Epidemiology and environmental factors in preterm labour

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An epidemiological and environmental approach is the appropriate starting point to understanding preterm labour. Although there are multiple aetiologies it seems likely that anthropometric and environmental risk factors in combination with inherent genetic susceptibilities contribute to an increased risk of preterm labour for certain women. Population-based studies identifying risk factors and quantifying outcomes facilitate informed counselling and provide a framework for developing prediction tools. Carefully conducted case-control and cohort studies identify associations that may contribute to an understanding of causation. A combined approach encompassing epidemiology, pathophysiology and clinical research is required to understand the aetiologies, prevention and optimal management of preterm labour. This review focuses on the epidemiology of preterm labour and the role of environmental factors.

Key words: preterm labour; epidemiology; environmental factors; risk factor; risk assessment.

The precise aetiologies of preterm labour remain elusive, limiting the development of preventative and therapeutic strategies. An understanding of the pathogenesis and mechanisms of preterm labour should start with an exploration of epidemiological and environmental factors. There may be clues within patient demographics, fetal demographics, the intrauterine and extraterine environment, genetic profiling (maternal, paternal and fetal) and interactions between these factors. Epidemiological research aims to identify causative risk factors and, although our current knowledge may not prevent preterm labour, it may allow prediction and early intervention with optimisation of the clinical circumstances around birth. Risk-based screening and assessment can influence the type of care received, place of birth and judicious use of steroids, all determinants of perinatal outcome. Epidemiological research has an important role in patient counselling for any pregnancy complicated by preterm labour.

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but particularly for future potential pregnancies where there may be significant risks for the mother and baby.

**EPIDEMIOLOGY**

**Defining the problem**

Preterm birth may result from preterm labour, spontaneous or induced, or it may be planned by caesarean section due to maternal or fetal complications. The term ‘indicated’ delivery is used to describe circumstances where preterm birth is the preferred management approach and preterm labour usually refers to unplanned spontaneous labour. It is now recognised that there is a degree of overlap between ‘indicated’ preterm birth and spontaneous preterm labour, and that these two clinical subtypes may share common aetiologies. For example, a woman may present at 36 weeks’ gestation and be diagnosed clinically with a placental abruption. The decision may be to proceed to delivery (induced labour or caesarean section) because of unacceptable maternal and fetal risks. Equally, it is likely that she would labour spontaneously with an evolving retroplacental bleed. The former would be described as an ‘indicated’ delivery in many studies although clearly antepartum haemorrhage is a recognised aetiology of preterm labour. For the purposes of this review the emphasis will be on spontaneous preterm labour with recognition that there is an overlap with ‘indicated’ delivery.

Preterm labour refers to labour with an onset before 37 weeks’ gestation. This is essentially an arbitrary lower cut-off for a ‘term’ pregnancy and there is clearly a big difference between labour at 27 weeks’ gestation and labour at 36 weeks and 6 days. From an epidemiological perspective it is possible to evaluate exposures (potential risk factors) and outcomes (morbidity or mortality) on a gestational week by week basis and this approach offers certain statistical advantages. However, most studies categorise births to allow comparisons of gestational age groups that share similarities and are of a reasonable sample size. Epidemiological studies of preterm labour vary in terms of categorisation but in general terms labour at <24 weeks is considered pre-viable, <28 weeks is extremely preterm, 28–31 weeks very preterm and 32–36 weeks mildly (or moderately) preterm. The risk factors for worsening degrees of prematurity may be similar but there is evidence that the strength of associations increases. The emphasis in this review will be on preterm labour at <32 weeks’ gestation where there is greatest risk and the strongest evidence base.

Many studies categorise neonatal events and outcomes by birth weight but clearly this has the added complication of including small for gestational age babies who may not be preterm. In addition the presence within a cohort of small for gestational age babies, some of whom may be growth restricted, may confound associations. Therefore, studies that are defined by gestational age are preferred when exploring the aetiologies and outcomes of preterm labour.

The critics of epidemiology will argue that population-based studies may describe any number of associations but they do not define the cause of disease. The argument between association and causation is an old one and in fact the epidemiological approach has remarkable similarities to laboratory-based approaches. Careful systematic research of clearly defined questions with biologically plausible mechanisms repeated in different settings and different populations, and with a dose–response relationship leads to a tentative suggestion of causation. These criteria were laid down by Bradford Hill in 1965 and are outlined in Table 1. This approach can be demonstrated in some
carefully designed epidemiological studies of preterm labour and has been exploited by geneticists and laboratory-based scientists within the relatively new fields of ‘genetic epidemiology’ and ‘bioinformatics’. Recent studies have recognised the importance of looking at the interaction between epidemiological, environmental and genetic factors when seeking to understand the origins of preterm labour.

Changing epidemiology

Preterm births comprise 6–10% of all births in Western countries and account for more than two-thirds of all perinatal deaths. Even small changes in rates of preterm birth could have a major impact on perinatal mortality, disability and healthcare needs within communities. There are challenges in comparing rates of preterm labour over time and between different settings due to inconsistent approaches to registration, ascertainment and classification of preterm birth. Nonetheless, factors that might be contributing to epidemiological changes in preterm birth include social inequality, maternal age, marital status, immigration, maternal anthropometry and exposure to cigarettes, drugs and alcohol.

A Swedish population-based register study reported that the preterm birth rate had decreased from 6.3% in 1984 to 5.6% in 2001 ($p < 0.0001$) but with an increase in the proportion of multiple births born preterm from 0.34% to 0.71%. The composition of different subtypes in the Scandinavian low-risk population appeared to be similar to populations with higher incidence of preterm birth and perinatal infections. In contrast, the overall proportion of preterm deliveries in Denmark increased by 22% from 1995 to 2004. Spontaneous preterm deliveries in primiparous women at low risk rose 51% from 3.8% to 5.7%. There was also a significant increase in multiple births. There was a similar increase in singleton preterm rates in New Zealand over a 20 year period (1980–1999) and of note, the greatest increase (72%) was among those living in the most affluent areas. There was evidence of a change in risk factors for preterm births in France between 1981 and 1995, suggesting that the classification of high-risk groups should be brought up to date regularly.

Recently evaluated risk factors for preterm labour are summarised in Table 2. The search for epidemiological risk factors for preterm labour needs to be a dynamic process as the profile of populations and the environment in which we live is subject to change over time.

Table 1. Epidemiological studies – association or causation.

<table>
<thead>
<tr>
<th>Bradford Hill criteria for causation$^6$</th>
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<tbody>
<tr>
<td>Strength  —  strong magnitude of association</td>
</tr>
<tr>
<td>Consistency — consistent findings between different studies/settings</td>
</tr>
<tr>
<td>Specificity — exposure associated with very specific disease</td>
</tr>
<tr>
<td>Temporality — plausible temporal relationship</td>
</tr>
<tr>
<td>Biological gradient — dose–response relationship; increased risk with greater exposure</td>
</tr>
<tr>
<td>Plausibility — credible scientific mechanism</td>
</tr>
<tr>
<td>Coherence — consistent with natural history of disease</td>
</tr>
<tr>
<td>Experimental evidence — exposure shows results consistent with association</td>
</tr>
<tr>
<td>Analogy — similar result we can draw a relationship to</td>
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</tbody>
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Maternal factors

Race and ethnicity

African–American women are over-represented in rates of preterm birth which is thought to reflect multiple aetiologies. The race/ethnic-specific relations between pre-pregnancy body mass index (BMI) and vaginal inflammation have been explored in a multicentre cohort of over 11,000 American women. Ethnicity substantially modified the magnitude of the BMI effect with underweight having a greater impact on preterm birth among blacks and Hispanics than among whites. Low BMI also

### Table 2. Epidemiological and environmental risk factors for preterm labour.

<table>
<thead>
<tr>
<th>Maternal</th>
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<tbody>
<tr>
<td><strong>Demographic</strong></td>
</tr>
<tr>
<td>African—American/Aboriginal/Hispanic races</td>
</tr>
<tr>
<td>Low BMI/poor weight gain/excess weight gain</td>
</tr>
<tr>
<td>Young maternal age</td>
</tr>
<tr>
<td><strong>Obstetric</strong></td>
</tr>
<tr>
<td>Previous early pregnancy loss — induced/miscarriage</td>
</tr>
<tr>
<td>Previous preterm birth — indicated or spontaneous labour</td>
</tr>
<tr>
<td>Short inter-pregnancy interval (&lt;12 months)</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
</tr>
<tr>
<td>Procedure — LLETZ/amniocentesis</td>
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<tr>
<td><strong>Fetal</strong></td>
</tr>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>Multi-fetal pregnancy</td>
</tr>
<tr>
<td>Assisted conception</td>
</tr>
<tr>
<td><strong>Paternal</strong></td>
</tr>
<tr>
<td>Older paternal age</td>
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<table>
<thead>
<tr>
<th>Environmental</th>
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</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
</tr>
<tr>
<td>Bacterial vaginosis/sexually transmitted infection</td>
</tr>
<tr>
<td>Periodontal infection</td>
</tr>
<tr>
<td><strong>Socioeconomic/psychosocial</strong></td>
</tr>
<tr>
<td>Social inequality/poverty/neighbourhood disadvantage</td>
</tr>
<tr>
<td>Physical violence</td>
</tr>
<tr>
<td>Marital status — single/cohabitation in context of high marriage rates</td>
</tr>
<tr>
<td>Stressful/traumatic life events/anxiety/depression</td>
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<tr>
<td><strong>Substance use/toxins</strong></td>
</tr>
<tr>
<td>Excess alcohol — ≥3 drinks per day/≥7 drinks per week</td>
</tr>
<tr>
<td>Smoking — any but particularly moderate or heavy</td>
</tr>
<tr>
<td>Cocaine — usually influenced by smoking</td>
</tr>
<tr>
<td>Pollutants — sulphur dioxide, particulate matter</td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
</tr>
<tr>
<td>Elevated homocysteine/suboptimal vitamin B-12 and B-6</td>
</tr>
<tr>
<td>Unbalanced polyunsaturated fatty acids (PUFA)</td>
</tr>
<tr>
<td>Multivitamin (non-use)</td>
</tr>
<tr>
<td><strong>Genetic</strong></td>
</tr>
<tr>
<td>TNF-α pro-inflammatory cytokine — polymorphisms</td>
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<td>Factor VII/XIII — polymorphisms</td>
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increased the risk of a high level of neutrophils and high vaginal pH measurement. Cardiovascular reactivity was examined in another US study of black and white military women. The two-fold increase in risk of preterm delivery among black women may reflect their higher cardiac reactivity on computerised stress testing (autonomic dysfunction) compared to white women.\textsuperscript{13}

In Minnesota, USA, native-born black women were at almost 1.5 times the risk of foreign-born blacks for delivery preterm, suggesting an association with residential racial segregation.\textsuperscript{14} The social context has been explored further in a study in Ohio, USA, including measures of neighbourhood disadvantage.\textsuperscript{15} Neighbourhood poverty rates and housing vacancy rates increased the rate of very preterm birth for blacks but with direct effects of cumulative exposure to inequality only for Hispanics.

There are higher rates of spontaneous preterm birth among aboriginal women in Canada compared to non-aboriginal women with modifiable risk factors, including low weight gain during pregnancy, inadequate prenatal care and high levels of perceived stress.\textsuperscript{16} Similarly, rates of preterm birth are much higher for women living in France who were born in the overseas French territories in the Caribbean, Indian Ocean and sub-Saharan Africa. Excess risk was reported for spontaneous and medically indicated preterm delivery.\textsuperscript{17}

\textbf{Anthropometric and demographic factors}

There has been a growing awareness of the adverse pregnancy consequences of maternal obesity; however, preterm labour may be associated with extremes of maternal weight. Three anthropometric measurements were evaluated as predictors for spontaneous preterm birth in a systematic review.\textsuperscript{18} The predictive value of BMI, weight gain in pregnancy and maternal height were reported in eight primary studies of 122,647 women. All three maternal factors were poor predictors of preterm labour with heterogeneity between studies. The main criticism of the studies related to the use of a 37 weeks’ gestation cut-off with a recommendation for future studies to use a more clinically appropriate reference standard of birth before 32–34 weeks’ gestation. A more recent study has evaluated the combined effects of pre-pregnancy BMI and weight gain during pregnancy with categorisation of prematurity as very (20–31 weeks) and moderately (32–36 weeks) preterm.\textsuperscript{18} There was a strong association between very low weight gain and very preterm delivery that was of greatest magnitude among underweight women (adjusted OR 9.8, 95% CI 7.0–13.8). Women with very high weight gain had approximately twice the odds of very preterm delivery, regardless of pre-pregnancy BMI.

Physical activity correlates with weight and weight gain but there is a need to differentiate between leisure time exercise and the activities of daily living. In a study of low income women in Maryland, USA, leisure-time exercise (≥60 days in first and second trimester) had a protective effect on preterm delivery (<37 weeks) (OR 0.51, 95% CI 0.27–0.95) but the risk was increased for women who had to climb stairs more than ten times per day (OR 1.60, 95% CI 1.05–2.46).\textsuperscript{19} There was a U-shaped relationship with television watching. These findings warrant further investigation with attention to potential confounding or interaction with maternal weight. Similarly, women with poor physical function reflecting the mother’s pre-pregnancy health status were nearly twice as likely to deliver preterm (OR 1.97; 95% CI 1.18–3.30) even after adjusting for sociodemographic and pregnancy risk factors.\textsuperscript{20}

The association between young maternal age and preterm labour remains controversial. In a Brazilian study where the prevalence of teenage pregnancy was high (29%)
the risks of preterm birth were compared for women aged under 18 years, 18–19 years and a reference group aged 25–29 years. In the analysis adjusted for relevant confounding factors, the risk of preterm birth was higher for women aged under 18 years (OR 1.70, 95% CI 1.02–3.08) but the risk was no higher for woman aged 18–19 years or among non-primiparous teenagers. This suggests that the association between young maternal age and preterm birth may have a biological basis or may be due to residual confounding. The adolescents in a US study were significantly more likely to be African–American, single and to have been diagnosed with a sexually transmitted infection in pregnancy which may confound the reported association with preterm delivery (RR 1.12, 95% CI 1.04–1.21).

Previous obstetric history

There is an increased tendency for preterm birth to recur in subsequent pregnancies. In a US study of over 150,000 consecutive singleton births, if the first pregnancy resulted in a spontaneous preterm birth, then affected women were more likely to deliver preterm spontaneously in the subsequent pregnancy (adjusted OR 3.6, 95% CI 3.2–4.0). This applied even if the first pregnancy was a medically indicated preterm birth (OR 1.6, 95% CI 1.3–2.1). The greatest risk of recurrence tended to occur around the same gestational age as the preterm birth in the first pregnancy.

The inter-pregnancy interval appears to contribute to the recurrence of preterm birth. Women in Taiwan with inter-pregnancy intervals of <12 months were at increased risk for a preterm birth in the subsequent pregnancy (OR 4.2, 95% CI 3.0–6.0). The risk decreased as the inter-pregnancy interval increased with a relatively low risk at 18–48 months. Similarly, in a case-control study in Israel an interval of <12 months was associated with an increased risk of preterm labour before 34 weeks.

In a Swedish study of over 600,000 women, previous spontaneous and missed miscarriages were associated with an increased risk of preterm premature rupture of membranes and preterm labour with the strongest association for delivery before 32 weeks. Similarly, threatened miscarriage in the first trimester has been associated with preterm delivery (OR 3.0) in a large US prospective study. Induced abortion has been associated with very preterm delivery (<33 weeks) in the French regional EPIPAGE study (OR 1.5, 95% CI 1.1–2.0) and this was confirmed by the International EUROPOP study across ten European countries. The strength of association increased with decreasing gestational age and was consistent across countries with varying rates of induced abortion. The increased risk included idiopathic preterm labour, preterm premature rupture of membranes and antepartum haemorrhage, but not maternal hypertension indicated delivery. In a high-risk population of American women a previous second trimester delivery or termination before 20 weeks was associated with pre-viable premature rupture of membranes or labour (14–24 weeks).

Medical procedures

A systematic review of obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions explored the relationship between large loop excision of the transformation zone (LLETZ) and the risk of preterm delivery. The risk of preterm delivery was increased (RR 1.70, 95% CI 1.24–2.35) as was the risk of premature rupture of the membranes (RR 2.69, 95% CI 1.62–4.46).
For the index pregnancy, genetic amniocentesis performed in the second trimester is associated with an increased risk of both spontaneous and induced preterm delivery (adjusted OR 1.59, 95% CI 1.31–1.92).\textsuperscript{31}

**Fetal factors**

The existence of a male excess among preterm births may shed some light on the etiology of preterm labour. A study measuring the association between fetal sex and preterm birth in four original datasets reported more males among preterm and very preterm births in most populations, including in vitro fertilisation (IVF) births (OR 1.09–1.24).\textsuperscript{32} There was no male excess for two cohorts of black births or for spontaneous onset births after IVF. The male excess appeared to be strongest for spontaneous preterm births but not for induced births in the general population, and remains unexplained.

Multi-fetal pregnancy is a well known contributor to spontaneous preterm labour and accounts for 10% of all preterm births.\textsuperscript{3} The impact of increasing numbers of twins and triplets on rates of preterm births has been investigated in an International study.\textsuperscript{33} In each country (Canada, England and Wales, France, United States) the increase in preterm delivery among multiple births contributed to the rise or stabilisation of the overall rates of preterm delivery. The increase in multi-fetal pregnancy as a result of subfertility treatment has an important role to play as twins resulting from subfertility treatment have an increased risk of preterm birth compared with naturally conceived twins, albeit confined to mildly preterm birth (34–36 weeks) (OR 1.6, 95% CI 1.3–1.8).\textsuperscript{34}

**Paternal factors**

Advanced paternal age has been reported to impair pregnancy outcome. In an Italian study of women aged 20–29 years the odds of preterm birth increased with paternal age, with the strongest association for very preterm birth (<32 weeks).\textsuperscript{35} The OR among men aged 45–49 years reached 1.91 (95% CI 1.08–3.38). Similarly, in a Danish study of first born babies to mothers aged 20–29 years the risk of preterm birth increased with paternal age almost entirely resulting from an association with very preterm birth (<32 weeks).\textsuperscript{36} Compared with fathers aged 20–24 years the odds ratios increased linearly to 2.1 for fathers aged 50+. The relationship between paternal and maternal age differences and adverse perinatal outcomes was investigated in a US study of almost 9 million births.\textsuperscript{37} An increase in preterm delivery was reported among white women who were older than their partners but there was little evidence of an increase for black women with varying parental age differences. This study demonstrated that race and maternal age contribute to the effects of parental age difference on the risk of preterm birth.

**ENVIRONMENTAL FACTORS**

**Infection**

Many studies have confirmed associations between genital tract infection and preterm labour. A large number of clinical trials have evaluated antibiotic regimens as potential therapeutic strategies. Bacterial vaginosis and *Trichomonas vaginalis* are two of the most
studied organisms in this context, with two recent large scale trials.\textsuperscript{38,39} Concomitant infection with \textit{Chlamydia trachomatis} among women with bacterial vaginosis or \textit{Trichomonas vaginalis} was not associated with a statistically increased risk of preterm birth.\textsuperscript{40} Similarly, the gestational age at which bacterial vaginosis was screened and diagnosed did not influence the increased risk of preterm birth.\textsuperscript{41} However, in a prospective longitudinal study of 3614 women, increased psychosocial stress was associated with greater bacterial vaginosis prevalence and incidence independent of other risk factors.\textsuperscript{42} There is also evidence to suggest that a change in vaginal flora following antibiotic therapy, with an increase in \textit{Escherichia coli} or \textit{Klebsiella pneumoniae}, results in an increased risk of preterm birth (OR 1.5, 95% CI 1.05–2.1).\textsuperscript{43} The role of oral pathogens in the aetiology of preterm labour is a relatively recent area of research. The hypothesis is that chronic periodontal infection serves as a reservoir for bacterial products and/or inflammatory mediators that play a role in the development of preterm labour and preterm low birth weight.\textsuperscript{44} The Oral Conditions and Pregnancy (OCAP) study investigated 1020 women with antepartum and postpartum periodontal examination.\textsuperscript{45} Antepartum moderate–severe periodontal disease was associated with an increased incidence of spontaneous preterm births (adjusted RR 2.0, 95% CI 1.2–3.2). There was also a higher rate of very preterm delivery among women with periodontal disease progression (RR 2.4, 95% CI 1.1–5.2). A case-control study of 161 mothers in Hungary reported an association between maternal periodontal disease and preterm delivery with more than six implicated pathogens (e.g. \textit{Prevotella} and \textit{Pophyromonas} species).\textsuperscript{46} However, earlier results conflict with studies reporting no association.\textsuperscript{47} There appears to be an association between vaginal bleeding, fetal exposure to oral pathogens and preterm birth at <35 weeks.\textsuperscript{48} It remains to be determined whether the bleeding is the cause or result of fetal exposure to oral pathogens but it is certainly a plausible hypothesis.

Socioeconomic factors

Preterm labour is strongly associated with social disadvantage and recurs in successive pregnancies, increasing the burden of healthcare needs and disability on vulnerable families. The role of social class inequality was examined in a Scottish cohort study between 1980 and 2000.\textsuperscript{49} The distribution of social class changed over time with greater inequalities by the end of the 1990s than at the start of the 1980s. Over that time period the relative index of inequality (RII) for preterm birth increased from 1.52 (95% CI 1.44–1.61) to 1.75 (95% CI 1.65–1.86). Despite a previous decrease in the 1980s, social inequality and its effects on preterm birth increased in the 1990s. Social factors are also reported to be important determinants of preterm birth in transitional Russia with increased risk among women with lower levels of education and in students.\textsuperscript{50} Physical violence during pregnancy has been evaluated in a number of studies. Severe physical violence was significantly associated with spontaneous preterm labour in a study of 550 participants in North Carolina, USA.\textsuperscript{51} The body site injured, timing of violence and number of violent incidents were significant factors. A further study in Birmingham, Alabama, USA confirmed this finding with preterm birth in 10.2% of women subjected to physical violence (OR 1.6, 95% CI 1.3–2.5).\textsuperscript{52} In a South African study of 229 interviewees, violence alone did not seem to cause preterm labour but was part of a low socioeconomic lifestyle, including high maternal alcohol use.\textsuperscript{53} There is a significant elevated risk of preterm birth associated with both cohabitation (OR 1.29, 95% CI 1.08–1.55) and single motherhood (OR 1.61, 95% CI 1.26–2.07)
for women living in European countries where fewer than 20% of births occur outside marriage. In contrast, there is no excess risk associated with marital status when out-of-marriage births are more common.

**Stress and psychosocial factors**

It has been postulated that maternal stress may modulate the pregnant woman's susceptibility to preterm labour. A biobehavioural model has been proposed wherein maternal stress may act via a neuroendocrine pathway that activates the maternal–placental–fetal endocrine systems that promote parturition, and/or via an immune/inflammatory pathway where maternal stress may increase susceptibility to intrauterine and fetal infectious–inflammatory processes. A review of published studies reports conflicting results but the combined evidence from the three largest Scandinavian studies suggests an association between perceived maternal life event stress and preterm delivery. The concept of ‘premature ageing’ has been suggested as a result of cumulative stress or a major traumatic event. Maternal stress has been suggested as an explanation for racial disparity in preterm labour; however, the results of the few studies to date are mixed.

In a study of French women, anxiety and depression combined with specific biomedical factors (underweight) was associated with spontaneous preterm labour. Similarly, thin women with a poor psychosocial profile who were depressed during pregnancy were at increased risk of preterm birth in a prospective study of low-income, predominantly African–American, women in Alabama, USA. In another study of maternal psychosocial factors, an unplanned pregnancy was not associated with an increased risk of preterm birth.

**Substance use**

The difficulty with studies evaluating alcohol exposure in pregnancy relates to under-reporting of intake and discrepancies in the description of a ‘drink’ or unit of alcohol. Moderate intake defined as three or more drinks a day increased the risk of preterm birth in an Italian study (OR 2.0, 1.8 and 1.9, respectively, for each trimester of pregnancy). There appeared to be a dose–response effect in a large Danish study with the highest risk for very preterm delivery among women consuming seven or more drinks per week (RR 3.26, 95% CI 0.80–13.24).

The relationship between smoking and adverse pregnancy outcomes, including preterm birth, has been described. Smokers were more likely to give birth to very preterm babies in a French study (adjusted OR 1.7, 95% CI 1.3–2.2). The relationship between heavy smoking and very preterm birth was complex with a reduced risk of very preterm birth due to gestational hypertension but an increased risk due to other causes for both low to moderate and heavy smoking. Similarly, in a Swedish study, moderate and heavy smokers were at increased risk of preterm labour from all causes (OR 1.9; 95% CI 1.0–3.6 and OR 2.6, 95% CI 1.1–1.6, respectively).

Prenatal cocaine exposure increased the risk of prematurity (OR 2.24) in a study of women in Kentucky, USA. Tobacco but not marijuana significantly influenced the outcome with a greater aetiological fraction attributable to tobacco. In another study of psychiatric and substance use disorders, each had an independent association with preterm delivery (OR 2.4, 95% CI 2.3–2.6 for substance use).
Few therapeutic drugs are tested in pregnancy but inadvertent or clinically indicated exposure can occur. A pharmaco-epidemiological study of Danish women reported that sumatriptan (for headache) was associated with an increased risk of preterm delivery and low birth weight. The authors acknowledged that this may reflect the impact of disease severity or residual confounding rather than the treatment itself.

**Nutrition**

A few studies have explored nutritional factors as potential aetiological factors for preterm labour. A small case-control study of Chinese women reported elevated homocysteine and suboptimal vitamin B-12 and B-6 status in association with preterm birth (<37 weeks). Folate status was not associated with preterm birth. These results would need to be confirmed in larger studies. Women who take pre-conceptional multivitamins appear to have a lower risk of both early (<35 weeks) and late (35–36 weeks) preterm birth (OR 0.59, 95% CI 0.12–2.76, and OR 0.40, 95% CI 0.12–1.40, respectively).

Dietary supplementation of omega-3 has been suggested as secondary prophylaxis of preterm delivery in response to data suggesting that omega-3 fatty acids are capable of prolonging the duration of gestation in the range of 4–7 days and that dietary intake is marginal in Western populations. Carefully conducted randomised controlled trials would be required to establish the efficacy and effectiveness of such an approach. The research on polyunsaturated fatty acids (PUFA) is not entirely consistent and may depend on the environmental setting. The relation between intake of seafood in pregnancy and preterm delivery was evaluated in a Danish prospective cohort of 8729 women. Adjusted odds for preterm delivery were increased by a factor of 3.6 (95% CI 1.2–11.2) in the zero consumption group compared with the highest consumption group. There was a dose–response relation reflecting an intake of up to 0.15 g n-3 fatty acids. It was postulated that small amounts of fish or fish oil may confer protection against preterm delivery. However, in a US study of seafood intake and length of gestation, elongated n-3 PUFA intake and seafood intake were not associated with length of gestation or risk of preterm birth.

Coffee drinking in pregnancy was evaluated in a case-control study of over 2000 women in Italy. Compared with no consumption, a low consumption of coffee during pregnancy did not have any significant effects on preterm birth, with results close to unity for overall intake of caffeine.

**Pollution**

Low level air pollution was evaluated in a cohort of 3988 newborn singletons in the city of Kaunas, Lithuania. The risk of preterm birth increased by 25% (adjusted OR 1.25; 95% CI 1.07–1.46) per 10 μg/m³ increase in nitrogen dioxide concentration but there was no association with formaldehyde exposure. A time series analysis of preterm births in Pennsylvania, USA provided evidence of an increase in preterm birth with exposure to particulate matter ≤10 μm (PM₁₀) and increasing levels of sulphur dioxide. Traffic air pollution in Los Angeles, USA disproportionately affected low socioeconomic status neighbourhoods in a study of traffic-related air pollution, economic hardship and preterm birth. The authors concluded that efforts need to focus not only on individual risk factors but also on the reduction of localised air pollution in any strategy to reduce preterm births.
There was little effect of occupational exposures to pesticides on pregnancy outcomes among gardeners and farmers in Denmark, although the authors emphasised that these findings may not apply to other countries. Similarly the risk of preterm birth was not increased with use of the pesticides DDT and DDE in a study of 20,754 pregnancies in San Francisco, USA, but more robust studies were recommended prior to concluding safety, especially given the continuing role of these agents in malaria control. A number of studies from Taiwan have addressed industrial air pollution from the petrochemical, petroleum, cement and thermal power industries. Each study reported a significant association between air pollution and the risk of preterm delivery with varying odds ratios (1.14–1.30).

GENETIC EPIDEMIOLOGY

Recent attention has focussed on the potential for genetic epidemiology to contribute to our understanding of preterm labour. The emphasis is not only on identifying potential maternal and fetal genetic susceptibilities but on exploring how these factors interact with demographic, socioeconomic and psychosocial factors in activating neuroendocrine and inflammatory pathophysiological processes.

In a review of 18 studies that examined associations between polymorphisms in the maternal or fetal genome and preterm birth, polymorphisms in tumour necrosis factor alpha (TNF-α), a proinflammatory cytokine, showed the most consistent increase in the risk of preterm birth. A case-control study from Philadelphia, USA reported an increased risk of spontaneous preterm birth with maternal carriage of the TNF-2 allele and the association was modified by the presence of bacterial vaginosis (OR 6.1, 95% CI 1.9–21.0). This study provides preliminary evidence that an interaction between TNF genetic susceptibility and environmental factors (i.e. bacterial vaginosis) is associated with an increased risk of spontaneous preterm birth. In a further study, selected TNF haplotypes were associated with spontaneous preterm birth in both African–American and white subjects.

The impact of genetic polymorphisms with prothrombotic and antithrombotic effects on the occurrence of preterm birth has been investigated in a large cohort of very low birth weight infants and their mothers. Factor V Leiden, Factor VII, Factor XIII and the prothrombin G20210A mutation were examined. The maternal carrier status of the Factor VII-121del/ins polymorphism (OR 1.7, 95% CI 1.1–2.5) and the lower frequency of infant's factor XIII-Val34Leu polymorphism (OR 0.5, 95% CI 0.3–0.96) were found to be independently associated with preterm delivery.

Dihydrofolate reductase (DHFR) is required to convert the folic acid used in supplements and food fortification to the reduced folate forms used for cell division. The DHFR 19-base pair deletion allele was associated with a greater risk of preterm delivery in a US study of 324 women (adjusted OR 3.0, 95% CI 1.0–8.8). In the presence of low dietary folate, the allele may be a risk factor for preterm birth, reflecting a gene–environment interaction.

Intergenerational effects would support the role for genetic susceptibility in the aetiology of preterm labour, although clearly environmental factors may persist through generations of families. The Scandinavian countries have high quality longitudinal birth registries that allow an evaluation of intergenerational effects on perinatal outcomes. In a study of over 38,000 Swedish mother–first born offspring pairs, there was no consistent evidence of an intergenerational effect for preterm birth, although such an association was present for reduced intrauterine growth.
and environmental risk factors were investigated in a Danish study of over 10,000 women with successive births. There was a strong tendency to repeat preterm delivery with a moderate increase in recurrence with social decline and moving from a rural to an urban municipality, but no change in recurrence risk with change of male partner.

**PREDICTION OF PRETERM LABOUR**

The epidemiological and environmental risk factors for preterm labour can be exploited to allow identification of high-risk women. The challenge lies in identifying the high-risk first time mother given the wide range of risk factors that could apply to the entire pregnant population in settings of deprivation. The woman who has laboured preterm in a previous pregnancy is readily identifiable and this is one of the strongest predictors of recurrent preterm labour.

The accuracy of risk scores in predicting preterm birth has been explored in a systematic review of 19 primary accuracy articles evaluating 12 different risk-scoring systems. The point estimates for the likelihood ratios varied widely among the different risk-scoring systems. In otherwise asymptomatic women risk scoring in early pregnancy had a wide range of accuracy in predicting spontaneous preterm birth and poor specificity.

The combination of individual patient factors with cervical length scanning and/or rapid fetal fibronectin testing has been proposed to allow prediction of preterm delivery in patients with preterm labour. One such risk score (CLEOPATRA) has been evaluated in 170 patients with preterm labour at 24–34 weeks. The model with fetal fibronectin (CLEOPATRA II) performed better, with a discriminatory power 0.81 (95% CI 0.69–0.93). In contrast, for twins the prediction of spontaneous preterm delivery was not improved by combining maternal characteristics and measurement of cervical length at 22–24 weeks. It has been proposed that new screening tests (epidemiological and clinical) should not be applied systematically to all pregnant women until their advantages and drawbacks are fully evaluated.

**SUMMARY**

There are many clues to the aetiologies of preterm labour within carefully conducted epidemiological and environmental studies. It is clear that no single approach will be effective for prevention or treatment as there appear to be complex interactions between maternal anthropometry, environmental exposures and genetic susceptibility of the mother and fetus. In some ways this should be a source of optimism as there may be several targets for intervention once the complete pathway to preterm labour is understood. Risk-scoring tools have been disappointing for low-risk populations but the woman who has laboured and delivered preterm in a previous pregnancy should be advised to delay pregnancy for at least a year and can be monitored closely for recurrence. Women should be counselled on modifiable risk factors which will also encourage a healthier lifestyle. A coordinated research approach that brings together the disciplines of epidemiology, laboratory-based science and clinical trials offers the best hope of significant advances in this important aspect of perinatal care.
### Practice points

- A careful antenatal booking history can screen for risk factors for preterm labour, although the predictive value and specificity of scoring systems are poor.
- Advise women about modifiable risk factors for preterm labour, including low pregnancy weight gain, excess weight gain, smoking, alcohol consumption and use of recreational drugs.
- Advise women who have delivered preterm in a previous pregnancy that the optimal inter-pregnancy interval is between 18 and 48 months.
- Social contributors to preterm labour include poor housing, environmental pollution, domestic violence and stressful life events and require a public health policy approach.
- Polymorphisms of the proinflammatory cytokine TNF-α and possibly some key prothrombotic factors may interact with maternal and environmental factors to increase the risk of preterm labour.

### Research agenda

- A combined approach to research encompassing epidemiology, pathophysiology and clinical care is required to understand the aetiologies, prevention and optimal management of preterm labour.
- The March of Dimes (US-based research charity) Scientific Advisory Committee on Prematurity recommend targeting of six overlapping categories: epidemiology, genetics, disparities (social inequality), inflammation, biological stress and clinical trials.

### REFERENCES*


* Of special interest.


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