. Several possible explanations exist: increased/altered genital infections, increased maternal stress during pregnancy, changes in dietary intake, increased occurrence of chronic maternal disease during pregnancy, altered clinical management and changes and deterioration in antenatal care. The current study cannot explain this finding; future studies are thus required.

Total preterm delivery proportions, based on crude national figures, do not necessarily provide an overview of development over time. This is illustrated by the Norwegian national crude data indicating an increased preterm delivery problem, while findings in the reference population gave no reason for concern. In Denmark, the increasing preterm delivery proportion was also seen in the reference population, including in spontaneous preterm deliveries. Using reference populations in the assessment and comparison of preterm delivery proportions is simple and may prove useful at the local, national and international level in the future as it facilitates interpretation without the use of complex statistics. This method may thus yield more adequate time trend analyses, facilitating international comparison.

Paper IV

This study reveals that the two main subgroups of preterm birth are related to different pediatric outcomes. For the first time, an association between CP and spontaneous preterm birth is supported by a large nationwide study.

There was no increased risk of early neonatal death, neonatal death or infant death in infants born after spontaneous preterm onset. The only significant findings were in the gestational age group near term (34-36 weeks), indicating that infants born after iatrogenic preterm onset were at increased risk of death, compared to the infants born after spontaneous onset. These findings reflect the fact that the deliveries of the former are induced due to severe pregnancy complications which increase their risk of death, compared to infants born after spontaneous preterm onset. No differences in mortality were evident between spontaneous and iatrogenic preterm births in the lower gestational ages. Gestational age is certainly the most important risk factor; type of delivery onset seems to make no difference.

Seizures/convulsions, intra-ventricular hemorrhage and peri-ventricular leukomalacia were merged into one outcome variable, CNS disorders, as the rarity of each outcome made interpretation of results difficult. Intra-ventricular hemorrhage and peri-ventricular leukomalacia have been shown to be more common in spontaneous preterm infants weighing 500-1750 g in a previous hospital-based study (35). An association was found between spontaneous preterm birth and CNS disorders at gestational ages <28 weeks and 32-33 weeks, but it was not statistically significant. There was a statistically significant negative association at gestational age 34-36 weeks, indicating that CNS disorders occurring near term are more common among infants born after iatrogenic delivery onset. Pulmonary problems, gastrointestinal complications and retinopathy of the premature are related to iatrogenic rather than spontaneous onset of preterm labor.

The hypothesis of inflammation and a presumed linkage between infection, inflammation, spontaneous preterm birth and CP is well known (419). The finding in this study of an increased risk of CP among infants born after a spontaneous preterm delivery onset at gestational age 28-31 weeks is interesting as this association has thus been confirmed for the first time in a large nationwide study. CP is often diagnosed between the ages of one and a half and four years, leaving a rather long latency phase before it is verified that a child suffers

from the disorder. The association between spontaneous preterm birth and CP was evident in our study, despite these data being obtained from a population with a low frequency of perinatal infections (420) and a low proportion of preterm birth.

A previous study from Sweden found that antenatal infections only provoked a marginal increase in the CP risk (379). Infection is considered to be a more common cause of very and extremely preterm birth (<28-31 weeks) than of moderately and late preterm births (32-36 weeks) (421). In this study, no association between sepsis after birth at the lower gestational ages (<28 weeks and 28-31 weeks) and spontaneous onset of preterm birth was found. There was a statistically significant association between sepsis and spontaneous preterm birth at gestational age 32-33 weeks. This outcome variable does not reflect exposure to intrauterine infection; these infants are likely to be vulnerable to infection after birth as well. These findings do not rule out an infectious relationship between spontaneous preterm birth and CP, but neither do they confirm it. Discrepancy between culture-positive (infection) and IL-6-positive (inflammation) cases has been found in women presenting with preterm labor and intact membranes (422). Inflammation-positive pregnancies may not result in clinically evident infection in the infants, which are therefore not diagnosed as sepsis cases.

Different subgroups of preterm birth are associated with different pediatric outcomes in this study. The associations between spontaneous preterm delivery onset and the investigated outcome variables were, however, fewer than expected. Iatrogenic preterm birth is associated with both respiratory and gastrointestinal diagnoses. Our findings do support the previously reported link between spontaneous preterm birth and CP, but they are not consistent across the gestational range and should therefore be interpreted with caution. There are few previous studies investigating the association between different subgroups of preterm birth and morbidity and mortality (404, 406, 423-425). The classification of preterm birth in subgroups is not consistent in different studies. Differences in terms of outcome have been found, but the findings are also inconsistent. The previous studies on this issue are rather small and the final conclusions are difficult to interpret at present. Further studies are needed.

The question of whether spontaneous and iatrogenic preterm births should be separated or combined when studying etiology has been raised in a recent report (68). The authors concluded that the complexity of the etiological pathways in preterm birth justifies both combination and separation. It could also be argued that different ways of categorizing

preterm birth might be useful (69). The intention of our study was to assess whether differences in outcome between iatrogenic and spontaneous preterm-born children were evident. This categorization of preterm births is, after all, the one most extensively used. In our opinion, the results of this study support the arguments for separating the subgroups.

Paper V

The results of the development of risk-scoring systems and diagnostic tests have so far been rather disappointing and no appropriate screening tool is available for early detection of preterm delivery. The numerous previously developed risk-scoring systems (293-301) aim at predicting the risk of preterm delivery based on past obstetric history. These scoring systems are not as useful to nulliparas as to multiparas and substantial numbers of women considered to be at low risk actually give birth to preterm infants. No scoring system has been shown to be superior to clinical judgment (292). The risk-scoring systems currently used in early pregnancy have a wide range of accuracy in predicting preterm delivery in otherwise asymptomatic women and they can not be recommended in clinical practice (302).

Smith and colleagues' development of a statistical method combining logistic and Bayesian methods has been successfully applied in the prediction of cesarean section risk (328). It was suggested by the authors that this method may be generally applicable for clinical estimation of risk, which evoked our curiosity regarding its actual usefulness in risk prediction of spontaneous preterm delivery. The most important benefit from the applied statistical technique is that calculation of optimal replacement coefficients makes missing data easy to handle and the model more robust. The issue of whether calculation of LRs is required is debatable, when multiple logistic regression models with acceptable fit are developed. Logistic regression modeling helps identify the important available independent variables in the register, which can help predict spontaneous preterm delivery. We have for instance, identified vaginal bleeding in early pregnancy as a strong predictor of spontaneous preterm delivery, at least in singleton pregnancies. The subsequent calculation of adjusted LRs, based on the output of the final logistic regression models, has an advantage in that it makes it easy to handle missing data. In addition, the final output provides an estimate of the individual risk. However, the latter is of minor importance at present, as we intend to develop these models

further. It seems likely that we have identified the explanatory register variables of major importance in the prediction of the outcome of interest.

The presented models in this study, at least those developed for singleton pregnancies, can be applied in clinical situations. We will most certainly be more cautious in using the twin models; they are more uncertain since they were developed from small datasets. The main argument for a clinically useful application of these models is that missing data is easily handled through the use of replacement coefficients. It is our belief that the discriminative and predictive ability will further improve in the future by the addition of biological data concerning genes, proteins and metabolites, hopefully making these models into an even more useful bedside tool. We are in the process of developing simple software providing an individual estimated risk in percent as its output.

Compared to the most recently presented predictive model for preterm birth (292) using artificial neural networks, published by Catley et al, we studied a more specific subgroup of preterm delivery, i.e. spontaneous preterm deliveries, and did not analyze the spontaneous and iatrogenic subgroups together. We have included more independent variables in our models than Catley et al, and we achieved even better predictive ability. None of the other described prediction tools and risk-scoring systems is used in daily clinical practice and our study clearly shows that high-quality epidemiological and clinical data can provide at least the same or even better predictive ability than more sophisticated methods.

 The predictive ability of the six models varies with the type of pregnancy-singleton or twin, primiparous or multiparous-for which they are meant to predict. Prediction of risk in multiparas alone is more reliable than when they are combined with primiparas. These findings are true for both singleton and twin pregnancies. Multiparity clearly adds useful information about the previous delivery, and it is tempting to speculate on the importance of genes and their contribution to the tendency to repeat gestational age at delivery in subsequent pregnancies (226, 426).

These prediction models have been developed and validated in a large sample from a Scandinavian population at low risk of spontaneous preterm delivery and in epidemiological and clinical data of high quality from a compulsory national birth register, considered to be one of the most complete registers in the world. One crucial question is: "Can the models be

generalized to different populations with a different subgroup composition and a different proportion of spontaneous preterm delivery?" The models are applicable to populations with similar preterm birth proportions, but their usefulness in more heterogeneous populations, especially those with greater ethnic diversity is an open question. On the other hand, we did consider ethnicity as an independent variable, as ethnicity is regarded as a risk factor for spontaneous preterm delivery (160, 161). Ethnicity was, however, not included as there was conflicting relationships to spontaneous preterm delivery, depending on which other factors were part of the model, for some ethnic groups, e g. Arabic. When Arabic ethnicity was an independent variable in the multiple logistic regression models together with maternal height, it was a protective factor for spontaneous preterm delivery. On the other hand, when Arabic ethnicity was an independent variable and maternal height was not, it emerged as a risk factor for the outcome. In our final models we therefore decided to include maternal height and exclude ethnicity, based on these results and because maternal height was found to be a stronger and more consistent predictor of spontaneous preterm delivery.

CONCLUSIONS

Paper I

- The proportion of preterm birth in Sweden has decreased significantly, beginning in the mid-1980s.

- This decrease is evident among singleton births at gestational age 34-36 weeks.

- The decrease is evident despite an increasing contribution of multiple births and increasing maternal age.

- According to this study, spontaneous preterm births constitute the largest subgroup in a proportion similar to that seen in populations with higher incidence of perinatal infections and preterm birth.

- This indicates that the composition of the preterm population seems to be identical, regardless of different rates of both preterm birth and perinatal infections.

Paper II

- Deviation of fetal weight from the expected mean, both larger than the population mean at gestational age near term (34-36 weeks) and smaller than the population mean in all preterm gestational age groups, is associated with spontaneous preterm delivery.

- Among all preterm infants, 11% were SGA and 72% of preterm SGA infants were born after medical interventions.

- The SGA proportion among spontaneous preterm births was 4.3%, whereas the corresponding percentage among iatrogenic preterm births was 30%.

- The peak proportion of SGA among spontaneous preterm births was at 28-31 gestational weeks (9.7%), whereas the corresponding peak proportion among the iatrogenic preterm births was at gestational age <28 weeks (64%).

Paper III

- Total preterm delivery proportion, based on crude national figures, do not necessarily provide an overview of development over time, as illustrated by the Norwegian national crude data indicating an increased preterm delivery problem, while findings in the reference population gave no reason for concern.

- In Denmark, the increasing national crude preterm delivery proportion was also seen in the reference population, including among spontaneous preterm deliveries, indicating a disquieting development.

- The use of reference populations in the assessment and comparison of preterm delivery proportions is simple and may prove useful at the local, national and international levels in the future, as it facilitates interpretation without the use of complex statistics and yields more adequate time trend analyses.

Paper IV

- Our findings support the previously reported link between spontaneous preterm birth and CP.

- Iatrogenic preterm birth is associated with both respiratory and gastrointestinal diagnoses.

- Different subgroups of preterm birth are associated with different pediatric outcomes.

Paper V

- Prediction of spontaneous preterm delivery is possible and good predictive ability was achieved with the proposed models, combining logistic regression and Bayesian methods.

- It is our true belief that a more complete prediction model, which will be developed in the future, will make it possible to predict spontaneous preterm delivery to an even greater extent.

Finally, it is my sincere hope that these findings may serve as a very small contribution to increased understanding of the science and art of preventing disease, prolonging life and promoting health through the organized efforts and informed choices of society, public and private organizations, communities and individuals, in accordance with Charles Edward Amory Winslow's definition of public health.

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References

1.	Steer P. The epidemiology of preterm labour-why have advances not equated to reduced incidence? Bjog 2006;113 Suppl 3:1-3.
2.	Steer P. Prematurity or immaturity? BJOG 2006;113((Suppl. 3)):136-138.
3.	Hamilton BE, Minino AM, Martin JA, Kochanek KD, Strobino DM, Guyer B. Annual summary of vital statistics: 2005. Pediatrics 2007;119(2):345-60.
4.	Langhoff-Roos J, Kesmodel U, Jacobsson B, Rasmussen S, Vogel I. Spontaneous preterm delivery in primiparous women at low risk in Denmark: population based study. Bmj 2006;332(7547):937-9.
5.	Mattison DR, Damus K, Fiore E, Petrini J, Alter C. Preterm delivery: a public health perspective. Paediatr Perinat Epidemiol 2001;15 Suppl 2:7-16.
6.	Bryce J, Boschi-Pinto C, Shibuya K, Black RE. WHO estimates of the causes of death in children. Lancet 2005;365(9465):1147-52.
7.	Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990's. Early Hum Dev 1999;53(3):193-218.
8.	McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med 1985;2(312):82-90.
9.	Costeloe K. EPICure: facts and figures: why preterm labour should be treated. Bjog 2006;113(Suppl.3):10-12.
10.	Markestad T, Kaaresen PI, Ronnestad A, Reigstad H, Lossius K, Medbo S, et al. Early death, morbidity, and need of treatment among extremely premature infants. Pediatrics 2005;115(5):1289-98.
11.	Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005;352(1):9-19.
12.	Marlow N, Hennessy EM, Bracewell MA, Wolke D. Motor and executive function at 6 years of age after extremely preterm birth. Pediatrics 2007;120(4):793-804.
13.	Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics 2000;106(4):659-71.
14.	Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. N Engl J Med 2000;343(6):378-84.
15.	Finnstrom O, Olausson PO, Sedin G, Serenius F, Svenningsen N, Thiringer K, et al. The Swedish national prospective study on extremely low birthweight (ELBW) infants. Incidence, mortality, morbidity and survival in relation to level of care. Acta Paediatr 1997;86(5):503-11.
16.	Kramer MS, Demissie K, Yang H, Platt RW, Sauve R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. Jama 2000;284(7):843-9.
17.	Goldenberg RL, Jobe AH. Prospects for research in reproductive health and birth outcomes. Jama 2001;285(5):633-9.
18.	Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. J Matern Fetal Neonatal Med 2006;19(12):773-82.
19.	Slattery MM, Morrison JJ. Preterm delivery. Lancet 2002;360(9344):1489-97.
20.	Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N. Outcomes in young adulthood for very-low-birth-weight infants. N Engl J Med 2002;346(3):149-57.
21.	Stjernqvist K, Svenningsen NW. Ten-year follow-up of children born before 29 gestational weeks: health, cognitive development, behaviour and school achievement. Acta Paediatr 1999;88(5):557-62.
22.	McCormick MC, Richardson DK. Premature infants grow up. N Engl J Med 2002;346(3):197-8.
23.	Doyle LW, Cheung MM, Ford GW, Olinsky A, Davis NM, Callanan C. Birth weight <1501 g and respiratory health at age 14. Arch Dis Child 2001;84(1):40-44.
24.	Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163(7):1723-9.
25.	Siltanen M, Savilahti E, Pohjavuori M, Kajosaari M. Respiratory symptoms and lung function in relation to atopy in children born preterm. Pediatr Pulmonol 2004;37(1):43-9.
26.	Jacobson LK, Dutton GN. Periventricular leukomalacia: an important cause of visual and ocular motility dysfunction in children. Surv Ophthalmol 2000;45(1):1-13.
27.	Hard AL, Niklasson A, Svensson E, Hellstrom A. Visual function in school-aged children born before 29 weeks of gestation: a population-based study. Dev Med Child Neurol 2000;42(2):100-5.
28.	Goldenberg RL, Hoffman HJ, Cliver SP. Neurodevelopmental outcome of small-for-gestational-age infants. Eur J Clin Nutr 1998;52 Suppl 1:S54-8.
29.	Escobar GJ, Clark RH, Greene JD. Short-term outcomes of infants born at 35 and 36 weeks gestation: we need to ask more questions. Semin Perinatol 2006;30(1):28-33.

30.   Escobar GJ, McCormick MC, Zupancic JA, Coleman-Phox K, Armstrong MA, Greene JD, et al. Unstudied infants: outcomes of moderately premature infants in the neonatal intensive care unit. Arch Dis Child Fetal Neonatal Ed 2006;91(4):F238-44.

31.   Goldenberg RL, Rouse DJ. Preterm birth, cerebral palsy and magnesium. Nat Med 1997;3(2):146-7.

32.   Hagberg B, Hagberg G, Beckung E, Uvebrant P. Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991-94. Acta Paediatr 2001;90(3):271-7.

33.   Stanley FJ. The aetiology of cerebral palsy. Early Hum Dev 1994;36(2):81-8.

34.   Yoon BH, Jun JK, Romero R, Park KH, Gomez R, Choi JH, et al. Amniotic fluid inflammatory cytokines (interleukin-6, interleukin-1beta, and tumor necrosis factor-alpha), neonatal brain white matter lesions, and cerebral palsy. Am J Obstet Gynecol 1997;177(1):19-26.

35.   Verma U, Tejani N, Klein S, Reale MR, Beneck D, Figueroa R, et al. Obstetric antecedents of intraventricular hemorrhage and periventricular leukomalacia in the low-birth-weight neonate. Am J Obstet Gynecol 1997;176(2):275-81.

36.   Goldenberg RL, Rouse DJ. Prevention of premature birth. N Engl J Med 1998;339(5):313-20.

37.   Swamy GK, Ostbye T, Skjaerven R. Association of preterm birth with long-term survival, reproduction, and next-generation preterm birth. Jama 2008;299(12):1429-36.

38.   Lumley J. The epidemiology of preterm birth. Baillieres Clin Obstet Gynaecol 1993;7(3):477-98.

39.   Moutquin JM. Classification and heterogeneity of preterm birth. Bjog 2003;110 Suppl 20:30-3.

40.   Wang ML, Dorer DJ, Fleming MP, Catlin EA. Clinical outcomes of near-term infants. Pediatrics 2004;114(2):372-6.

41.   Tomashek KM, Shapiro-Mendoza CK, Weiss J, Kotelchuck M, Barfield W, Evans S, et al. Early discharge among late preterm and term newborns and risk of neonatal morbidity. Semin Perinatol 2006;30(2):61-8.

42.   Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, Barfield W, Weiss J, Evans S. Risk factors for neonatal morbidity and mortality among "healthy," late preterm newborns. Semin Perinatol 2006;30(2):54-60.

43.   Gilbert WM, Nesbitt TS, Danielsen B. The cost of prematurity: quantification by gestational age and birth weight. Obstet Gynecol 2003;102(3):488-92.

44.   Sarici SU, Serdar MA, Korkmaz A, Erdem G, Oran O, Tekinalp G, et al. Incidence, course, and prediction of hyperbilirubinemia in near-term and term newborns. Pediatrics 2004;113(4):775-80.

45.   Klassen AF, Lee SK, Raina P, Chan HW, Matthew D, Brabyn D. Health status and health-related quality of life in a population-based sample of neonatal intensive care unit graduates. Pediatrics 2004;113(3 Pt 1):594-600.

46.   Jones JS, Istwan NB, Jacques D, Coleman SK, Stanziano G. Is 34 weeks an acceptable goal for a complicated singleton pregnancy? Manag Care 2002;11(10):42-7.

47.   Huddy CL, Johnson A, Hope PL. Educational and behavioural problems in babies of 32-35 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;85(1):F23-8.

48.   Arnon S, Dolfin T, Litmanovitz I, Regev R, Bauer S, Fejgin M. Preterm labour at 34--36 weeks of gestation: should it be arrested? Paediatr Perinat Epidemiol 2001;15(3):252-6.

49.   Seubert DE, Stetzer BP, Wolfe HM, Treadwell MC. Delivery of the marginally preterm infant: what are the minor morbidities? Am J Obstet Gynecol 1999;181(5 Pt 1):1087-91.

50.   Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J. US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, hispanics, and blacks. Pediatrics 2003;111(1):e61-6.

51.   Raju TN. Epidemiology of late preterm (near-term) births. Clin Perinatol 2006;33(4):751-63; abstract vii.

52.   Davidoff MJ, Dias T, Damus K, Russell R, Bettegowda VR, Dolan S, et al. Changes in the gestational age distribution among U.S. singleton births: impact on rates of late preterm birth, 1992 to 2002. Semin Perinatol 2006;30(1):8-15.

53.   Petrou S. Economic consequences of preterm birth and low birthweight. Bjog 2003;110 Suppl 20:17-23.

54.   Berhman RE BA. Preterm birth: causes, consequences and prevention. Washington DC: Institute of Medicine of the National Academies; 2006.

55.   St John EB, Nelson KG, Cliver SP, Bishnoi RR, Goldenberg RL. Cost of neonatal care according to gestational age at birth and survival status. Am J Obstet Gynecol 2000;182(1 Pt 1):170-5.

56.   Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. Bmj 2001;323(7323):1213-7.

57.   Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet 2001;357(9273):2002-6.

58.   Catov JM, Newman AB, Roberts JM, Kelsey SF, Sutton-Tyrrell K, Harris TB, et al. Preterm delivery and later maternal cardiovascular disease risk. Epidemiology 2007;18(6):733-9.

59.   Engle WA. A recommendation for the definition of "late preterm" (near-term) and the birth weight-gestational age classification system. Semin Perinatol 2006;30(1):2-7.

60.	Cockburn F DC. The low-birth-weight infants. Osney Mead, Australia: Blackwell Scientific Publications; 1974.
61.	The prevention of perinatal mortality and morbidity. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser 1970;457:1-60.
62.	American Academy of Pediatrics and the American College of Obstetricians and Gynecologists. Guidelines for Perinatal Care. Elk Grove Village (IL); 2005.
63.	Miller HC, Jekel JF. Epidemiology of spontaneous premature rupture of membranes: factors in pre-term births. Yale J Biol Med 1989;62(3):241-51.
64.	Ferraz EM, Gray RH, Cunha TM. Determinants of preterm delivery and intrauterine growth retardation in north-east Brazil. Int J Epidemiol 1990;19(1):101-8.
65.	Windham GC, Hopkins B, Fenster L, Swan SH. Prenatal active or passive tobacco smoke exposure and the risk of preterm delivery or low birth weight. Epidemiology 2000;11(4):427-33.
66.	Pickett KE, Abrams B, Selvin S. Defining preterm delivery--the epidemiology of clinical presentation. Paediatr Perinat Epidemiol 2000;14(4):305-8.
67.	Berkowitz GS, Blackmore-Prince C, Lapinski RH, Savitz DA. Risk factors for preterm birth subtypes. Epidemiology 1998;9(3):279-85.
68.	Savitz DA, Dole N, Herring AH, Kaczor D, Murphy J, Siega-Riz AM, et al. Should spontaneous and medically indicated preterm births be separated for studying aetiology? Paediatr Perinat Epidemiol 2005;19(2):97-105.
69.	Klebanoff MA, Shiono PH. Top down, bottom up and inside out: reflections on preterm birth. Paediatr Perinat Epidemiol 1995;9(2):125-9.
70.	Raju TN, Higgins RD, Stark AR, Leveno KJ. Optimizing care and outcome for late-preterm (near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. Pediatrics 2006;118(3):1207-14.
71.	Williams MA, Mittendorf R, Stubblefield PG, Lieberman E, Schoenbaum SC, Monson RR. Cigarettes, coffee, and preterm premature rupture of the membranes. Am J Epidemiol 1992;135(8):895-903.
72.	Tucker JM, Goldenberg RL, Davis RO, Copper RL, Winkler CL, Hauth JC. Etiologies of preterm birth in an indigent population: is prevention a logical expectation? Obstet Gynecol 1991;77(3):343-7.
73.	Savitz DA, Blackmore CA, Thorp JM. Epidemiologic characteristics of preterm delivery: etiologic heterogeneity. Am J Obstet Gynecol 1991;164(2):467-71.
74.	Hadley CB, Main DM, Gabbe SG. Risk factors for preterm premature rupture of the fetal membranes. Am J Perinatol 1990;7(4):374-9.
75.	Hagberg H, Wennerholm UB. [Spontaneous premature birth: physiopathology, predictors and management. The frequency is constant--early detection can improve therapeutic possibilities]. Lakartidningen 2000;97(4):301-6, 308-10.
76.	Arias F, Tomich P. Etiology and outcome of low birth weight and preterm infants. Obstet Gynecol 1982;60(3):277-81.
77.	Main DM, Gabbe SG, Richardson D, Strong S. Can preterm deliveries be prevented? Am J Obstet Gynecol 1985;151(7):892-8.
78.	Piekkala P, Kero P, Erkkola R, Sillanpaa M. Perinatal events and neonatal morbidity: an analysis of 5380 cases. Early Hum Dev 1986;13(3):249-68.
79.	Meis PJ, Ernest JM, Moore ML, Michielutte R, Sharp PC, Buescher PA. Regional program for prevention of premature birth in northwestern North Carolina. Am J Obstet Gynecol 1987;157(3):550-6.
80.	Meis PJ, Ernest JM, Moore ML. Causes of low birth weight births in public and private patients. Am J Obstet Gynecol 1987;156(5):1165-8.
81.	Zhang J, Savitz DA. Preterm birth subtypes among blacks and whites. Epidemiology 1992;3(5):428-33.
82.	Lunde A, Melve KK, Gjessing HK, Skjaerven R, Irgens LM. Genetic and environmental influences on birth weight, birth length, head circumference, and gestational age by use of population-based parent-offspring data. Am J Epidemiol 2007;165(7):734-41.
83.	Menon R, Merialdi M, Betran AP, Dolan S, Jiang L, Fortunato SJ, et al. Analysis of association between maternal tumor necrosis factor-alpha promoter polymorphism (-308), tumor necrosis factor concentration, and preterm birth. Am J Obstet Gynecol 2006;195(5):1240-8.
84.	Gottesman, II, Shields J. Genetic theorizing and schizophrenia. Br J Psychiatry 1973;122(566):15-30.
85.	Flint J, Munafo MR. The endophenotype concept in psychiatric genetics. Psychol Med 2007;37(2):163-80.
86.	Hall MH. Definitions used in relation to gestational age. Paediatr Perinat Epidemiol 1990;4(2):123-8.
87.	Engle WA. Age terminology during the perinatal period. Pediatrics 2004;114(5):1362-4.
88.	Nguyen TH, Larsen T, Engholm G, Moller H. Increased adverse pregnancy outcomes with unreliable last menstruation. Obstet Gynecol 2000;95(6 Pt 1):867-73.

89. Treloar AE, Behn BG, Cowan DW. Analysis of gestational interval. Am J Obstet Gynecol 1967;99(1):34-45.
90. Frazier TM. Error in reported date of last menstrual period. Am J Obstet Gynecol 1959;77(4):915-8.
91. Hammes LM, Treloar AE. Gestational interval from vital records. Am J Public Health Nations Health 1970;60(8):1496-505.
92. Wenner WH, Young EB. Nonspecific date of last menstrual period: an indication of poor reproductive outcome. Am J Obstet Gynecol 1974;120(8):1071-9.
93. Buekens P, Delvoye P, Wollast E, Robyn C. Epidemiology of pregnancies with unknown last menstrual period. J Epidemiol Community Health 1984;38(1):79-80.
94. Hall MH, Carr-Hill RA, Fraser C, Campbell D, Samphier ML. The extent and antecedents of uncertain gestation. Br J Obstet Gynaecol 1985;92(5):445-51.
95. Hall MH, Carr-Hill RA. The significance of uncertain gestation for obstetric outcome. Br J Obstet Gynaecol 1985;92(5):452-60.
96. Alexander GR, Tompkins ME, Cornely DA. Gestational age reporting and preterm delivery. Public Health Rep 1990;105(3):267-75.
97. Kramer MS, McLean FH, Boyd ME, Usher RH. The validity of gestational age estimation by menstrual dating in term, preterm, and postterm gestations. Jama 1988;260(22):3306-8.
98. Parker JD, Schoendorf KC. Implications of cleaning gestational age data. Paediatr Perinat Epidemiol 2002;16(2):181-7.
99. Alexander GR, Allen MC. Conceptualization, measurement, and use of gestational age. I. Clinical and public health practice. J Perinatol 1996;16(1):53-9.
100. Dubowitz LM, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. J Pediatr 1970;77(1):1-10.
101. Finnstrom O. Studies on maturity in newborn infants. VI. Comparison between different methods for maturity estimation. Acta Paediatr Scand 1972;61(1):33-41.
102. Capurro H, Konichezky S, Fonseca D, Caldeyro-Barcia R. A simplified method for diagnosis of gestational age in the newborn infant. J Pediatr 1978;93(1):120-2.
103. Jimenez JM, Tyson JE, Reisch JS. Clinical measures of gestational age in normal pregnancies. Obstet Gynecol 1983;61(4):438-43.
104. Campbell S, Warsof SL, Little D, Cooper DJ. Routine ultrasound screening for the prediction of gestational age. Obstet Gynecol 1985;65(5):613-20.
105. Ott WJ. Accurate gestational dating. Obstet Gynecol 1985;66(3):311-5.
106. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr 1991;119(3):417-23.
107. Kieler H, Axelsson O, Nilsson S, Waldenstrom U. Comparison of ultrasonic measurement of biparietal diameter and last menstrual period as a predictor of day of delivery in women with regular 28 day-cycles. Acta Obstet Gynecol Scand 1993;72(5):347-9.
108. Yang H, Kramer MS, Platt RW, Blondel B, Breart G, Morin I, et al. How does early ultrasound scan estimation of gestational age lead to higher rates of preterm birth? Am J Obstet Gynecol 2002;186(3):433-7.
109. Waldenstrom U, Axelsson O, Nilsson S. A comparison of the ability of a sonographically measured biparietal diameter and the last menstrual period to predict the spontaneous onset of labor. Obstet Gynecol 1990;76(3 Pt 1):336-8.
110. Tunon K, Eik-Nes SH, Grottum P. A comparison between ultrasound and a reliable last menstrual period as predictors of the day of delivery in 15,000 examinations. Ultrasound Obstet Gynecol 1996;8(3):178-85.
111. Mongelli M, Wilcox M, Gardosi J. Estimating the date of confinement: ultrasonographic biometry versus certain menstrual dates. Am J Obstet Gynecol 1996;174(1 Pt 1):278-81.
112. Wennerholm UB, Bergh C, Hagberg H, Sultan B, Wennergren M. Gestational age in pregnancies after in vitro fertilization: comparison between ultrasound measurement and actual age. Ultrasound Obstet Gynecol 1998;12(3):170-4.
113. Henriksen TB, Wilcox AJ, Hedegaard M, Secher NJ. Bias in studies of preterm and postterm delivery due to ultrasound assessment of gestational age. Epidemiology 1995;6(5):533-7.
114. Kallen K. Mid-trimester ultrasound prediction of gestational age: advantages and systematic errors. Ultrasound Obstet Gynecol 2002;20(6):558-63.
115. Savitz DA, Terry JW, Jr., Dole N, Thorp JM, Jr., Siega-Riz AM, Herring AH. Comparison of pregnancy dating by last menstrual period, ultrasound scanning, and their combination. Am J Obstet Gynecol 2002;187(6):1660-6.
116. Taipale P, Hiilesmaa V. Predicting delivery date by ultrasound and last menstrual period in early gestation. Obstet Gynecol 2001;97(2):189-94.
117. Klebanoff MA. Gestational age: not always what it seems. Obstet Gynecol 2007;109(4):798-9.

118. Mustafa G, David RJ. Comparative accuracy of clinical estimate versus menstrual gestational age in computerized birth certificates. Public Health Rep 2001;116(1):15-21.
119. Wingate MS, Alexander GR, Buekens P, Vahratian A. Comparison of Gestational Age Classifications: Date of Last Menstrual Period vs. Clinical Estimate. Ann Epidemiol 2007;17(6):425-30.
120. Health Canada. Canadian Perinatal Health Report, 2003. Ottawa: Minister of Public Works and Government Services Canada; 2003 2003.
121. Laws PJ, Sullivan EA. Australia's Mothers and Babies 2002. Sydney: AIHW National Perinatal Statistics Unit (Perinatal Statistics Series No. 15); 2004.
122. Hoyert DL, Mathews TJ, Menacker F, Strobino DM, Guyer B. Annual summary of vital statistics: 2004. Pediatrics 2006;117(1):168-83.
123. Hogberg U, Larsson N. Early dating by ultrasound and perinatal outcome. A cohort study. Acta Obstet Gynecol Scand 1997;76(10):907-12.
124. Agdestein S. Perinatal and infant mortality: trends and risk factors in Norway 1967-90. Acta Obstet Gynecol Scand Suppl 1994;160:1-30.
125. Joseph KS, Kramer MS, Marcoux S, Ohlsson A, Wen SW, Allen A, et al. Determinants of preterm birth rates in Canada from 1981 through 1983 and from 1992 through 1994. N Engl J Med 1998;339(20):1434-9.
126. Joseph KS, Kramer MS. Recent versus historical trends in preterm birth in Canada. Cmaj 1999;161(11):1409.
127. Berkowitz GS, Papiernik E. Epidemiology of preterm birth. Epidemiol Rev 1993;15(2):414-43.
128. Bergsjo P, Hoffman HJ, Davis RO, Goldenberg RL, Lindmark G, Jacobsen G, et al. Preliminary results from the Collaborative Alabama and Scandinavian Study of Successive Small-for-Gestational Age Births. Acta Obstet Gynecol Scand 1989;68(1):19-25.
129. Goldenberg RL, Davis RO, Cutter GR, Hoffman HJ, Brumfield CG, Foster JM. Prematurity, postdates, and growth retardation: the influence of use of ultrasonography on reported gestational age. Am J Obstet Gynecol 1989;160(2):462-70.
130. Barros FC, Victora CG, Barros AJ, Santos IS, Albernaz E, Matijasevich A, et al. The challenge of reducing neonatal mortality in middle-income countries: findings from three Brazilian birth cohorts in 1982, 1993, and 2004. Lancet 2005;365(9462):847-54.
131. Hall MH. Incidence and distribution of preterm labour. London: Royal College of Obstetricians and Gynaecologists.; 1985.
132. David RJ, Siegel E. Decline in neonatal mortality, 1968 to 1977: better babies or better care? Pediatrics 1983;71(4):531-40.
133. Herron MA, Katz M, Creasy RK. Evaluation of a preterm birth prevention program: preliminary report. Obstet Gynecol 1982;59(4):452-6.
134. Papiernik E, Bouyer J, Dreyfus J, Collin D, Winisdorffer G, Guegen S, et al. Prevention of preterm births: a perinatal study in Haguenau, France. Pediatrics 1985;76(2):154-8.
135. Papiernik E. Prevention of preterm labour and delivery. Baillieres Clin Obstet Gynaecol 1993;7(3):499-521.
136. Papiernik E, Bouyer J, Yaffe K, Winisdorffer G, Collin D, Dreyfus J. Women's acceptance of a preterm birth prevention program. Am J Obstet Gynecol 1986;155(5):939-46.
137. Bouyer J, Dreyfus J, Lazar P, Collin D, Winisdoerffer G, Papiernik E. [Prevention of prematurity: Haguenau perinatal survey, 1971-1985]. Rev Epidemiol Sante Publique 1988;36(2):83-8.
138. Breart G, Blondel B, Tuppin P, Grandjean H, Kaminski M. Did preterm deliveries continue to decrease in France in the 1980s? Paediatr Perinat Epidemiol 1995;9(3):296-306.
139. Blondel B, Norton J, du Mazaubrun C, Breart G. [Development of the main indicators of perinatal health in metropolitan France between 1995 and 1998. Results of the national perinatal survey]. J Gynecol Obstet Biol Reprod (Paris) 2001;30(6):552-64.
140. Olsen P, Laara E, Rantakallio P, Jarvelin MR, Sarpola A, Hartikainen AL. Epidemiology of preterm delivery in two birth cohorts with an interval of 20 years. Am J Epidemiol 1995;142(11):1184-93.
141. Jakobsson M, Gissler M, Paavonen J, Tapper AM. The incidence of preterm deliveries decreases in Finland. Bjog 2008;115(1):38-43.
142. Holmgren PA, Hogberg U. The very preterm infant - a population-based study. Acta Obstet Gynecol Scand 2001;80(6):525-31.
143. Joseph KS, Huang L, Liu S, Ananth CV, Allen AC, Sauve R, et al. Reconciling the high rates of preterm and postterm birth in the United States. Obstet Gynecol 2007;109(4):813-22.
144. Laws PJ, Sullivan, E.A. Australia's mothers and babies 2003. Sydney, Australia: Australian Institute of Health and Welfare's (AIHW) National Perinatal Statistics Unit; 2005.
145. Buitendijk S, Zeitlin J, Cuttini M, Langhoff-Roos J, Bottu J. Indicators of fetal and infant health outcomes. Eur J Obstet Gynecol Reprod Biol 2003;111 Suppl 1:S66-77.

146. Craig ED, Mantell CD, Ekeroma AJ, Stewart AW, Mitchell EA. Ethnicity and birth outcome: New Zealand trends 1980-2001. Part 1. Introduction, methods, results and overview. Aust N Z J Obstet Gynaecol 2004;44(6):530-6.
147. Gissler M. Perinatal statistics in the Nordic countries. Statistical Summary. Helsinki: National Research and Development Centre for Welfare and Health; 2007. Report No.: 22/2007.
148. Szatmari P, Paterson AD, Zwaigenbaum L, Roberts W, Brian J, Liu XQ, et al. Mapping autism risk loci using genetic linkage and chromosomal rearrangements. Nat Genet 2007;39(3):319-28.
149. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447(7145):661-78.
150. Papiernik E, Zeitlin J, Rivera L, Bucourt M, Topuz B. Preterm birth in a French population: the importance of births by medical decision. Bjog 2003;110(4):430-2.
151. Lee SJ, Steer PJ, Filippi V. Seasonal patterns and preterm birth: a systematic review of the literature and an analysis in a London-based cohort. Bjog 2006;113(11):1280-8.
152. Rayco-Solon P, Fulford AJ, Prentice AM. Differential effects of seasonality on preterm birth and intrauterine growth restriction in rural Africans. Am J Clin Nutr 2005;81(1):134-9.
153. Matsuda S, Kahyo H. Seasonality of preterm births in Japan. Int J Epidemiol 1992;21(1):91-100.
154. Keller CA, Nugent RP. Seasonal patterns in perinatal mortality and preterm delivery. Am J Epidemiol 1983;118(5):689-98.
155. Cooperstock M, Wolfe RA. Seasonality of preterm birth in the Collaborative Perinatal Project: demographic factors. Am J Epidemiol 1986;124(2):234-41.
156. Hort KP. Seasonal variation of birthweight in Bangladesh. Ann Trop Paediatr 1987;7(1):66-71.
157. Friis H, Gomo E, Nyazema N, Ndhlovu P, Krarup H, Kaestel P, et al. Maternal body composition, HIV infection and other predictors of gestation length and birth size in Zimbabwe. Br J Nutr 2004;92(5):833-40.
158. Konte JM, Creasy RK, Laros RK, Jr. California North Coast Preterm Birth Prevention project. Obstet Gynecol 1988;71(5):727-30.
159. Hulsey TC, Levkoff AH, Alexander GR, Tompkins M. Differences in black and white infant birth weights: the role of maternal demographic factors and medical complications of pregnancy. South Med J 1991;84(4):443-6.
160. Foster HW, Jr. The enigma of low birth weight and race. N Engl J Med 1997;337(17):1232-3.
161. Iams JD. The epidemiology of preterm birth. Clin Perinatol 2003;30(4):651-64.
162. Thompson JM, Irgens LM, Rasmussen S, Daltveit AK. Secular trends in socio-economic status and the implications for preterm birth. Paediatr Perinat Epidemiol 2006;20(3):182-7.
163. Peacock JL, Bland JM, Anderson HR. Preterm delivery: effects of socioeconomic factors, psychological stress, smoking, alcohol, and caffeine. Bmj 1995;311(7004):531-5.
164. Parker JD, Schoendorf KC, Kiely JL. Associations between measures of socioeconomic status and low birth weight, small for gestational age, and premature delivery in the United States. Ann Epidemiol 1994;4(4):271-8.
165. de Sanjose S, Roman E. Low birthweight, preterm, and small for gestational age babies in Scotland, 1981-1984. J Epidemiol Community Health 1991;45(3):207-10.
166. Berkowitz GS. An epidemiologic study of preterm delivery. Am J Epidemiol 1981;113(1):81-92.
167. Basso O, Olsen J, Christensen K. Study of environmental, social, and paternal factors in preterm delivery using sibs and half sibs. A population-based study in Denmark. J Epidemiol Community Health 1999;53(1):20-3.
168. Pickett KE, Ahern JE, Selvin S, Abrams B. Neighborhood socioeconomic status, maternal race and preterm delivery: a case-control study. Ann Epidemiol 2002;12(6):410-8.
169. Tough SC, Newburn-Cook C, Johnston DW, Svenson LW, Rose S, Belik J. Delayed childbearing and its impact on population rate changes in lower birth weight, multiple birth, and preterm delivery. Pediatrics 2002;109(3):399-403.
170. 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.
171. Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. Obstet Gynecol 2004;103(2):219-24.
172. Jensen DM, Damm P, Sorensen B, Molsted-Pedersen L, Westergaard JG, Ovesen P, et al. Pregnancy outcome and prepregnancy body mass index in 2459 glucose-tolerant Danish women. Am J Obstet Gynecol 2003;189(1):239-44.
173. Rosenberg TJ, Garbers S, Lipkind H, Chiasson MA. Maternal obesity and diabetes as risk factors for adverse pregnancy outcomes: differences among 4 racial/ethnic groups. Am J Public Health 2005;95(9):1545-51.
174. Cnattingius S, Bergstrom R, Lipworth L, Kramer MS. Prepregnancy weight and the risk of adverse pregnancy outcomes. N Engl J Med 1998;338(3):147-52.

175.   Hendler I, Goldenberg RL, Mercer BM, Iams JD, Meis PJ, Moawad AH, et al. The Preterm Prediction Study: association between maternal body mass index and spontaneous and indicated preterm birth. Am J Obstet Gynecol 2005;192(3):882-6.
176.   Barros FC, Huttly SR, Victora CG, Kirkwood BR, Vaughan JP. Comparison of the causes and consequences of prematurity and intrauterine growth retardation: a longitudinal study in southern Brazil. Pediatrics 1992;90(2 Pt 1):238-44.
177.   Kramer MS, Coates AL, Michoud MC, Dagenais S, Hamilton EF, Papageorgiou A. Maternal anthropometry and idiopathic preterm labor. Obstet Gynecol 1995;86(5):744-8.
178.   Macfarlane A, Cole S, Johnson A, Botting B. Epidemiology of birth before 28 weeks of gestation. Br Med Bull 1988;44(4):861-93.
179.   Neggers Y, Goldenberg RL. Some thoughts on body mass index, micronutrient intakes and pregnancy outcome. J Nutr 2003;133(5 Suppl 2):1737S-1740S.
180.   Hickey CA, Cliver SP, McNeal SF, Goldenberg RL. Low pregravid body mass index as a risk factor for preterm birth: variation by ethnic group. Obstet Gynecol 1997;89(2):206-12.
181.   Carmichael SL, Abrams B. A critical review of the relationship between gestational weight gain and preterm delivery. Obstet Gynecol 1997;89(5 Pt 2):865-73.
182.   Gosselink CA, Ekwo EE, Woolson RF, Moawad A, Long CR. Dietary habits, prepregnancy weight, and weight gain during pregnancy. Risk of pre term rupture of amniotic sac membranes. Acta Obstet Gynecol Scand 1992;71(6):425-38.
183.   Khoury J, Henriksen T, Christophersen B, Tonstad S. Effect of a cholesterol-lowering diet on maternal, cord, and neonatal lipids, and pregnancy outcome: a randomized clinical trial. Am J Obstet Gynecol 2005;193(4):1292-301.
184.   Haugen M, Meltzer HM, Brantsaeter AL, Mikkelsen T, Osterdal ML, Alexander J, et al. Mediterranean-type diet and risk of preterm birth among women in the Norwegian Mother and Child Cohort Study (MoBa): a prospective cohort study. Acta Obstet Gynecol Scand 2008;87(3):319-24.
185.   Mikkelsen TB, Osterdal ML, Knudsen VK, Haugen M, Meltzer HM, Bakketeig L, et al. Association between a Mediterranean-type diet and risk of preterm birth among Danish women: a prospective cohort study. Acta Obstet Gynecol Scand 2008;87(3):325-30.
186.   Mainous AG, 3rd, Hueston WJ. The effect of smoking cessation during pregnancy on preterm delivery and low birthweight. J Fam Pract 1994;38(3):262-6.
187.   Simpson WJ. A preliminary report on cigarette smoking and the incidence of prematurity. Am J Obstet Gynecol 1957;73(4):807-15.
188.   Meyer MB, Tonascia JA. Maternal smoking, pregnancy complications, and perinatal mortality. Am J Obstet Gynecol 1977;128(5):494-502.
189.   Shiono PH, Klebanoff MA, Rhoads GG. Smoking and drinking during pregnancy. Their effects on preterm birth. Jama 1986;255(1):82-4.
190.   McDonald AD, Armstrong BG, Sloan M. Cigarette, alcohol, and coffee consumption and prematurity. Am J Public Health 1992;82(1):87-90.
191.   Meis PJ, Michielutte R, Peters TJ, Wells HB, Sands RE, Coles EC, et al. Factors associated with preterm birth in Cardiff, Wales. I. Univariable and multivariable analysis. Am J Obstet Gynecol 1995;173(2):590-6.
192.   Kallen K. The impact of maternal smoking during pregnancy on delivery outcome. Eur J Public Health 2001;11(3):329-33.
193.   Wisborg K, Henriksen TB, Hedegaard M, Secher NJ. Smoking during pregnancy and preterm birth. Br J Obstet Gynaecol 1996;103(8):800-5.
194.   Kyrklund-Blomberg NB, Cnattingius S. Preterm birth and maternal smoking: risks related to gestational age and onset of delivery. Am J Obstet Gynecol 1998;179(4):1051-5.
195.   Haug K, Irgens LM, Skjaerven R, Markestad T, Baste V, Schreuder P. Maternal smoking and birthweight: effect modification of period, maternal age and paternal smoking. Acta Obstet Gynecol Scand 2000;79(6):485-9.
196.   Lumley J. Defining the problem: the epidemiology of preterm birth. Bjog 2003;110 Suppl 20:3-7.
197.   Lumley J, Oliver SS, Chamberlain C, Oakley L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst Rev 2004(4):CD001055.
198.   Mamelle N, Laumon B, Lazar P. Prematurity and occupational activity during pregnancy. Am J Epidemiol 1984;119(3):309-22.
199.   Newman RB, Goldenberg RL, Moawad AH, Iams JD, Meis PJ, Das A, et al. Occupational fatigue and preterm premature rupture of membranes. National Institute of Child Health and Human Development Maternal-Fetal Medicine, Units Network. Am J Obstet Gynecol 2001;184(3):438-46.
200.   Escriba-Aguir V, Perez-Hoyos S, Saurel-Cubizolles MJ. Physical load and psychological demand at work during pregnancy and preterm birth. Int Arch Occup Environ Health 2001;74(8):583-8.

201.   Luke B, Mamelle N, Keith L, Munoz F, Minogue J, Papiernik E, et al. The association between occupational factors and preterm birth: a United States nurses' study. Research Committee of the Association of Women's Health, Obstetric, and Neonatal Nurses. Am J Obstet Gynecol 1995;173(3 Pt 1):849-62.
202.   Mozurkewich EL, Luke B, Avni M, Wolf FM. Working conditions and adverse pregnancy outcome: a meta-analysis. Obstet Gynecol 2000;95(4):623-35.
203.   Saurel-Cubizolles MJ, Zeitlin J, Lelong N, Papiernik E, Di Renzo GC, Breart G. Employment, working conditions, and preterm birth: results from the Europop case-control survey. J Epidemiol Community Health 2004;58(5):395-401.
204.   Raga F, Bauset C, Remohi J, Bonilla-Musoles F, Simon C, Pellicer A. Reproductive impact of congenital Mullerian anomalies. Hum Reprod 1997;12(10):2277-81.
205.   Meis PJ, Goldenberg RL, Mercer BM, Iams JD, Moawad AH, Miodovnik M, et al. The preterm prediction study: risk factors for indicated preterm births. Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development. Am J Obstet Gynecol 1998;178(3):562-7.
206.   Kaufman RH, Adam E, Hatch EE, Noller K, Herbst AL, Palmer JR, et al. Continued follow-up of pregnancy outcomes in diethylstilbestrol-exposed offspring. Obstet Gynecol 2000;96(4):483-9.
207.   Goepfert AR, Andrews WW, Carlo W, Ramsey PS, Cliver SP, Goldenberg RL, et al. Umbilical cord plasma interleukin-6 concentrations in preterm infants and risk of neonatal morbidity. Am J Obstet Gynecol 2004;191(4):1375-81.
208.   Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, et al. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol 1996;67(10 Suppl):1103-13.
209.   Okun N, Mitchell BF, Willan AR, Armson BA, Hannah M. Perspectives on the management of the short cervix identified by transvaginal ultrasound during pregnancy: an update for Canadian obstetrical caregivers. J Obstet Gynaecol Can 2006;28(3):203-5.
210.   Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005;366(9499):1809-20.
211.   Dortbudak O, Eberhardt R, Ulm M, Persson GR. Periodontitis, a marker of risk in pregnancy for preterm birth. J Clin Periodontol 2005;32(1):45-52.
212.   Jeffcoat MK, Geurs NC, Reddy MS, Cliver SP, Goldenberg RL, Hauth JC. Periodontal infection and preterm birth: results of a prospective study. J Am Dent Assoc 2001;132(7):875-80.
213.   Davenport ES, Williams CE, Sterne JA, Murad S, Sivapathasundram V, Curtis MA. Maternal periodontal disease and preterm low birthweight: case-control study. J Dent Res 2002;81(5):313-8.
214.   Moore S, Ide M, Randhawa M, Walker JJ, Reid JG, Simpson NA. An investigation into the association among preterm birth, cytokine gene polymorphisms and periodontal disease. Bjog 2004;111(2):125-32.
215.   Xiong X, Buekens P, Fraser WD, Beck J, Offenbacher S. Periodontal disease and adverse pregnancy outcomes: a systematic review. Bjog 2006;113(2):135-43.
216.   Lobel M, Dunkel-Schetter C, Scrimshaw SC. Prenatal maternal stress and prematurity: a prospective study of socioeconomically disadvantaged women. Health Psychol 1992;11(1):32-40.
217.   Lockwood CJ. Stress-associated preterm delivery: the role of corticotropin-releasing hormone. Am J Obstet Gynecol 1999;180(1 Pt 3):S264-6.
218.   Hobel CJ, Dunkel-Schetter C, Roesch SC, Castro LC, Arora CP. Maternal plasma corticotropin-releasing hormone associated with stress at 20 weeks' gestation in pregnancies ending in preterm delivery. Am J Obstet Gynecol 1999;180(1 Pt 3):S257-63.
219.   Copper RL, Goldenberg RL, Das A, Elder N, Swain M, Norman G, et al. The preterm prediction study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1996;175(5):1286-92.
220.   Smith GC, Pell JP, Dobbie R. Interpregnancy interval and risk of preterm birth and neonatal death: retrospective cohort study. Bmj 2003;327(7410):313.
221.   DeFranco EA, Stamilio DM, Boslaugh SE, Gross GA, Muglia LJ. A short interpregnancy interval is a risk factor for preterm birth and its recurrence. Am J Obstet Gynecol 2007;197(3):264 e1-6.
222.   Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. Jama 2006;295(15):1809-23.
223.   Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008;371(9606):75-84.
224.   Hoffman HJ, Bakketeig LS. Risk factors associated with the occurrence of preterm birth. Clin Obstet Gynecol 1984;27(3):539-52.
225.   Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. Br J Obstet Gynaecol 1985;92(9):921-8.
226.   Porter TF, Fraser AM, Hunter CY, Ward RH, Varner MW. The risk of preterm birth across generations. Obstet Gynecol 1997;90(1):63-7.

227.   Bakketeig LSH, H.J. Epidemiology of preterm birth. results from a longitudinal study of births in Norway. In: Elder MGH, C.H., editor. Preterm Labour. London: Butterworth; 1981. p. 17-46.
228.   Berghella V, Odibo AO, To MS, Rust OA, Althuisius SM. Cerclage for short cervix on ultrasonography: meta-analysis of trials using individual patient-level data. Obstet Gynecol 2005;106(1):181-9.
229.   Hewitt BG, Newnham JP. A review of the obstetric and medical complications leading to the delivery of infants of very low birthweight. Med J Aust 1988;149(5):234, 236, 238 passim.
230.   Linhart Y, Bashiri A, Maymon E, Shoham-Vardi I, Furman B, Vardi H, et al. Congenital anomalies are an independent risk factor for neonatal morbidity and perinatal mortality in preterm birth. Eur J Obstet Gynecol Reprod Biol 2000;90(1):43-9.
231.   Hartikainen-Sorri AL, Sorri M. Occupational and socio-medical factors in preterm birth. Obstet Gynecol 1989;74(1):13-6.
232.   Chen CP, Wang KG, Yang YC, See LC. Risk factors for preterm birth in an upper middle class Chinese population. Eur J Obstet Gynecol Reprod Biol 1996;70(1):53-9.
233.   Cooperstock M, Campbell J. Excess males in preterm birth: interactions with gestational age, race, and multiple birth. Obstet Gynecol 1996;88(2):189-93.
234.   Ingemarsson I. Gender aspects of preterm birth. Bjog 2003;110 Suppl 20:34-8.
235.   Harlow BL, Frigoletto FD, Cramer DW, Evans JK, LeFevre ML, Bain RP, et al. Determinants of preterm delivery in low-risk pregnancies. The RADIUS Study Group. J Clin Epidemiol 1996;49(4):441-8.
236.   Brodsky JB, Cohen EN, Brown BW, Jr., Wu ML, Whitcher C. Surgery during pregnancy and fetal outcome. Am J Obstet Gynecol 1980;138(8):1165-7.
237.   Radman HM. Pregnancy Complicated by Nonobstetric Surgical Disease. Arch Surg 1964;88:279-86.
238.   Smith BE. Fetal Prognosis after Anesthesia During Gestation. Anesth Analg 1963;42:521-6.
239.   Shnider SM, Webster GM. Maternal and Fetal Hazards of Surgery During Pregnancy. Am J Obstet Gynecol 1965;92:891-900.
240.   Visser BC, Glasgow RE, Mulvihill KK, Mulvihill SJ. Safety and timing of nonobstetric abdominal surgery in pregnancy. Dig Surg 2001;18(5):409-17.
241.   Mazze RI, Kallen B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5405 cases. Am J Obstet Gynecol 1989;161(5):1178-85.
242.   Jenkins TM, Mackey SF, Benzoni EM, Tolosa JE, Sciscione AC. Non-obstetric surgery during gestation: risk factors for lower birthweight. Aust N Z J Obstet Gynaecol 2003;43(1):27-31.
243.   Krampl E, Klein K. [Prematurity in multiple pregnancies]. Gynakol Geburtshilfliche Rundsch 2007;47(2):64-9.
244.   Daltveit AK, Vollset SE, Skjaerven R, Irgens LM. Impact of multiple births and elective deliveries on the trends in low birth weight in Norway, 1967-1995. Am J Epidemiol 1999;149(12):1128-33.
245.   Gardner MO, Goldenberg RL, Cliver SP, Tucker JM, Nelson KG, Copper RL. The origin and outcome of preterm twin pregnancies. Obstet Gynecol 1995;85(4):553-7.
246.   Tucker J, McGuire W. Epidemiology of preterm birth. Bmj 2004;329(7467):675-8.
247.   Ventura SJ, Martin JA, Curtin SC, Mathews TJ. Births: final data for 1997. Natl Vital Stat Rep 1999;47(18):1-96.
248.   Glinianaia SV, Rankin J, Renwick M. Time trends in twin perinatal mortality in northern England, 1982-94. Northern Region Perinatal Mortality Survey Steering Group. Twin Res 1998;1(4):189-95.
249.   Joseph KS, Allen AC, Dodds L, Vincer MJ, Armson BA. Causes and consequences of recent increases in preterm birth among twins. Obstet Gynecol 2001;98(1):57-64.
250.   Blondel B, Kogan MD, Alexander GR, Dattani N, Kramer MS, Macfarlane A, et al. The impact of the increasing number of multiple births on the rates of preterm birth and low birthweight: an international study. Am J Public Health 2002;92(8):1323-30.
251.   Perri T, Chen R, Yoeli R, Merlob P, Orvieto R, Shalev Y, et al. Are singleton assisted reproductive technology pregnancies at risk of prematurity? J Assist Reprod Genet 2001;18(5):245-9.
252.   Kallen B, Finnstrom O, Nygren KG, Olausson PO. In vitro fertilization (IVF) in Sweden: infant outcome after different IVF fertilization methods. Fertil Steril 2005;84(3):611-7.
253.   Wang JX, Norman RJ, Kristiansson P. The effect of various infertility treatments on the risk of preterm birth. Hum Reprod 2002;17(4):945-9.
254.   Romero R, Espinoza J, Goncalves LF, Kusanovic JP, Friel L, Hassan S. The role of inflammation and infection in preterm birth. Semin Reprod Med 2007;25(1):21-39.
255.   Hibbard L, Thrupp L, Summeril S, Smale M, Adams R. Treatment of pyelonephritis in pregnancy. Am J Obstet Gynecol 1967;98(5):609-15.
256.   Patrick MJ. Influence of maternal renal infection on the foetus and infant. Arch Dis Child 1967;42(222):208-13.
257.   Wren BG. Subclinical renal infection and prematurity. Med J Aust 1969;2(12):596-600.

258.   Cunningham FG, Morris GB, Mickal A. Acute pyelonephritis of pregnancy: A clinical review. Obstet Gynecol 1973;42(1):112-7.
259.   Fan YD, Pastorek JG, 2nd, Miller JM, Jr., Mulvey J. Acute pyelonephritis in pregnancy. Am J Perinatol 1987;4(4):324-6.
260.   Benedetti TJ, Valle R, Ledger WJ. Antepartum pneumonia in pregnancy. Am J Obstet Gynecol 1982;144(4):413-7.
261.   Madinger NE, Greenspoon JS, Ellrodt AG. Pneumonia during pregnancy: has modern technology improved maternal and fetal outcome? Am J Obstet Gynecol 1989;161(3):657-62.
262.   Oxorn H. The changing aspects of pneumonia complicating pregnancy. Am J Obstet Gynecol 1955;70(5):1057-63.
263.   Kalanda BF, Verhoeff FH, Chimsuku L, Harper G, Brabin BJ. Adverse birth outcomes in a malarious area. Epidemiol Infect 2006;134(3):659-66.
264.   Heard N, Jordan T. An investigation of malaria during pregnancy in Zimbabwe. Cent Afr J Med 1981;27(4):62-3, 66-8.
265.   Gilles HM, Lawson JB, Sibelas M, Voller A, Allan N. Malaria, anaemia and pregnancy. Ann Trop Med Parasitol 1969;63(2):245-63.
266.   Osman NB, Folgosa E, Gonzales C, Bergstrom S. Genital infections in the aetiology of late fetal death: an incident case-referent study. J Trop Pediatr 1995;41(5):258-66.
267.   Horowitz S, Mazor M, Romero R, Horowitz J, Glezerman M. Infection of the amniotic cavity with Ureaplasma urealyticum in the midtrimester of pregnancy. J Reprod Med 1995;40(5):375-9.
268.   Gray DJ, Robinson HB, Malone J, Thomson RB, Jr. Adverse outcome in pregnancy following amniotic fluid isolation of Ureaplasma urealyticum. Prenat Diagn 1992;12(2):111-7.
269.   Cassell GH, Davis RO, Waites KB, Brown MB, Marriott PA, Stagno S, et al. Isolation of Mycoplasma hominis and Ureaplasma urealyticum from amniotic fluid at 16-20 weeks of gestation: potential effect on outcome of pregnancy. Sex Transm Dis 1983;10(4 Suppl):294-302.
270.   Yoon BH, Oh SY, Romero R, Shim SS, Han SY, Park JS, et al. An elevated amniotic fluid matrix metalloproteinase-8 level at the time of mid-trimester genetic amniocentesis is a risk factor for spontaneous preterm delivery. Am J Obstet Gynecol 2001;185(5):1162-7.
271.   Wenstrom KD, Andrews WW, Hauth JC, Goldenberg RL, DuBard MB, Cliver SP. Elevated second-trimester amniotic fluid interleukin-6 levels predict preterm delivery. Am J Obstet Gynecol 1998;178(3):546-50.
272.   Romero R, Espinoza J, Kusanovic J, Gotsch F, Hassan S, Erez O, et al. The preterm parturition syndrome. Bjog 2006;113 Suppl 3:17-42.
273.   Goncalves LF, Chaiworapongsa T, Romero R. Intrauterine infection and prematurity. Ment Retard Dev Disabil Res Rev 2002;8(1):3-13.
274.   Romero R, Salafia CM, Athanassiadis AP, Hanaoka S, Mazor M, Sepulveda W, et al. The relationship between acute inflammatory lesions of the preterm placenta and amniotic fluid microbiology. Am J Obstet Gynecol 1992;166(5):1382-8.
275.   Fidel P, Ghezzi F, Romero R, Chaiworapongsa T, Espinoza J, Cutright J, et al. The effect of antibiotic therapy on intrauterine infection-induced preterm parturition in rabbits. J Matern Fetal Neonatal Med 2003;14(1):57-64.
276.   Smaill F. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev 2001(2):CD000490.
277.   Romero R, Oyarzun E, Mazor M, Sirtori M, Hobbins JC, Bracken M. Meta-analysis of the relationship between asymptomatic bacteriuria and preterm delivery/low birth weight. Obstet Gynecol 1989;73(4):576-82.
278.   Goldenberg RL, Nelson KG, Koski JF, Cutter GR. Low birth weight, intrauterine growth retardation, and preterm delivery. Am J Obstet Gynecol 1985;152(8):980-4.
279.   Ott WJ. Intrauterine growth retardation and preterm delivery. Am J Obstet Gynecol 1993;168(6 Pt 1):1710-5; discussion 1715-7.
280.   Bukowski R, Gahn D, Denning J, Saade G. Impairment of growth in fetuses destined to deliver preterm. Am J Obstet Gynecol 2001;185(2):463-7.
281.   Lackman F, Capewell V, Richardson B, daSilva O, Gagnon R. The risks of spontaneous preterm delivery and perinatal mortality in relation to size at birth according to fetal versus neonatal growth standards. Am J Obstet Gynecol 2001;184(5):946-53.
282.   Zeitlin J, Ancel PY, Saurel-Cubizolles MJ, Papiernik E. The relationship between intrauterine growth restriction and preterm delivery: an empirical approach using data from a European case-control study. Bjog 2000;107(6):750-8.
283.   Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr 1996;85(7):843-8.
284.   Vatten LJ, Skjaerven R. Is pre-eclampsia more than one disease? Bjog 2004;111(4):298-302.
285.   Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. Lancet 2001;357(9249):53-6.

286.   Roberts JM, Redman CW. Pre-eclampsia: more than pregnancy-induced hypertension. Lancet 1993;341(8858):1447-51.
287.   Ness RB, Roberts JM. Heterogeneous causes constituting the single syndrome of preeclampsia: a hypothesis and its implications. Am J Obstet Gynecol 1996;175(5):1365-70.
288.   Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 2005;365(9461):785-99.
289.   Jakobsson M, Gissler M, Sainio S, Paavonen J, Tapper AM. Preterm delivery after surgical treatment for cervical intraepithelial neoplasia. Obstet Gynecol 2007;109(2 Pt 1):309-13.
290.   Sjoborg KD, Vistad I, Myhr SS, Svenningsen R, Herzog C, Kloster-Jensen A, et al. Pregnancy outcome after cervical cone excision: a case-control study. Acta Obstet Gynecol Scand 2007;86(4):423-8.
291.   Iams JD, Goldenberg RL, Mercer BM, Moawad AH, Meis PJ, Das AF, et al. The preterm prediction study: can low-risk women destined for spontaneous preterm birth be identified? Am J Obstet Gynecol 2001;184(4):652-5.
292.   Catley C, Frize M, Walker CR, Petriu DC. Predicting high-risk preterm birth using artificial neural networks. IEEE Trans Inf Technol Biomed 2006;10(3):540-9.
293.   Ross MG, Hobel CJ, Bragonier JR, Bear MB, Bemis RL. A simplified risk-scoring system for prematurity. Am J Perinatol 1986;3(4):339-44.
294.   Creasy RK, Gummer BA, Liggins GC. System for predicting spontaneous preterm birth. Obstet Gynecol 1980;55(6):692-5.
295.   Berglund A, Lindmark G. The usefulness of initial risk assessment as a predictor of pregnancy complications and premature delivery. Acta Obstet Gynecol Scand 1999;78(10):871-6.
296.   Fedrick J. Antenatal identification of women at high risk of spontaneous pre-term birth. Br J Obstet Gynaecol 1976;83(5):351-4.
297.   Guzick DS, Daikoku NH, Kaltreider DF. Predictability of pregnancy outcome in preterm delivery. Obstet Gynecol 1984;63(5):645-50.
298.   Humphrey MD. The beneficial use of risk scoring in a remote and high-risk pregnant population. Aust N Z J Obstet Gynaecol 1995;35(2):139-43.
299.   Kaminski M, Goujard J, Rumeau-Rouquette C. Prediction of low birthweight and prematurity by a multiple regression analysis with maternal characteristics known since the beginning of the pregnancy. Int J Epidemiol 1973;2(2):195-204.
300.   Mercer BM, Goldenberg RL, Das A, Moawad AH, Iams JD, Meis PJ, et al. The preterm prediction study: a clinical risk assessment system. Am J Obstet Gynecol 1996;174(6):1885-93; discussion 1893-5.
301.   Nesbitt RE, Jr., Aubry RH. High-risk obstetrics. II. Value of semiobjective grading system in identifying the vulnerable group. Am J Obstet Gynecol 1969;103(7):972-85.
302.   Honest H, Bachmann LM, Sundaram R, Gupta JK, Kleijnen J, Khan KS. The accuracy of risk scores in predicting preterm birth--a systematic review. J Obstet Gynaecol 2004;24(4):343-59.
303.   Dyson DC, Danbe KH, Bamber JA, Crites YM, Field DR, Maier JA, et al. Monitoring women at risk for preterm labor. N Engl J Med 1998;338(1):15-9.
304.   Mauldin JG, Newman RB. Preterm birth risk assessment. Semin Perinatol 2001;25(4):215-22.
305.   Darne J, McGarrigle HH, Lachelin GC. Saliva oestriol, oestradiol, oestrone and progesterone levels in pregnancy: spontaneous labour at term is preceded by a rise in the saliva oestriol:progesterone ratio. Br J Obstet Gynaecol 1987;94(3):227-35.
306.   Darne J, McGarrigle HH, Lachelin GC. Increased saliva oestriol to progesterone ratio before preterm delivery: a possible predictor for preterm labor? Br Med J (Clin Res Ed) 1987;294(6567):270-2.
307.   McGarrigle HH, Lachelin GC. Increasing saliva (free) oestriol to progesterone ratio in late pregnancy: a role for oestriol in initiating spontaneous labour in man? Br Med J (Clin Res Ed) 1984;289(6443):457-9.
308.   Heine RP, McGregor JA, Goodwin TM, Artal R, Hayashi RH, Robertson PA, et al. Serial salivary estriol to detect an increased risk of preterm birth. Obstet Gynecol 2000;96(4):490-7.
309.   Moran DJ, McGarrigle HH, Lachelin GC. Lack of normal increase in saliva estriol/progesterone ratio in women with labor induced at 42 weeks' gestation. Am J Obstet Gynecol 1992;167(6):1563-4.
310.   Ramsey PS, Andrews WW. Biochemical predictors of preterm labor: fetal fibronectin and salivary estriol. Clin Perinatol 2003;30(4):701-33.
311.   Krupa FG, Faltin D, Cecatti JG, Surita FG, Souza JP. Predictors of preterm birth. Int J Gynaecol Obstet 2006;94(1):5-11.
312.   Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, et al. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. N Engl J Med 1996;334(9):567-72.
313.   Iams JD, Casal D, McGregor JA, Goodwin TM, Kreaden US, Lowensohn R, et al. Fetal fibronectin improves the accuracy of diagnosis of preterm labor. Am J Obstet Gynecol 1995;173(1):141-5.
314.   Peaceman AM, Andrews WW, Thorp JM, Cliver SP, Lukes A, Iams JD, et al. Fetal fibronectin as a predictor of preterm birth in patients with symptoms: a multicenter trial. Am J Obstet Gynecol 1997;177(1):13-8.

315.   Iams JD. Prediction and early detection of preterm labor. Obstet Gynecol 2003;101(2):402-12.
316.   Goffinet F. Primary predictors of preterm labour. Bjog 2005;112 Suppl 1:38-47.
317.   Lockwood CJ, Senyei AE, Dische MR, Casal D, Shah KD, Thung SN, et al. Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery. N Engl J Med 1991;325(10):669-74.
318.   Goldenberg RL, Mercer BM, Iams JD, Moawad AH, Meis PJ, Das A, et al. The preterm prediction study: patterns of cervicovaginal fetal fibronectin as predictors of spontaneous preterm delivery. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1997;177(1):8-12.
319.   Goldenberg RL, Thom E, Moawad AH, Johnson F, Roberts J, Caritis SN. The preterm prediction study: fetal fibronectin, bacterial vaginosis, and peripartum infection. NICHD Maternal Fetal Medicine Units Network. Obstet Gynecol 1996;87(5 Pt 1):656-60.
320.   Joffe GM, Jacques D, Bemis-Heys R, Burton R, Skram B, Shelburne P. Impact of the fetal fibronectin assay on admissions for preterm labor. Am J Obstet Gynecol 1999;180(3 Pt 1):581-6.
321.   Leitich H, Kaider A. Fetal fibronectin--how useful is it in the prediction of preterm birth? Bjog 2003;110 Suppl 20:66-70.
322.   Owen J, Iams JD. What we have learned about cervical ultrasound. Semin Perinatol 2003;27(3):194-203.
323.   Crane JM, Van den Hof M, Armson BA, Liston R. Transvaginal ultrasound in the prediction of preterm delivery: singleton and twin gestations. Obstet Gynecol 1997;90(3):357-63.
324.   Iams JD, Paraskos J, Landon MB, Teteris JN, Johnson FF. Cervical sonography in preterm labor. Obstet Gynecol 1994;84(1):40-6.
325.   Watson WJ, Stevens D, Welter S, Day D. Observations on the sonographic measurement of cervical length and the risk of premature birth. J Matern Fetal Med 1999;8(1):17-9.
326.   Berghella V, Kuhlman K, Weiner S, Texeira L, Wapner RJ. Cervical funneling: sonographic criteria predictive of preterm delivery. Ultrasound Obstet Gynecol 1997;10(3):161-6.
327.   Leitich H, Brunbauer M, Kaider A, Egarter C, Husslein P. Cervical length and dilatation of the internal cervical os detected by vaginal ultrasonography as markers for preterm delivery: A systematic review. Am J Obstet Gynecol 1999;181(6):1465-72.
328.   Smith GC, Dellens M, White IR, Pell JP. Combined logistic and Bayesian modeling of cesarean section risk. Am J Obstet Gynecol 2004;191(6):2029-34.
329.   Smith GC, White IR, Pell JP, Dobbie R. Predicting cesarean section and uterine rupture among women attempting vaginal birth after prior cesarean section. PLoS Med 2005;2(9):e252.
330.   Thorsen P, Schendel DE, Deshpande AD, Vogel I, Dudley DJ, Olsen J. Identification of biological/biochemical marker(s) for preterm delivery. Paediatr Perinat Epidemiol 2001;15 Suppl 2:90-103.
331.   Goldenberg RL, Iams JD, Mercer BM, Meis P, Moawad A, Das A, et al. What we have learned about the predictors of preterm birth. Semin Perinatol 2003;27(3):185-93.
332.   Eroglu D, Yanik F, Oktem M, Zeyneloglu HB, Kuscu E. Prediction of Preterm Delivery among Women with Threatened Preterm Labor. Gynecol Obstet Invest 2007;64(2):109-116.
333.   Goldenberg RL, Culhane JF. Infection as a cause of preterm birth. Clin Perinatol 2003;30(4):677-700.
334.   Romero R, Brody DT, Oyarzun E, Mazor M, Wu YK, Hobbins JC, et al. Infection and labor. III. Interleukin-1: a signal for the onset of parturition. Am J Obstet Gynecol 1989;160(5 Pt 1):1117-23.
335.   Cox SM, King MR, Casey ML, MacDonald PC. Interleukin-1 beta, -1 alpha, and -6 and prostaglandins in vaginal/cervical fluids of pregnant women before and during labor. J Clin Endocrinol Metab 1993;77(3):805-15.
336.   Casey ML, MacDonald PC. Biomolecular processes in the initiation of parturition: decidual activation. Clin Obstet Gynecol 1988;31(3):533-52.
337.   Gomez R, Ghezzi F, Romero R, Munoz H, Tolosa JE, Rojas I. Premature labor and intra-amniotic infection. Clinical aspects and role of the cytokines in diagnosis and pathophysiology. Clin Perinatol 1995;22(2):281-342.
338.   Wadhwa PD, Garite TJ, Porto M, Glynn L, Chicz-DeMet A, Dunkel-Schetter C, et al. Placental corticotropin-releasing hormone (CRH), spontaneous preterm birth, and fetal growth restriction: a prospective investigation. Am J Obstet Gynecol 2004;191(4):1063-9.
339.   Miyoshi H, Boyle MB, MacKay LB, Garfield RE. Voltage-clamp studies of gap junctions between uterine muscle cells during term and preterm labor. Biophys J 1996;71(3):1324-34.
340.   Orsino A, Taylor CV, Lye SJ. Connexin-26 and connexin-43 are differentially expressed and regulated in the rat myometrium throughout late pregnancy and with the onset of labor. Endocrinology 1996;137(5):1545-53.
341.   Lockwood CJ, Kuczynski E. Risk stratification and pathological mechanisms in preterm delivery. Paediatr Perinat Epidemiol 2001;15 Suppl 2:78-89.

342.   Dammann O, Leviton A. Maternal intrauterine infection, cytokines, and brain damage in the preterm newborn. Pediatr Res 1997;42(1):1-8.
343.   Vergani P, Locatelli A, Doria V, Assi F, Paterlini G, Pezzullo JC, et al. Intraventricular hemorrhage and periventricular leukomalacia in preterm infants. Obstet Gynecol 2004;104(2):225-31.
344.   Dammann O, Allred EN, Veelken N. Increased risk of spastic diplegia among very low birth weight children after preterm labor or prelabor rupture of membranes. J Pediatr 1998;132(3 Pt 1):531-5.
345.   Alexander JM, Gilstrap LC, Cox SM, McIntire DM, Leveno KJ. Clinical chorioamnionitis and the prognosis for very low birth weight infants. Obstet Gynecol 1998;91(5 Pt 1):725-9.
346.   de Vries LS, Eken P, Groenendaal F, Rademaker KJ, Hoogervorst B, Bruinse HW. Antenatal onset of haemorrhagic and/or ischaemic lesions in preterm infants: prevalence and associated obstetric variables. Arch Dis Child Fetal Neonatal Ed 1998;78(1):F51-6.
347.   Murphy DJ, Sellers S, MacKenzie IZ, Yudkin PL, Johnson AM. Case-control study of antenatal and intrapartum risk factors for cerebral palsy in very preterm singleton babies. Lancet 1995;346(8988):1449-54.
348.   Spinillo A, Capuzzo E, Stronati M, Ometto A, Orcesi S, Fazzi E. Effect of preterm premature rupture of membranes on neurodevelopmental outcome: follow up at two years of age. Br J Obstet Gynaecol 1995;102(11):882-7.
349.   Dammann O, Leviton A. Inflammatory brain damage in preterm newborns--dry numbers, wet lab, and causal inferences. Early Hum Dev 2004;79(1):1-15.
350.   Dammann O, Leviton A. Brain damage in preterm newborns: biological response modification as a strategy to reduce disabilities. J Pediatr 2000;136(4):433-8.
351.   Iams JD, Romero R, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet 2008;371(9607):164-75.
352.   McDonald H, Brocklehurst P, Parsons J. Antibiotics for treating bacterial vaginosis in pregnancy. Cochrane Database Syst Rev 2005(1):CD000262.
353.   Okun N, Gronau KA, Hannah ME. Antibiotics for bacterial vaginosis or Trichomonas vaginalis in pregnancy: a systematic review. Obstet Gynecol 2005;105(4):857-68.
354.   Andrews WW, Klebanoff MA, Thom EA, Hauth JC, Carey JC, Meis PJ, et al. Midpregnancy genitourinary tract infection with Chlamydia trachomatis: association with subsequent preterm delivery in women with bacterial vaginosis and Trichomonas vaginalis. Am J Obstet Gynecol 2006;194(2):493-500.
355.   Kenyon SL, Taylor DJ, Tarnow-Mordi W. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. ORACLE Collaborative Group. Lancet 2001;357(9261):979-88.
356.   Kenyon SL, Taylor DJ, Tarnow-Mordi W. Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. ORACLE Collaborative Group. Lancet 2001;357(9261):989-94.
357.   Chandiramani M, Shennan A. Preterm labour: update on prediction and prevention strategies. Curr Opin Obstet Gynecol 2006;18(6):618-24.
358.   Dodd JM, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth. Cochrane Database Syst Rev 2006(1):CD004947.
359.   Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, Thom EA, Spong CY, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. N Engl J Med 2007;357(5):454-61.
360.   Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007;357(5):462-9.
361.   Thornton JG. Progesterone and preterm labor--still no definite answers. N Engl J Med 2007;357(5):499-501.
362.   Simcox R, Shennan A. Cervical cerclage: a review. Int J Surg 2007;5(3):205-9.
363.   Lotgering FK. Clinical aspects of cervical insufficiency. BMC Pregnancy Childbirth 2007;7 Suppl 1:S17.
364.   Daskalakis G, Papantoniou N, Mesogitis S, Antsaklis A. Management of cervical insufficiency and bulging fetal membranes. Obstet Gynecol 2006;107(2 Pt 1):221-6.
365.   Debby A, Sadan O, Glezerman M, Golan A. Favorable outcome following emergency second trimester cerclage. Int J Gynaecol Obstet 2007;96(1):16-9.
366.   Treatment of preterm labor with the beta-adrenergic agonist ritodrine. The Canadian Preterm Labor Investigators Group. N Engl J Med 1992;327(5):308-12.
367.   Anotayanonth S, Subhedar NV, Garner P, Neilson JP, Harigopal S. Betamimetics for inhibiting preterm labour. Cochrane Database Syst Rev 2004(4):CD004352.
368.   Dodd JM, Crowther CA, Dare MR, Middleton P. Oral betamimetics for maintenance therapy after threatened preterm labour. Cochrane Database Syst Rev 2006(1):CD003927.
369.   Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour. The Worldwide Atosiban versus Beta-agonists Study Group. Bjog 2001;108(2):133-42.

370.	Valenzuela GJ, Sanchez-Ramos L, Romero R, Silver HM, Koltun WD, Millar L, et al. Maintenance treatment of preterm labor with the oxytocin antagonist atosiban. The Atosiban PTL-098 Study Group. Am J Obstet Gynecol 2000;182(5):1184-90.
371.	Crowley P. Prophylactic corticosteroids for preterm birth. Cochrane Database Syst Rev 2000(2):CD000065.
372.	Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. Scand J Soc Med 1990;18(2):143-8.
373.	The Swedish Medical Birth Register - A summary of content and quality. Stockholm: Swedish National Board of Health and Welfare; 2003.
374.	Nilsson AC, Spetz CL, Carsjo K, Nightingale R, Smedby B. [Reliability of the hospital registry. The diagnostic data are better than their reputation]. Lakartidningen 1994;91(7):598, 603-5.
375.	Langhoff-Roos J RS. [Validering af Landspatientregisteret (LPR) med henblik på obstetrisk forskning og kvalitetssikring]; 2003.
376.	Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. Acta Obstet Gynecol Scand 2000;79(6):435-9.
377.	World Health Organisation. The prevention of perinatal mortality and morbidity. Geneva, Switzerland; 1970.
378.	Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. Acta Obstet Gynecol Scand 2000;79(6):440-9.
379.	Jacobsson B, Hagberg G, Hagberg B, Ladfors L, Niklasson A, Hagberg H. Cerebral palsy in preterm infants: a population-based case-control study of antenatal and intrapartal risk factors. Acta Paediatr 2002;91(8):946-51.
380.	Olsen J, Basso O, Sorensen HT. What is a population-based registry? Scand J Public Health 1999;27(1):78.
381.	Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22(4):719-48.
382.	Miettinen O. Confounding and effect-modification. Am J Epidemiol 1974;100(5):350-3.
383.	Greenhalgh T. How to read a paper. The basics of evidence based medicine. London: Blackwell Publishing; 2006.
384.	Rothman K. Epidemiology. An Introduction. New York: Oxford University Press; 2002.
385.	Kuh D, Hardy R. Women's health in midlife: findings from a British birth cohort study. J Br Menopause Soc 2003;9(2):55-60.
386.	Steele F, Joshi H, Kallis C, Goldstein H. Changing compatibility of cohabitation and childbearing between young British women born in 1958 and 1970. Popul Stud (Camb) 2006;60(2):137-52.
387.	Gissler M, Louhiala P, Hemminki E. Nordic Medical Birth Registers in epidemiological research. Eur J Epidemiol 1997;13(2):169-75.
388.	Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C. Cohort profile: The Norwegian Mother and Child Cohort Study (MoBa). Int J Epidemiol 2006;35(5):1146-1150.
389.	Ronningen KS, Paltiel L, Meltzer HM, Nordhagen R, Lie KK, Hovengen R, et al. The biobank of the Norwegian mother and child cohort Study: A resource for the next 100 years. Eur J Epidemiol 2006;21(8):619-25.
390.	Olsen J, Melbye M, Olsen SF, Sorensen TI, Aaby P, Andersen AM, et al. The Danish National Birth Cohort--its background, structure and aim. Scand J Public Health 2001;29(4):300-7.
391.	Kallen K. Maternal smoking and congenital malformations. Lund: Lund University; 1999.
392.	Magnus P, Bakketeig L. Epidemiologi. Oslo: Gyldendal Akademisk; 2003.
393.	Steineck G, Hunt H, Adolfsson J. A hierarchical step-model for causation of bias-evaluating cancer treatment with epidemiological methods. Acta Oncol 2006;45(4):421-9.
394.	Steineck G, Kass PH, Ahlbom A. A comprehensive clinical epidemiological theory based on the concept of the source person-time and four distinct study stages. Acta Oncol 1998;37(1):15-23.
395.	Gullen WH, Bearman JE, Johnson EA. Effects of misclassification in epidemiologic studies. Public Health Rep 1968;83(11):914-8.
396.	Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for epidemiological research. Int J Epidemiol 1996;25(2):435-42.
397.	Johanzon M, Odesjo H, Jacobsson B, Sandberg K, Wennerholm UB. Extreme preterm birth: onset of delivery and its effect on infant survival and morbidity. Obstet Gynecol 2008;111(1):42-50.
398.	Morken NH, Magnus P, Jacobsson B. Subgroups of preterm delivery in the Norwegian Mother and Child Cohort Study. Manuscript.
399.	Kallen B KK, Otterblad Olausson P. The Swedish Medical Birth Register. A summary of content and quality: Socialstyrelsen, Epidemiologiskt Centrum; 2003.

400.	Patientregistret. Utskrivningar från sluten vård 1964-2001. Kvalitet och innehåll. Stockholm: Socialstyrelsen, Epdemiologisk Centrum; 2003.
401.	Spetz CL, Carlsson CL, Engqvist M, Forsberg L, Aberg A, Akesson LO, et al. [Reintroduction of social security numbers gives better basis for evaluation. The patient registry is open for research]. Lakartidningen 1996;93(19):1844-7.
402.	Andres RL, Day MC. Perinatal complications associated with maternal tobacco use. Semin Neonatol 2000;5(3):231-41.
403.	Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, Barfield W, Nannini A, Weiss J, et al. Effect of late-preterm birth and maternal medical conditions on newborn morbidity risk. Pediatrics 2008;121(2):e223-32.
404.	Wolf EJ, Vintzileos AM, Rosenkrantz TS, Rodis JF, Salafia CM, Pezzullo JG. Do survival and morbidity of very-low-birth-weight infants vary according to the primary pregnancy complication that results in preterm delivery? Am J Obstet Gynecol 1993;169(5):1233-9.
405.	Hagan R, Benninger H, Chiffings D, Evans S, French N. Very preterm birth--a regional study. Part 1: Maternal and obstetric factors. Br J Obstet Gynaecol 1996;103(3):230-8.
406.	Kimberlin DF, Hauth JC, Owen J, Bottoms SF, Iams JD, Mercer BM, et al. Indicated versus spontaneous preterm delivery: An evaluation of neonatal morbidity among infants weighing </=1000 grams at birth. Am J Obstet Gynecol 1999;180(3 Pt 1):683-9.
407.	Tamura RK, Sabbagha RE, Depp R, Vaisrub N, Dooley SL, Socol ML. Diminished growth in fetuses born preterm after spontaneous labor or rupture of membranes. Am J Obstet Gynecol 1984;148(8):1105-10.
408.	MacGregor SN, Sabbagha RE, Tamura RK, Pielet BW, Feigenbaum SL. Differing fetal growth patterns in pregnancies complicated by preterm labor. Obstet Gynecol 1988;72(6):834-7.
409.	Zeitlin JA, Ancel PY, Saurel-Cubizolles MJ, Papiernik E. Are risk factors the same for small for gestational age versus other preterm births? Am J Obstet Gynecol 2001;185(1):208-15.
410.	Majzoub JA, McGregor JA, Lockwood CJ, Smith R, Taggart MS, Schulkin J. A central theory of preterm and term labor: putative role for corticotropin-releasing hormone. Am J Obstet Gynecol 1999;180(1 Pt 3):S232-41.
411.	Dudley DJ. Immunoendocrinology of preterm labor: the link between corticotropin-releasing hormone and inflammation. Am J Obstet Gynecol 1999;180(1 Pt 3):S251-6.
412.	Goland RS, Jozak S, Warren WB, Conwell IM, Stark RI, Tropper PJ. Elevated levels of umbilical cord plasma corticotropin-releasing hormone in growth-retarded fetuses. J Clin Endocrinol Metab 1993;77(5):1174-9.
413.	Gibbs RS, Eschenbach DA. Use of antibiotics to prevent preterm birth. Am J Obstet Gynecol 1997;177(2):375-80.
414.	Thilaganathan B, Plachouras N, Makrydimas G, Nicolaides KH. Fetal immunodeficiency: a consequence of placental insufficiency. Br J Obstet Gynaecol 1993;100(11):1000-4.
415.	Kalsbeek W, Heiss G. Building bridges between populations and samples in epidemiological studies. Annu Rev Public Health 2000;21:147-69.
416.	Papiernik E. Fetal growth retardation: a limit for the further reduction of preterm births. Matern Child Health J 1999;3(2):63-9.
417.	Smulian JC, Ananth CV, Kinzler WL, Kontopoulos E, Vintzileos AM. Twin deliveries in the United States over three decades: an age-period-cohort analysis. Obstet Gynecol 2004;104(2):278-85.
418.	Orskou J, Kesmodel U, Henriksen TB, Secher NJ. An increasing proportion of infants weigh more than 4000 grams at birth. Acta Obstet Gynecol Scand 2001;80(10):931-6.
419.	Leviton A. Preterm birth and cerebral palsy: is tumor necrosis factor the missing link? Dev Med Child Neurol 1993;35(6):553-8.
420.	Ladfors L, Tessin I, Mattsson LA, Eriksson M, Seeberg S, Fall O. Risk factors for neonatal sepsis in offspring of women with prelabor rupture of the membranes at 34-42 weeks. J Perinat Med 1998;26(2):94-101.
421.	Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342(20):1500-7.
422.	Yoon BH, Romero R, Moon JB, Shim SS, Kim M, Kim G, et al. Clinical significance of intra-amniotic inflammation in patients with preterm labor and intact membranes. Am J Obstet Gynecol 2001;185(5):1130-6.
423.	Villar J, Abalos E, Carroli G, Giordano D, Wojdyla D, Piaggio G, et al. Heterogeneity of perinatal outcomes in the preterm delivery syndrome. Obstet Gynecol 2004;104(1):78-87.
424.	Gray PH, Hurley TM, Rogers YM, O'Callaghan MJ, Tudehope DI, Burns YR, et al. Survival and neonatal and neurodevelopmental outcome of 24-29 week gestation infants according to primary cause of preterm delivery. Aust N Z J Obstet Gynaecol 1997;37(2):161-8.
425.	Owen J, Baker SL, Hauth JC, Goldenberg RL, Davis RO, Copper RL. Is indicated or spontaneous preterm delivery more advantageous for the fetus? Am J Obstet Gynecol 1990;163(3):868-72.
426.	Bakketeig LS, Hoffman HJ, Harley EE. The tendency to repeat gestational age and birth weight in successive births. Am J Obstet Gynecol 1979;135(8):1086-103.