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The epidemiology of preterm labour and delivery

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Defining the problem

The true incidence of preterm delivery and preterm labour can only be ascertained if a consistent definition is used, and if the data are population based. The reported incidence of preterm delivery is affected by the method of gestational age assessment, and by the differing definitions of viability used and therefore the registration of every preterm delivery. Further problems occur in the measurement of outcome because of the heterogeneity of preterm birth – delivery may occur near to the 37-week upper limit of gestation where there may be no pathological cause and the baby has relatively few if any problems, or it may occur at the extreme of prematurity at around 24 weeks’ gestation, where survival rates are poor, and the risk of severe morbidity in those survivors is high. The birth may be spontaneous or elective (iatrogenic); the spontaneous delivery may be uncomplicated (and the outcome usually better (Chng 1981)) or complicated, for example by prelabour rupture of the membranes. The outcomes of such wide variations in aetiology and gestational age will obviously be dissimilar, and so comparisons are difficult and often of little clinical relevance.

Although there is widespread agreement that ‘preterm’ should refer to a gestational age below 37 completed weeks, there is poor agreement on the definition of the lower limit that defines fetal viability, and on the sub-division of the preterm period into intervals defined by outcome. There is often inaccuracy in the determination of gestational age, especially where there is no facility for routine checking of menstrual dates with early ultrasound scanning. Additionally, the group of women most likely to have inaccurate ascertainment of gestational age are often those women most likely to have the multiple socioeconomic risk factors associated with preterm delivery. These limitations must always be considered when comparisons are made between different countries, and when interpreting epidemiological data on the possible causes and outcomes of preterm delivery.

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Table 1.1. Conditions prompting elective preterm delivery

Maternal	Severe pre-eclampsia or eclampsia
	Major antepartum haemorrhage
	Chorioamnionitis
	Maternal disease: cardiac respiratory renal
Fetal	Rhesus (or other) isoimmunisation
	Severe intrauterine growth restriction
	Fetal compromise: anaemia hypoxia/acidosis cardiac/other organ failure
	Cord entanglement (monoamniotic twins)

Definition of preterm delivery

An agreed definition of ‘preterm’ is essential to enable the epidemiology of preterm delivery to be analysed, and comparisons between different populations to be made. Although the World Health Organization (WHO) has recommended that preterm be defined as a gestational age of less than 37 completed weeks (259 days) from the first day of the last menstrual period (WHO 1993), earlier WHO classifications were by birthweight (USPHS 1980) because this is more easily ascertained in countries where the routine ultrasound dating of pregnancy is not routinely or readily available. However gestational age is much more predictive of outcome than birthweight, especially in the developed world, and therefore the definition should be by gestational age if at all possible. There may also be some value in subdividing the definition of preterm to reflect prognostic significance: in the developed world, delivery at 36 weeks’ gestation will usually have a vastly different outcome compared with delivery at 24 weeks. Although terms such as ‘very preterm’ and ‘extremely preterm’ have been suggested, at the present time, there is no widespread agreement on these subdivisions of the preterm period.

There is also no agreement on the defined lower limit of gestational age at which a delivery might be considered to be a birth – the WHO has suggested only including babies of birthweight more than 500 g, however this would exclude babies of relatively late gestations with severe in utero growth restriction (IUGR). Many countries have a legal definition of the lowest gestational age at which viability is deemed to be present, and will include all cases delivering above this limit in any statistics produced, but the definition varies greatly depending

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on the local provision of neonatal intensive care facilities, local definitions of viability and often other cultural factors. Countries with poorly developed neonatal facilities will thus often exclude any babies born below a certain birthweight on the grounds of non-viability, whatever the gestational age. Even within the United Kingdom, where the legal definition of viability is currently 24 weeks' gestational age and above throughout the country, there are local differences in the official data produced. For example Scotland considers all deliveries greater than 20 weeks in its official maternity statistics on the premise that the causes of pregnancy loss between 20 and 24 weeks will often be similar to those resulting in extreme preterm delivery at 24 to 26 weeks' gestation.

Determination of gestational age

Determination of gestational age is also of utmost importance in defining preterm delivery. Usually, unless the pregnancy has resulted from assisted conception, the exact date of conception is not known, and the first day of the last menstrual period is used to estimate gestational age. This assumes that the mother has a 28-day menstrual cycle, that she accurately recalls the date of her last period and that ovulation occurred mid-cycle. It is known that this method is inaccurate because of irregularity of the menstrual cycle, and because in many cases the first day of the last period is not known. This may be due to the taking of hormonal drugs for contraception which may affect the menstrual cycle, amenorrhoea because of breast feeding, or simply that the woman cannot recall the date accurately.

Because there is relatively little biological variation in size in early pregnancy, ultrasound examination at that time is a more accurate method of determining gestational age, and is used routinely in the developed world. The use of ultrasound can, however, lead to apparent higher rates of preterm birth (Yang *et al.* 2002). It has also been found that women with a known date of menstruation but with an early ultrasound scan that suggests that conception took place late in the menstrual cycle are more at risk of preterm delivery (Gardosi and Francis 2000). Whether this is a true risk factor is uncertain. There are, however, many developing countries that do not have the resources to offer this investigation to the majority of their pregnant population. In addition, in the developed world, women of poorer socioeconomic or educational backgrounds are more likely both to have uncertain menstrual dates and to attend so late in the antenatal period that ultrasound examination is no longer an accurate means of determining gestational age. The same group of women is also more likely to have poorer perinatal outcomes, including preterm delivery, and to be subject to many of the risk factors associated with preterm delivery (Hall and Carr-Hill 1985).

It is common practice in epidemiological studies of preterm delivery to describe the gestational age to the nearest completed week of pregnancy. Thus a pregnancy

of 24 weeks and 6 days' gestation will usually be described as 24 weeks. This convention, especially if used in conjunction with ultrasound dating, can cause an apparent increase in the incidence of preterm delivery of up to 0.25% (Goldenberg *et al.* 1989).

Incidence and secular trends

The incidence of preterm delivery varies between 5% and 11% (Andrews *et al.* 2000). In the developed world the rate in general has been rising slowly or has been static over the past 10 to 20 years, but has fallen even in some developed countries. In New Zealand the singleton preterm birth rate rose from 4.3% in 1980 to 5.9% in 1999, a rise of 37% (Craig *et al.* 2002). Interestingly, the rate rose by 72% in high socioeconomic groups but only by 3.5% in the most deprived groups. This is due to the effects of delayed childbearing in affluent career-women, and to the increase in assisted reproduction in that group. In Canada the proportion of births to women aged over 35 years has increased from 8.4% in 1990 to 12.6% in 1996, an increase of more than 50%. Among these women the preterm delivery rate has increased by 14%. It is estimated that 36% of this increase is attributable to delayed childbearing, and there was also a 15% increase in twin rates and a 14% increase in triplet rates (Tough *et al.* 2002). This has led to a reversal of the traditional socioeconomic risk in many western societies; in the USA the relative risk of preterm delivery in low socioeconomic-status and black ethnic groups, although still higher in absolute terms, diminished relative to the more affluent groups between 1981 and 1997 (Kogan *et al.* 2002); in another similar study, the preterm delivery rate in a black ethnic group hardly increased (15.5% to 16.0%) between 1975 and 1995, whereas the white ethnic group rate increased dramatically from 6.9% to 8.4%, a 22% increase (Ananth *et al.* 2001). In Finland, the rate of preterm birth fell from 9% in 1966 to 4.8% in 1986, however the proportion of the preterm deliveries that were spontaneous fell from 97% to 71%, and the iatrogenic cases rose from 3% to 29%. The iatrogenic births were commoner in the lower socioeconomic groups in 1966, but this had been reversed by 1986 (Olsen *et al.* 1995). This increase in iatrogenic preterm delivery is due to improvements in neonatal care, and in the detection of IUGR and other fetal problems necessitating early delivery. In a Canadian (twin) study, the rate of preterm delivery had only increased from 42% to 48% over the period 1988–97, but the proportion of preterm induction of labour had risen from 3.5% to 8.6% (Joseph *et al.* 2001).

The other principal contributing factor to the preterm delivery rate is the increase in multiple births associated with the use of assisted reproduction techniques, and to the rise in iatrogenic preterm delivery of these women (Blondel *et al.* 2002). Although there had been a decline in twinning rates

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since the mid nineteenth century, there has been a rise more recently because of the increased use of assisted reproduction and ovulation induction techniques. The rate of triplet and higher-order births in the UK rose from 10 per 100 000 maternities before 1975 to 35 per 100 000 maternities in 1993, with a similar rise reported in France (Tuppin *et al.* 1993). It has been estimated that 15%–20% of twins and up to 69% of higher-order multiples are due to assisted reproduction.

The twin birth rate in the UK was approximately 1.25% up to 1960, then fell to a low of approximately 0.9% by 1980, then rose steadily to 1.24% in 1993 (Murphy 1995) and in some units is now nearly 2% of all deliveries.

An improvement in assisted reproduction techniques and reduction of the number of embryos replaced has been introduced over the past five years and can reduce the multiple pregnancy rate. Replacing two embryos rather than three has not had the desired effect on twin rates because of improvements in the effectiveness of assisted reproduction techniques (Martikainen *et al.* 2001; Ng *et al.* 2001) but replacing a single embryo (rather than two) can reduce the multiple pregnancy rate associated with in vitro fertilisation (IVF) from 27% to 15% (Dhont 2001), but there is usually a small reduction in the proportion of successful IVF cycles.

Causes of preterm delivery

Iatrogenic

A significant and increasing number of preterm deliveries are iatrogenic, especially in the developed world where they may account for as many as 30% of all preterm births (Olsen *et al.* 1995). Clinicians will elect to undertake preterm delivery if it is felt that continuation of the pregnancy is a greater risk to the life or health of the mother or fetus. Maternal conditions commonly causing such a decision to be considered would include severe pre-eclampsia or eclampsia; major obstetric haemorrhage; chorioamnionitis; and severe or deteriorating maternal cardiac, respiratory or renal disease.

Preterm delivery may also be necessary for any fetal condition that is deteriorating, and for which early delivery would confer benefit, either by removing the fetus from an adverse intrauterine environment (e.g. infection) or by allowing treatment of the condition only possible ex utero. Such complications that may necessitate preterm delivery include rhesus isoimmunisation, severe IUGR, and any other evidence of fetal compromise' e.g. abnormal fetal heart rate.

The contribution of operative delivery to the rate of preterm delivery arises in several ways. When term elective Caesarean section (CS) is decided upon antenatally, it is usually scheduled for 39 weeks (which may be up to three weeks before labour would have started spontaneously). Hence the whole distribution of

gestational age at delivery is shifted to the left. This would not in itself increase the rate of preterm delivery, but occasionally elective CS may be inadvertently performed preterm.

Another problem arises when preterm labour seems to have started. It may be difficult to be sure whether labour is established or not. Evidence from trials of tocolytics show that many women recruited as being in active labour, but given placebo treatment, do not in fact deliver preterm. Hence if a woman scheduled for elective CS presents in apparent preterm labour, she may have a CS (and hence a preterm delivery) that might not have occurred if expectant management had been practised. In addition, even if elective CS were not the plan, when a woman presents preterm in possible labour, and has a breech presentation, early CS (for which there is no evidence of benefit in preterm delivery) may again cause delivery to be more preterm than necessary.

Whilst operative delivery may account for only a small proportion of preterm births, it is likely to be a bigger factor in units where there is a low threshold for delivery by CS than in units where the threshold is higher.

Idiopathic

Although in the past up to 50% of cases of preterm delivery were deemed to be idiopathic, this may represent an overestimate and, with improvements in the ability to detect probable causation, some authors have suggested that the term should be abandoned (Geary and Lamont 1993). However in clinical practice it is often impossible to determine a likely cause, and even in comparatively recent studies, idiopathic preterm delivery may account for up to 30% of cases (Hagan *et al.* 1996).

Infection

There is considerable evidence of an association between infection and preterm delivery, and a causative link is plausible and likely in some cases. Infection associated with or causing preterm labour may be lower genital tract, intrauterine or extra-uterine (generalised maternal infection).

Lower genital tract infections

Bacterial vaginosis

Bacterial vaginosis (BV) occurs when the normal vaginal microflora (principally lactobacilli) is replaced by other organisms, especially anaerobic bacteria, *Gardnerella vaginalis* and mycoplasmas. Women with BV detected antenatally are known to be at greater risk of preterm labour, although whether or not BV is a causal factor is more questionable. A systematic review of randomised trials of treatment of BV has concluded that antibiotic therapy is effective at eradicating BV

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Table 1.2. Infections associated with preterm delivery

Genital	Bacterial vaginosis (BV)
	Group B streptococcus
	Chlamydia
	Mycoplasmas
Intrauterine	Ascending (from genital tract)
	Transplacental (blood-borne)
	Transfallopian (intraperitoneal)
	Iatrogenic (invasive procedures)
Extra-uterine	Pyelonephritis
	Malaria
	Typhoid fever
	Pneumonia
	Listeria
	Asymptomatic bacteriuria

during pregnancy (odds ratio (OR) 0.22, 95% confidence interval (CI) 0.17–0.27), and at reducing preterm delivery in the subgroup of women with a previous preterm birth (OR 0.37, 95% CI 0.23–0.60). There is also a trend towards reducing preterm delivery overall (McDonald *et al.* 2003). A recent randomised trial has found a significant reduction in preterm delivery and late miscarriage in women with BV who were treated with clindamycin (Ugwumadu *et al.* 2003), but there was no associated benefit in terms of neonatal intensive care admissions, proportions of low birthweight (LBW) or very low birthweight (VLBW) babies or in mean birthweight.

Group B streptococcus

Group B streptococcus (GBS) is a common vaginal pathogen, and many studies have found it to be more common in cases of preterm labour and preterm prelabour rupture of the membranes than in controls (Divers and Lilford 1993). Other studies, however, have not found any increased prevalence of GBS women delivering preterm (Kubota 1998). Whether GBS is a cause of preterm delivery rather than an association remains uncertain.

Chlamydia trachomatis

Genital chlamydial infection is now the commonest sexually transmitted disease in developed countries, especially in younger women, with infection rates in pregnancy of up to 20% in some groups (Goldenberg *et al.* 1996; Macmillan *et al.* 2000) and is associated with up to three times the risk of preterm delivery, even after

controlling for confounding variables (Andrews *et al.* 2000a). There is little evidence of direct causation, but treatment has been shown to improve outcome in an observational study (Ryan *et al.* 1990).

Other genital organisms

Genital mycoplasmas (*Mycoplasma hominis*, *Ureaplasma urealyticum* and *Fusobacterium*) have been associated with preterm delivery (Divers and Lilford 1993; Hillier *et al.* 1995; Odendaal *et al.* 2002, but a causative role has not been established.

Other genital organisms that have been associated with an increased risk of preterm delivery include *Escherichia coli*, *Klebsiella*, *Haemophilus*, *Neisseria gonorrhoeae* and *Trichomonas vaginalis* (McDonald *et al.* 1991; Ekwo *et al.* 1993) but again the causative role is undetermined and some studies have either shown no effect of treatment on preterm delivery rate (Klebanoff *et al.* 2001; Gulmezoglu 2002) or have not even shown an association (McDonald *et al.* 1992).

Viral infections

Although there is little evidence that viruses are a common cause or association of preterm delivery, they may be implicated in some cases. One possible mechanism is that viral infection of the trophoblast could play a role in placental dysfunction, leading to complications including spontaneous miscarriage, pre-eclampsia, fetal growth restriction and preterm birth (Arechavaleta-Velasco *et al.* 2002), or preterm labour may occur secondary to host inflammatory responses to the viral infection (Salafia *et al.* 1991).

Intrauterine infection

Preterm delivery can result from intrauterine infection. Intrauterine infection may occur because of ascending infection from the vagina, blood-borne transmission via the placenta, transfallopian infection from the peritoneal cavity or by iatrogenic introduction following invasive procedures such as amniocentesis, chorion villus biopsy or fetal blood-sampling. The commonest cause of intrauterine infection is ascending infection from the lower genital tract. Ascending infection may follow rupture of the membranes, but can also occur with intact membranes. Pathogens ascend from the vagina through the cervix and cause infection of the decidua, the chorion, fetal blood vessels and can infect and cross the amnion to the amniotic fluid and the fetus. The fetus may inhale the infected amniotic fluid leading to pneumonia, or may become septicaemic from haematological infection secondary to decidual and villous infection.

There is a very strong association between intrauterine infection and preterm delivery. Up to 13% of women in preterm labour with intact membranes have

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positive amniotic fluid cultures, and these women are more likely to develop clinical chorioamnionitis, rupture the membranes and to go on to preterm delivery, than women with negative cultures. Similar results are found in women with preterm premature rupture of the membranes (pPROM) with 35% having positive amniotic fluid cultures. Positive cultures are more common in those women with pPROM who are in labour (75%) than those not in labour (Romero *et al.* 1988a). One study has also found that over 50% of women with suspected cervical incompetence (see p.10) have positive amniotic fluid cultures (Romero *et al.* 1992). There is a greater concentration of bacterial endotoxin in women in preterm labour than in those not in preterm labour (Romero *et al.* 1988b).

There is also strong evidence that intrauterine infection causes preterm labour and delivery. There is a plausible mechanism in that bacterial products are known to include proteases and collagenases, which could weaken the membranes, and phospholipase A₂ and endotoxins known to be able to stimulate prostaglandin production in vitro and in vivo. Prostaglandins are known to be involved in the initiation of human labour and are of course widely used for the pharmacological induction of labour. In addition, the host inflammatory response to infection causes the release of inflammatory cytokines which are involved in cervical ripening and possibly membrane rupture.

Extra-uterine infection

Generalised maternal infections such as pyelonephritis (Lang *et al.* 1996), and malaria (Luxemburger *et al.* 2001) remain relatively common antecedents of preterm delivery, and timely antimicrobial treatment usually reduces the risk. Infections such as typhoid fever and maternal pneumonia although historically associated with preterm delivery are usually sensitive to antibiotics and are now less important in most regions.

Listeria monocytogenes

Listeriosis is an uncommon infection that can cause intrauterine and fetal infection and subsequent preterm delivery. Contaminated food is the usual source of infection and transmission appears to be blood-borne following gastrointestinal infection (Lennon *et al.* 1984; Romero *et al.* 1988c).

Asymptomatic bacteriuria

Asymptomatic urinary tract infection is common in pregnancy and is associated with preterm delivery. Two meta-analyses have shown that antimicrobial treatment reduces the risk of preterm delivery (Villar *et al.* 1998; Smaill 2001) and therefore causation appears likely. The exact mechanism is unknown, but there is

evidence that there can be colonisation of the vagina with the same pathogen as found in the urine, and the bacteriuria may therefore be a surrogate marker for abnormal vaginal flora that could be the cause of preterm delivery (Thomsen *et al.* 1987).

Risk factors for preterm labour

There are many associated risk factors for spontaneous preterm delivery and often they are highly dependent on each other. This is particularly true for the socio-demographic variables, and therefore multivariate analysis is essential to account for possible confounding. In addition, there may be treatment paradox where an effective intervention reduces the incidence of preterm delivery and thus makes subsequent statistical proof of the effect more difficult to demonstrate. Although randomised controlled trials would be the most effective means of determining whether risk factors are causal or not, there are relatively few of these.

Maternal risk factors

Cervical incompetence

Cervical incompetence is a clinical diagnosis made when there appears to be dilation of the cervix in the absence of uterine contractions. The exact incidence of cervical incompetence is difficult to determine. It is possible that incompetence leads to preterm labour and delivery by allowing ascending infection or by causing rupture of the membranes and prostaglandin release, or that the delivery occurs simply because the fetus is too heavy to be retained in utero by the incompetent cervix. In a few cases incompetence of the cervix will be caused by previous surgery or by congenital abnormality of the genital tract. It is also possible that supposed cervical incompetence occurs as a result of vaginal and cervical infection causing ripening of the cervix as discussed above. In a randomised controlled trial of cervical cerclage in women thought to be at risk of preterm delivery, only 1 in 25 women benefited from the procedure (Macnaughton *et al.* 1993), which suggests that few patients have true incompetence.

Maternal reproductive risk factors

Previous preterm delivery

A previous preterm delivery is the most significant risk factor for subsequent preterm delivery and the relative risk increases with the number of prior preterm births, from 2.2 for one prior preterm birth to 4.9 for three or more (Hoffman and Bakketieg 1981). A study of only spontaneous onset preterm births from Aberdeen, Scotland found similar results, with a preterm delivery being three times more likely after a previous preterm delivery (Carr-Hill and Hall 1985).