A preterm baby is one born before 37 weeks' gestation. Women who have delivered prematurely in the past are at an increased risk of preterm delivery, as are smokers and those with a low body mass index

Neonatal care
pregnancy and preterm birth

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SUMMARY

The length of a normal pregnancy is around 40 weeks. Babies born before 37 weeks are classified as preterm. An infant born at or after 25 weeks will be transferred to a neonatal unit for supportive care. Whether or not aggressive measures will be taken to support infants born between the beginning of the 23rd week and the end of the 24th week will be based on assessments undertaken at birth.

The causes of preterm birth include infection, inflammation, multiple pregnancy, placental abruption and hormonal disruptions. Preterm birth may be prevented or delayed using pharmacological and non-pharmacological strategies. There is compelling evidence to support the use of antenatal corticosteroids to reduce the complications of premature birth.

Neonatal care is the bridge between obstetric and paediatric medicine. Clinical pharmacists will encounter three groups of infants on a neonatal unit, broadly those:

- Born before their due date
- Who have a developmental problem (be it reduced growth *in utero* or a definable malformation)
- Born around the time they were expected, but who are unwell

These three groups are not discrete and often overlap. In this article we outline the path of normal pregnancy and the role of the placenta, as well as the causes and prevention of preterm birth and some of the perinatal interventions used to reduce mortality.

Normal pregnancy

The length (or gestation) of a normal human pregnancy is approximately 40 weeks from the first day of the last menstrual period. A woman's "due date" is only an estimate because full-term birth can occur between 37 and 42 weeks.

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The 40 weeks can be divided into three trimesters. During the first 12 weeks (first trimester) the embryonic brain, spinal cord, heart and other major organs begin to form. By the end of the first trimester the embryo's face, toes, neck and genitals will have started to develop. During weeks 13–28 (second trimester) the risk of miscarriage drops considerably and the fetal organs start functioning (eg, the fetus will produce insulin). From week 29 until birth (third trimester) the fetus will grow rapidly and mature towards readiness for birth.[1]

The placenta starts to form during the fourth week of pregnancy, and continues to grow until birth. Functionally, the placenta is a lipid barrier connecting the developing embryo to the uterine wall to allow nutrient uptake, waste elimination and gas exchange via the mother's blood supply (see Box 1, p162).

Preterm birth

Births that occur at less than 28 weeks are classified as extremely preterm; at 28–31 weeks as very preterm; and at 32–36 weeks as moderate-to-late preterm.

Because most infants born at ≥25 weeks respond well to initial stabilisation in the delivery suite, current UK clinical practice is that they routinely receive neonatal intensive care. Population outcome measures for these infants are sufficiently compelling that this is standard practice.[4]

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Data on outcomes (both survival and quality of life) for UK infants born below 25 weeks do not suggest that an "at-all-costs" approach to management is appropriate. An infant born between 23 weeks (+0 days) and 24 weeks (+6 days) will be assessed for condition at delivery and response to simple resuscitative measures. Based on these assessments a decision can be made about the appropriateness of offering intensive care.[4]

For babies born earlier than 23 weeks, resuscitation is not usually performed because outcomes are poor — such infants rarely survive long enough to be taken home and the vast majority have overwhelming disability.[4]

Causes of preterm birth

Prematurity is the leading cause of newborn death and disability.[5] Preterm labour occurs in 5–13% of all pregnancies in developed countries.[6–8] Preterm birth accounted for 7.6% of all live births in England and Wales in 2005.[5] There has been a reported increase in the number of preterm births over recent years, with interventions such as assisted reproduction and the associated increase in multiple pregnancies contributing to this rise.[5,6] Preterm birth can follow:[7]

- Spontaneous labour — either with intact membranes or after preterm premature rupture of the membranes (PPROM)
- Induction of labour for maternal or fetal indications (eg, pregnancy-induced hypertension or intrauterine growth restriction)
- Caesarean section — used in instances when it is unsafe to induce labour or allow labour to progress

About two thirds of preterm births are spontaneous.[6] The cause is often unknown, but can include infection, inflammation, multiple gestation, placental abruption and hormonal disruptions.[7,8] Previous preterm birth increases a woman's risk of subsequent premature delivery by 20–25%.[9] Smoking, periodontal disease, low body mass index (<19kg/m^2) and short cervical length also increase risk of preterm delivery.[7] Infection alone is associated with over 40% of preterm births.[8] PPROM complicates 2–4% of all singleton pregnancies and 7–20% of twin pregnancies, and is associated with 18–20% of perinatal deaths.[8]

> STRATEGIES FOR PRIMARY PREVENTION OF PRETERM BIRTH INCLUDE PRECONCEPTION WEIGHT OPTIMISATION, NUTRITIONAL SUPPLEMENTATION AND SMOKING CESSATION

Box 1: Medicine use during pregnancy

With the exception of drugs with a high molecular weight (eg, insulin or heparin), all drugs will cross the placenta by passive diffusion. Lipid-soluble, non-ionised drugs of low molecular weight will cross more rapidly than polar drugs.[2,3] Drugs that, when given to a pregnant mother, will cause or contribute to malformation or abnormal physiological or mental development of a fetus (or in a child after birth) are classified as teratogens.[2]

The effect of a drug on a developing fetus is dependant on the timing of exposure, dosage, maternal disease and genetic susceptibility. During the pre-embryonic phase (first two weeks of pregnancy), drugs are most likely to have an "all-or-nothing" effect: damage to all or most of the cells results in death of the embryo or a medicine will not affect the embryo at all. The fetus is most vulnerable to teratogens during organogenesis in the first trimester. Deficiency of folic acid during the first 12 weeks of pregnancy, when the spinal cord develops, increases the risk of neural tube defects such as spina bifida. Drugs taken after this time (from the second trimester onwards) are more likely to cause damage to functional development within specific organ systems.[2,3]

Prevention of preterm birth

Measures to prevent preterm birth can be considered for all women before and during pregnancy (primary prevention) and for women who are already at a higher risk of preterm birth (secondary prevention).[6]

Primary prevention Strategies for primary prevention of preterm birth include preconception weight optimisation (to a normal body mass index), nutritional supplementation and smoking cessation. Nutritional and lifestyle adjustment are recommended to ensure that maternal weight is within the normal range in the preconception period. Low serum levels of micronutrients, such as iron and zinc, are associated with both preterm birth and stillbirth and are more common among pregnant women in low income settings.[6]

The National Institute for Health and Clinical Excellence recommends that folic acid is taken before conception and during the first 12 weeks of pregnancy to prevent fetal neural tube defects.[10] One cohort study looking at low-risk, singleton pregnancies found that folic acid supplementation for over one year before conception was associated with a reduction in the risk of preterm delivery compared with women who did not take folic acid.[11] However, more studies are needed before long-term preconception folic acid supplementation could be recommended for reducing the risk of preterm birth. Evidence is also lacking about the potential benefits of extended (non-folic acid) micronutrient supplementation in low-risk populations.

Smoking cessation interventions have been shown significantly to reduce low birth weight and preterm births.[12]

Secondary prevention Interventions to delay delivery focus on women who are already at risk of preterm birth, especially those who have a history of previous preterm birth. The various interventions used are outlined in Box 2 (p164). It should be noted that any secondary prevention intervention can have adverse effects if the fetus remains in an adverse intrauterine environment.[6]

Reducing complications of preterm birth

There is compelling evidence to suggest that administration of antenatal corticosteroids can reduce many of the complications of premature birth, especially respiratory distress syndrome (RDS) requiring respiratory support, intraventricular haemorrhage and neonatal death.[18] Antenatal corticosteroid use (compared with no treatment or placebo) is associated with a reduction in: the incidence of necrotising enterocolitis; the need for respiratory support; admission to intensive care; and systemic infection in the first 48 hours of life.[19] The Royal College of Obstetrics and Gynaecology recommends either two doses of betamethasone (12mg) given intramuscularly 24 hours apart or four doses of dexamethasone (6mg) given intramuscularly 12 hours apart.[19] Variations on this regimen are common; RCOG guidance suggests that, as long as

Box 2: Delaying preterm birth

The following techniques can be used to delay preterm delivery:

Cervical cerclage Cervical cerclage can be offered to women at high risk of mid-trimester loss (miscarriage) or spontaneous birth. A purse-string suture closes the cervical opening to prevent premature delivery through failure of a weakened, shortened cervix. Improvements in screening (detecting cervical shortening on ultrasound) have enhanced targeting of this intervention; however, debate continues around the optimal time to intervene.

Where proven cervical weakness exists (identified by previous miscarriage or premature delivery) it has been suggested cerclage may help reduce preterm birth. However, the technique is not useful in multiple pregnancies and has been shown to increase the rate of preterm delivery.[13] A clearly defined population that would consistently benefit from cerclage has not been identified. There is also no consensus on timing of this intervention.[5]

Progesterone administration Progesterone is responsible for establishing and maintaining a viable uterine environment during pregnancy. The administration of intramuscular and vaginal progesterone has been shown to reduce the incidence of preterm labour in specific populations of high-risk women. There is little evidence as yet for short-term or long-term benefit for the baby. The Royal College of Obstetricians and Gynaecologists therefore recommends that, in women at high risk of preterm delivery, progesterone administration should be restricted to clinical trials to determine whether its use is associated with improved fetal, neonatal or infant outcome.[14]

Treatment of infection Specific maternal bacterial infections have been shown to increase the risk of preterm birth, including bacterial vaginosis (BV) — which is characterised by an overgrowth of a variety of anaerobic organisms in the vagina. There are conflicting data as to whether screening and treating women with BV decreases the risk of preterm birth.

Few bacteria are easily cultured in the laboratory and newer, more sensitive methods (which detect bacterial DNA) are not widely available in the clinical setting. Nevertheless, the number of positive detections of bacteria and other pathogens in amniotic fluid has been shown to be inversely proportional to gestational age at delivery (and therefore survival).[15] Thus, it can be argued that any suspected infection during pregnancy, especially early pregnancy, should be proactively treated with antibiotics, as long as the benefits of such treatment outweigh the risks.[6]

Tocolytic administration Tocolysis is the inhibition of uterine contractions with the aim of postponing preterm labour. A Cochrane review compared tocolytics with no treatment or placebo.[16] Atosiban and nifedipine appear to have comparable effectiveness in delaying delivery, with minimised maternal side effects or rare serious adverse events. Nifedipine is unlicensed for tocolysis but, unlike atosiban, it has the advantage of oral administration.[17] There is little information about subsequent long-term growth and development of children born following use of either drug.

Tocolysis may be inappropriate if prolonging a pregnancy will be hazardous because of intrauterine infection or placental abruption. Tocolysis is only associated with a prolongation of pregnancy for up to seven days and there is no evidence that it improves the outcome of the preterm birth or has any effect on morbidity.[16] However, in practice, those few days can allow the mother to complete a course of corticosteroids or be transferred to a hospital with a neonatal intensive care unit before delivery.[17]

24mg of either drug is given within a 24–48-hour period, any dosing schedule can be used.[19]

Reduction of RDS is most significant when delivery occurs between one and seven days after the last dose of corticosteroid (depending on regimen). Beyond seven days after the last dose, the beneficial effects of antenatal corticosteroids are not present. However, not enough evidence exists to be able to recommend repeated courses of corticosteroids as a routine strategy. Delivery within the first 24 hours after completing a course of antenatal corticosteroids is also associated with a reduction in mortality. Most maternity units will begin a course of antenatal corticosteroids in the hope of completing them before preterm delivery.[19]

In the short term, antenatal corticosteroid use is associated with a reduction in neonatal weight and head circumference. Potential longer-term risks (eg, effects on growth or neurodevelopment) or beneficial effects have yet to been established.[19]

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