Commentary

Despite the long-standing focus on its prevention, spontaneous preterm birth (sPTB) remains the leading cause of neonatal death, and the second leading cause of mortality worldwide in children below five years of age, after pneumonia. Of those babies who survive, many have severe long-term physical and neurodevelopmental morbidity. A central problem is that the causes of preterm birth are multifactorial. About a third of preterm births are iatrogenic – that is, the baby is delivered electively because of maternal disease such as hypertension, or concerns about fetal well-being (e.g. fetal growth restriction). The causes of sPTB are equally varied, and include infection/inflammation, uterine distension (e.g. multiple pregnancy), antepartum haemorrhage, cervical dysfunction, and social factors. This Element will deal with sPTB (including preterm pre-labour rupture of membranes), concentrating on those aspects potentially amendable to preventative intervention (i.e. cervical dysfunction and premature uterine contractility).

The key to improving fetal outcomes for those at risk of sPTB are: first, the accurate prediction of preterm birth (using history, cervical length assessment using transvaginal ultrasonography, and biochemical tests of cervicovaginal mucus); second, the prevention of preterm birth using cervical cerclage or vaginal progesterone in selected cases; and, third, optimisation of outcomes for women with threatened preterm birth, including delaying delivery using tocolysis, administering antenatal therapy such as corticosteroids and magnesium sulphate for fetal lung development and neuroprotection, respectively, and ensuring appropriate place of birth, particularly important for those infants born at the extremes of viable gestation. Given that most women who present with preterm contractions do not go on to deliver preterm infants, the challenge is to accurately identify the appropriate recipients of these therapies, which do have some unwanted side effects. The balance of benefit is entirely negative if they are given to women who go on to deliver at term because the diagnosis of preterm labour (PTL) was incorrect. In this context, transvaginal ultrasound and fetal fibronectin testing are useful tools to assess risk and guide care. Preterm pre-labour rupture of membranes, in particular, requires careful balancing of clinical decision-making between optimising gestation of delivery for the infant and avoiding maternal or fetal infective morbidity. This involves monitoring closely for signs of chorioamnionitis, which, if diagnosed, necessitate urgent delivery. Current research strategies are focussed on in-depth understanding and individual phenotyping of the pathophysiology behind sPTB, in order to improve strategies to identify those at risk and prevent preterm birth.

Definitions and Epidemiology

Preterm labour is defined by the World Health Organization (WHO) as the onset of labour before 37 completed weeks or 259 days' gestation, and after the gestation of viability (this can be 22–8 weeks depending on definition and setting).[1] *Preterm birth* (PTB) is the birth of an infant before 37 completed weeks' gestation. Spontaneous PTB (sPTB) encompasses spontaneous onset of uterine contractions resulting in delivery, or preterm pre-labour rupture of membranes (PPROM), which is spontaneous rupture of the membranes before 37 completed weeks' gestation and before the onset of contractions. Spontaneous PTB accounts for approximately 70% of all preterm deliveries.[2] The remaining 30% are iatrogenic (physician-initiated for maternal or fetal health indications). Of sPTBs, just over 60% result from spontaneous onset of contractions, and the remainder follow PPROM.[3] Only spontaneous prematurity will be considered for this Element review.

The gestational endpoint of 37 completed weeks (i.e. 37^{+0}) was defined by the WHO as the beginning of 'term' from a statistical analysis of the distribution of gestation of birth based on the first day of the last menstrual period.[4] However, in terms of functional outcome, measured according to need for special care, while continued functional improvement in the newborn occurs up to the due date (e.g. babies born in the early term period at 37–8 weeks have more problems than those born at 39–40 weeks),[5] the major improvement occurs at 34–7 weeks' gestation in high-income settings, and there is a progressive rise in morbidity and mortality rates the further from term that birth occurs.

Internationally, the following PTB categories are recognised by the WHO: extremely preterm (<28 weeks), very preterm (28–32 weeks), and moderate to late preterm (32–7 weeks).[1] Moderate and late PTB can be further split to emphasise late prematurity (34 to under 37 completed weeks) in contrast to moderate prematurity (32–3 completed weeks).[6] Notably, even babies born at 37–8 weeks have higher adverse outcome risks than those born at 39–40 weeks,[7] although this may be related to the reason for delivery. Thus, being 'born early' should be seen as a continuum rather than as an 'all-or-nothing' phenomenon.

Despite the long-term focus on its prevention, sPTB (resulting from PTL or PPROM) remains the leading cause of neonatal death, and the second leading cause of under-5 mortality, after pneumonia, worldwide. While reliable global data are difficult to obtain, in 2010, an estimated 11.1% of all live births globally were preterm,[8] representing 15 million births <37 weeks' gestation and responsible for over 1 million neonatal deaths per year.[6] It may also contribute to at least 50% of neonatal deaths worldwide, as a risk factor for other causes of

neonatal death (e.g. infection).[9] Globally, the incidence of PTB ranges from 5 to 18% with the greatest burden in developing countries. Worryingly, the incidence of PTB is thought to be increasing in all regions with reliable data.[8,10]

Pathophysiology

Preterm birth is a complex health problem, with demographic, clinical, and behavioural determinants of individual risk. While the precise mechanisms are unknown, PTL may be initiated by a number of different factors with distinct biological pathways. These include inflammation and infection (e.g. clinical/subclinical chorioamnionitis, ascending genital tract infection, bacteriuria, and maternal systemic infection),[11,12,13] steroid hormone (including progesterone) imbalance, uterine distension (including multiple pregnancy and polyhydramnios), cervical insufficiency, and placental vascular causes, culminating in a common clinical scenario: cervical ripening, uterine contractions, and early birth.[14] Precursors vary by gestational age,[4] (85% of sPTB <28 weeks have evidence of subclinical chorioamnionitis) and by demographic and environmental factors, modulated by genetic factors[15,16,17,18,19] although the cause remains undetermined in up to half of all cases.

Consequences of PTB

Fetal/Neonatal

The health consequences for a baby born preterm are far-reaching, particularly for infants born at <32 weeks' gestation (Figure 1). Gestational age is highly related to outcome, both mortality and morbidity. The series of EPICure studies examined short- and longer-term health outcomes of infants born between 20 and 26 weeks' gestation in the UK and Ireland in 1995 and 2006 and demonstrated increased survival and lower rates of disability with each additional week of gestation.[20,21] Infants born at 23, 24, and 25 weeks' gestation in 2006 had 19, 40, and 66% survival to discharge from hospital respectively (as a proportion of all live births). Major morbidities associated with extreme prematurity include respiratory distress syndrome (RDS), necrotising enterocolitis (NEC), retinopathy of prematurity, and major cerebral injury (including intraventricular haemorrhage). Longer-term problems include cerebral palsy, neurodevelopmental delay, deafness, visual impairment, and chronic lung disease. The prevalence of long-term disability (neurodevelopmental impairment) is also negatively correlated with the length of gestation.

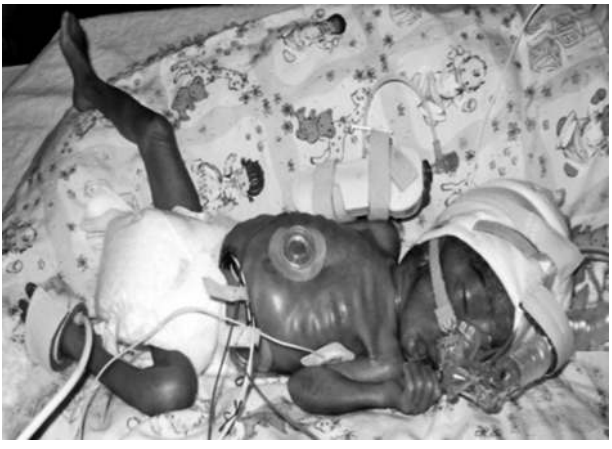

Figure 1 Preterm infant born at 23 weeks' gestation. Reproduced by kind permission of the mother.

Maternal

Much of the maternal risk associated with prematurity is derived from the inherent maternal pathology that precedes the birth, including preeclampsia, antepartum haemorrhage and maternal infection. These may precipitate PTB or necessitate iatrogenic delivery of the fetus by induction of labour or caesarean section, which also carry their own risks for the mother. In particular, caesarean section of a very preterm infant carries a risk of significant maternal morbidity related to a poorly formed lower uterine segment. Other maternal risks include the complications of prophylactic interventions to reduce the risk of sPTB (see later).

The psychological impact of premature birth on a woman, her partner, and her family can be substantial. Threatened PTB frequently involves a protracted hospital stay. This can involve geographic dislocation according to availability of neonatal cots. There is tremendous anxiety and uncertainty regarding timing of delivery and likely outcome. Extremely preterm infants have high mortality and morbidity rates, often involving care in a high-dependency neonatal unit with accompanied emotional upheaval and delayed maternal–infant bonding. The longer-term emotional, physical, and social consequences of caring for an infant with long-term chronic physical and developmental needs are difficult to quantify. Apart from the profound impact on the children and their families, additional consequences of PTB are the enormous economic consequences for health services.[22,23]

Clinical Risk Factors for PTB

There are a number of recognised modifiable and unmodifiable maternal pre-pregnancy risk factors for prematurity, the most significant and consistently identified being a woman's history of previous sPTB, with a recurrence risk of approximately 15%[24] and potentially higher when the previous PTB was <28 weeks,[25] or there has been more than one previous PTB.[26]

Invasive cervical surgery (including laser and cold knife conisation and loop electrosurgical excision procedures (LEEP)) performed for treatment of cervical intraepithelial neoplasia (CIN) is a risk factor for mid-trimester miscarriage, PPROM, and PTB.[27] Furthermore, damage to the cervix, not only after excision procedures, but also during caesarean section, particularly when performed at full dilatation, may also confer increased risk of sPTB.[28,29,30]

Müllerian duct abnormalities are associated with risk of prematurity,[31] as are various social, demographic and behavioural risk factors including extremes of maternal age, a short interpregnancy interval, low pre-pregnancy body mass index (BMI) and poor weight gain in pregnancy, low socioeconomic status, maternal smoking and drug use.[32,33] In the UK and USA, women of black African, African-American and Afro-Caribbean ethnic origin are consistently reported to be at higher risk of PTB than women of white European origin.[2] The biological basis of these risk factors is poorly understood, but persist even after correction for known PTB risk factors such as smoking, maternal education, and socioeconomic status. Biological risk factors such as the higher incidence of urogenital infection in black women (particularly bacterial vaginosis (BV)) are likely to contribute, as well as underlying genetic factors.[34] Healthcare also plays a significant role. There is little robust data on the effect of sexual intercourse during pregnancy, and observational studies are hindered by confounding factors (e.g. age, socioeconomic factors, avoidance of sexual intercourse in women at risk). In general, the data are reassuring that intercourse during pregnancy is not associated with PTB. However, in clinical practice, in the presence of a very short cervix (bulging membranes or diagnosed via transvaginal ultrasound scan), the authors do frequently advise women to abstain from intercourse, in order to avoid introduction of infection or disruption of precarious membranes. Risk factors for PPROM are largely similar to those related to preterm spontaneous labour with intact membranes, but infection is thought to play a particularly significant role.