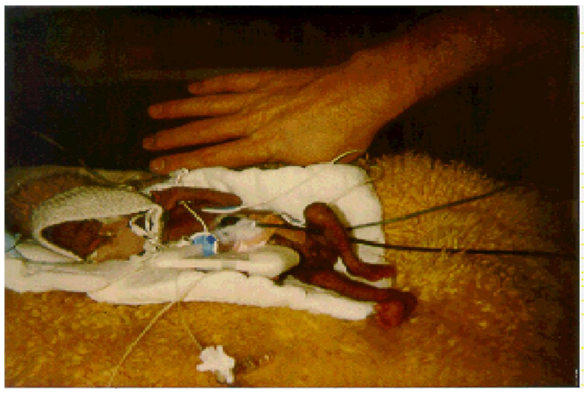
SPECIFIC PROBLEMS OF PREMATURITY and LOW BIRTH WEIGHT NEONATES

FACT FILE 3E

This unit addresses both the preterm and low birth weight neonate in relation to the specific problems and care issues they present with, addressing both similarities and differences between the two groups. How to distinguish between a neonate born prematurely and one that is near term but growth restricted shall also be discussed.

The Preterm neonate



A preterm baby is one who delivers before the 37th completed week of gestation. The causes of preterm labour are not well-understood but a number of risk factors have been identified.

Uterine abnormalities can cause preterm labour as can trauma to the cervix. Chronic or acute maternal illnesses are also associated with preterm labour. Intrauterine infections can cause labour to start and is implicated as a major causative factor for preterm labour. Anything that causes increased stretching of the uterine muscles appears to initiate preterm labour, particularly multiple pregnancy or polyhydramnios - excess production of amniotic fluid.

Social factors are also associated with preterm labour - being poor. Substance abuse - cigarettes, alcohol and drugs are also major risk factors.

It is difficult to predict preterm labour or prevent it. Prevention and treatment of preterm labour is important in order to reduce adverse events for the neonate. Bed rest has been commonly prescribed in the past but it is not effective Cervical stitches will only work if there is cervical incompetence. Tocolytic drugs can be used to relax the uterine muscles but have side effects and must be used with caution as they are associated with maternal and fetal tachycardia. Therefore their use remains controversial. Given the current evidence, the Royal College of Obstetricians and Gynaecologists (RCOG) recommend that if tocolysis is used, it should be given to carefully selected patients, duration of therapy limited and the drug selection based on minimising maternal risks and side effects. For many women in preterm labour it may not be appropriate to consider attempting tocolysis. Labour may be too advanced, for example, or prolonging the pregnancy may be hazardous because of intrauterine infection or placental abruption.

A wide variety of agents have been advocated as suppressing uterine contractions. Those in current use include beta-agonists, calcium channel blockers, prostaglandin synthetase inhibitors, nitric oxide donors and oxytocin receptor antagonists. There is little reliable information about current clinical practice but it is likely that ritodrine hydrochloride, a beta-agonist, remains the most widely used (See Green top Guideline RCOG)

If drugs do not stop labour, it is hoped they will at least slow down. This can have advantages for the baby and allow time for a neonatal cot to be found and for the mother to have corticosteroids.

Dexamethasone given intramuscularly has been shown to accelerate fetal surfactant production. The best response is obtained 24 hours after administration and is sustained for 7 days afterwards (See Green top Guideline RCOG). If the woman has an infection then the corticosteroids must be withheld. They should be used with caution in women with diabetes mellitus as they can alter the effect of insulin. However, the advent of antenatal steroids in preterm labour has significantly improved the survival rates of neonates born early (Roberts and Dalziel 2006).

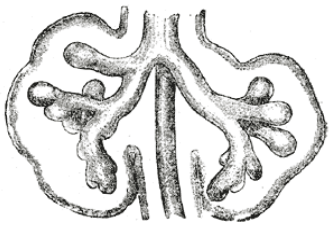
Degrees of Prematurity

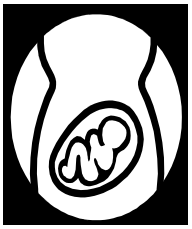
There are varying degrees of prematurity that determine outcome. It is the group born at extreme prematurity that present the more significant problems with the greatest morbidity and mortality. Refer to the Epicure website for outcome figures for cohorts of neonates born at 23-26 weeks gestation that have been followed up in relation to survival rates and long-term development problems (http://www.epicure.ac.uk). Neonates born at gestations greater than 28 weeks have a much better chance of survival and intact outcome compared to figures some 15-20 years ago due to advancements in care.

Related fetal development

To re-iterate from Unit 2a, there are stages during in –utero development that are significant in relation to their capabilities once born. Fetuses are legally 'viable' at 24 weeks gestation but again, due to advances in technology and care, some 23 week gestation neonates survive with varying degrees of future morbidity, much of which is moderate to severe. Viability at the 24 week stage is due to the state of lung development as at this time, the secretory epithelial cell or type 2 pneumocytes in the interalveolar walls of the lungs have begun to secrete surfactant. This is still very early however in view of ability to support breathing completely independently and RDS is common.

Lung development in-utero
Embryonic (weeks 4-5), then
Pseudoglandular (weeks 5-17),
Canalicular (weeks 16-25),
Saccular (weeks 24 to term) and
Alveolar (weeks 36 to years 2-5). Surfactant starts to be produced in the canalicular stage by type 2 pneumocytes from approx. 24 weeks gestation





Neonates at extreme prematurity before 28 weeks are vulnerable in relation to all body systems due to immaturity and complete lack of third trimester growth and stability.

After the immature and vulnerable period of extreme prematurity, saccular development continues moving towards alveolar formation during the last trimester. Certainly by 32-34 weeks, the lungs are capable of supporting the neonates own breathing as the primitive alveoli and pulmonary vasculature have developed sufficiently to provide gaseous exchange should the baby be born prematurely before the end of the third trimester. Lung maturity is now well into the alveolar stage of development resulting in an ability to self ventilate effectively providing no other risk factors are present. RDS is therefore less common.

In addition, from 32-34 weeks, the following important milestones develop which affect how the neonate presents if born prematurely.

The central nervous system has matured sufficiently to direct rhythmic breathing movements. The germinal matrix within the ventricles of the brain involutes and strengthens by 34 weeks so there is less propensity to bleeding should the baby be born prematurely. Before this time, brain stem immaturity and immature vascularisation can lead to apnoea and IVH respectively.

The third trimester is a period where reserves of fat and other nutrients are laid down. Subcutaneous fat increases under the skin and continues resulting in smoother skin and a more chubby appearance of the body and limbs by 34 weeks. Before this time, reduced nutritional reserves have consequences for the neonate as will be discussed.

Physiological flexion and good tone of their limbs is present which are tucked centrally in the mid-line in the characteristic fetal position by 34 weeks. Before this time, reduced tone will be seen and characteristic posture of limbs lacking full tone.

By 32-34 weeks, the vascularisation of the retina of the eyes is complete, again rendering damage from harmful stimuli such as oxygen much less likely. Retinopathy of Prematurity (ROP) is more likely before this time while the retina is still vascularising.

If born during this time, neonates should exhibit a coordinated suck-swallow reflex from 34 weeks; this is usually weaker than term neonates but nonetheless has implications for feeding ability within the neonatal unit.

Specific Biology of the preterm neonate

In Unit 2d, we discussed how neonatal biology differs to that of an older child or, adult in relation to all body systems. As stated above, being preterm means that each of the systems is immature and more vulnerable to the extra-uterine environment particularly at very early gestations.

Respiratory: In the preterm neonate, there is an underdeveloped respiratory centre leading to a predisposition to apnoea of prematurity. There is also immature pulmonary function due to less alveoli growth meaning the surface area for gaseous exchange is reduced and the lung functional residual capacity is lower. This is further exacerbated by potential surfactant deficiency particularly at very early gestations meaning the alveoli are more fragile with a high surface tension. Therefore the lungs are less compliant and so more easily damaged by the shearing forces of mechanical ventilation.

Cardiovascular / haematological: In the preterm neonate, the heart muscle is less contractile and the total blood volume is low leading to potential hypotension. Red blood cells have an even shorter life span (approximately 30-40 days) compared with term and there is a more rapid decline in HB. Clotting times are prolonged.

Immune status; Prematurity means that neonates will fail to receive the transfer of IgG across the placenta during the last trimester and will be further immune-compromised.

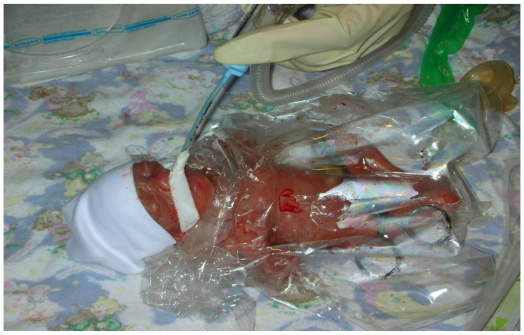
Renal /Fluid and electrolyte balance; The kidneys are immature in relation to tubule function with more limited ability than term to filtrate large volumes and predisposition to fluid overload is more common. Sodium loss is common in the preterm neonate due to limited ability to conserve this via the kidney.

Genito-urinary; In the preterm neonate, differences may be seen in the genitalia due to immaturity – for example, the testes may not have descended and the labia majora may not cover the minora, depending on the gestational age.

Digestive; The digestive tract is less mature in relation to intestine length, absorptive ability and motility.

Liver; Immaturity of the liver enzyme systems and reduced clotting factors lead to increased risk of jaundice and coagulation problems along with a reduced ability to metabolise drugs and other agents.

Thermoregulation: Preterm babies lack the ability to vasoconstrict and so are at greater risk of hypothermia. As brown fat accumulates in the fetus in the later stages of pregnancy, the more preterm a baby is, the less brown fat they will have. Non shivering thermogenesis therefore is difficult, if not impossible particularly in the baby born at extreme prematurity. In addition, very preterm babies born at 28 -30 weeks gestation lack keratin, the waterproofing layer in the corneum stratum of the skin and therefore will lose both water and heat from this very fragile surface much more rapidly. There is reduced ability to adapt to the extra-uterine environment after birth due to these factors and so hypothermia is a risk if thermal care is not addressed



Metabolism and reserves; As stated previously, glucose will be used up as part of the reaction to cooling. Preterm babies have low supplies of glucose availability due to limited glycogen stores laid down in the third trimester. They may become hypoglycaemic very quickly with a greater risk of unstable blood sugar. In addition, if the placental circulation is compromised, then maternal glucose will be less likely to diffuse across and this will lead to decreased fetal growth and decreased glycogen reserves. As well as more limited glycogen stores, they may also be lacking the nutritional reserves (fat, iron, and vitamins) laid down normally in the third trimester of pregnancy. In addition, glycogen stores are more easily exhausted in response to compromise.

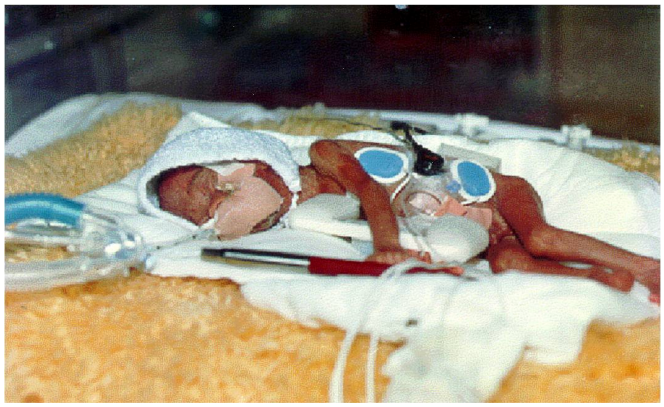
Overall, the preterm neonate is less able to achieve normal metabolic adaptation to extra-uterine life.

Neurological; The preterm neonate is more vulnerable to neurological injury due to an immature germinal matrix within the ventricles before 34 weeks gestation and the immature vascular cerebral blood supply. Therefore, they are prone to bleeding and ischaemic damage to the brain. The preterm neonate also has a poorer ability for autoregulation in response to compromise (the ability to maintain adequate cerebral perfusion in the event of low systemic blood pressure. The preterm neonate has an underdeveloped brain stem along with an increased sensitivity of the vagus nerve. This means they are more prone to apnoea, bradycardia and their chemoceptor responses to hypoxia and increased CO2 are immature compared to term neonates.

Sensory and Pain mechanisms; the preterm neonate's sensory, pain and behavioural systems are immature and behaviours may not follow the usual expected patterns as seen in the term neonate. Sensory function is at greater risk of damage as this is still developing; e.g.; the vascular layer of the retina, visual and auditory nerves prone to damage from various risk factors.

Muscular; The preterm neonate born before 34 weeks gestation has reduced tone and shows an extended posture with limbs lying straight and flat.

Skin; As stated, the preterm neonates skins may lack keratin, the water proofing layer and so can lose both heat and water via evaporation particularly at very early gestations. In addition, lack of collagen means that their skin is fragile, transparent and easily damaged. Moreover, skin acidity takes significantly longer to fall often taking weeks rather than days and delaying the acid mantle formation (Mancini, 2004, Blincoe, 2006, Newton et al, 2005). Skin frailty and susceptibility to damage and infection along with greater physiological and temperature instability means that bathing is not appropriate for a significant length of time until weight and condition allow and the neonate can maintain their body temperature sufficiently outside an incubator.



Related to this specific biology are the following conditions commonly seen in the care of the preterm neonate

SUMMARY: SPECIFIC CONDITIONS SEEN IN THE PRETERM NEONATE;

All conditions will be covered in more detail in subsequent Units

RDS; Respiratory Distress Syndrome. Lack of endogenous Surfactant leading to respiratory difficulties, oxygen requirement and poor compliance of the lungs.
APNOEA OF PREMATURITY; Cessation of breathing due to immaturity of the brain stem.
CLD; Chronic Lung Disease of prematurity. Long-term damage to the alveoli caused by shearing forces of mechanical ventilation oxygen toxicity in the preterm neonate. Broncho-pulmonary Dysplasia (BPD) is another term commonly used with respect to long-term structural damage to lung alveoli.
HYPOTENSION; Low blood pressure due to poorly contractive heart and low blood volume.
ANAEMIA; Low haemoglobin level due to significant nadir of Hb. A condition characterized by ↓ erythrocyte mass, which is most common in low- and very-low-birth weight infants (↓ Reticulocytes, ↓ erythropoietin production).
PDA; Patent Ductus Arterisosus. The duct connecting the pulmonary artery with the aorta in-utero which remains open or re-opens leading to unstable cardiovascular status.
INFECTION; Sepsis due to many pathogens is more common in the preterm neonate due to reduced defences.
IVH; Intraventricular haemorrhage -Bleeding into the germinal matrix of the immature brain ventricles which can extend into the parenchyma.
PVL; Periventricular Leukomalacia - a brain condition affecting fetuses and newborns in which there is softening, dysfunction, and death of the white matter of the brain.
ROP; Retinopathy of Prematurity; abnormal growth of blood vessels in the retina of the eyes.
THERMAL INSTABILITY / HYPOTHERMIA; Central temperature generally < 36 C.
HYPOGLYCAEMIA; Blood sugar less than 2.6 mmols as a generally accepted threshold / norm for this group of neonates.
JAUNDICE; Physiological jaundice is very common in the preterm neonate for reasons stated above.
FLUID IMBALANCES; common due to kidney immaturity - Examples are; delayed diuresis, inappropriate ADH (anti-diuretic hormone).
NEC; Necrotising Enterocolitis**;** a serious inflammatory condition of the intestine characterised by invasion of pathogens to a compromised bowel.
GUT DYSMOTILITY; Slow digestive motility due to bowel immaturity and difficulties in feeding.
OSTEOPENIA OF PREMATURITY; Metabolic Bone Disease, in which decreased bone mineral content occurs mainly as a result of lack of adequate calcium and phosphorus intake in extra uterine life.

The Low Birth Weight / Small for gestational age neonate

In neonatal care, the other very important group of neonates is the low-birth weight (LBW) group. Various terms are used both within practice and the literature when discussing small, LBW neonates which are outlined below. We are not addressing those neonates that are 'constitutionally small' and do not present any problems. We now focus on neonates that are born at weights whereby intervention is necessary to support their weight gain, feeding and metabolism until such a time that they are adequately growing and thriving. LBW neonates also present with specific problems also listed below, some of which are the same as the preterm neonate.

TERMINOLOGY USED FOR THE LOW BIRTH WEIGHT NEONATE

LBW; Low birth weight. Traditionally classified as <2.5 kg but there are degrees of LBW
VLBW; Very low birth weight Less than 1.5kg
ELBW Extremely low birth weight < 1kg
AGA; Appropriate for gestational age – growth is as expected for centile range for gestation.
SGA; Small for gestational age; also called 'small for dates'- growth is less than expected centile range for gestation (Some texts state < 10th centile is SGA, others state < 3rd centile - be aware of the variations that exist).
LGA; – Large for gestational age; Growth is more than expected centile ranges for gestation - > 90th centile.
IUGR; Intra-uterine growth restriction (sometimes termed fetal growth restriction – FGR) Growth that is not permitted to reach the max growth potential due to problems during pregnancy.
SYMMETRICAL IUGR; Growth restriction that is proportional for both head and body i.e. both are small and have remained so throughout pregnancy. Causes may be genetic, chromosomal or due to congenital infection.
ASYMMETRICAL IUGR; Growth restriction whereby head / brain growth is within expected norms but the body growth is reduced – i.e. head and body are disproportionate. Causes are now more likely to be third trimester related problems such as poor placental flow (from maternal hypertension, placental insufficiency) hindering transfer of nutrients and oxygen to the fetus.
CONSTITUTIONALLY SMALL; healthy neonates that are small due to genetic makeup without any problems.

SUMMARY – PROBLEMS OF THE LBW / GROWTH RESTRICTED NEONATE

A LBW neonate born at an advanced gestation, term, near term will have sound maturity of body systems and so will not be subject to the many problems outlined earlier relating to prematurity (e.g. surfactant deficiency, IVH, ROP etc.). However, since these neonates are small, lacking nutritional reserves and body mass, there are some problems that are the same as for neonates born preterm. These are thermal instability / hypothermia; hypoglycaemia, for example. In addition, some potential problems exist in any newborn / neonate due to neonatal specific biology as already discussed in 2d – e.g. jaundice, infection and so there are also overlaps here. The asymmetrically growth restricted neonate due to problems with placental transfer of nutrients and oxygen may also present with polycythaemia and nutritional deficiencies. A fetus with asymmetric IUGR has a normal head dimension but a small abdominal circumference (due to decreased weight gain), scrawny limbs (because of decreased muscle mass) and thinned skin (because of decreased fat).

Preterm neonates generally are LBW by virtue of the fact they are born early and have not had the third trimester maximum growth. The more preterm, the more likely they are to be VLBW or ELBW. Some preterm neonates however are appropriately grown for their gestation; i.e. they may be small & preterm *but* have been growing according to expected 'norms' up until the point of delivery. Likewise, some neonates born at term of near term are LBW. Therefore, it is more helpful / useful to consider whether growth is *appropriate for gestational age* (AGA) or indeed of the neonate is SGA (small for gestational age) or LGA (large for gestational age).

Antenatally, during fetal growth monitoring, SGA refers to a fetus that has failed to achieve a specific biometric or estimated weight threshold by a specific gestational age. Growth monitoring includes abdominal palpation, measurement of symphyseal fundal height, ultrasound biometry; ultrasound estimated fetal weight and ultrasound Doppler. But the most reliable appears to be abdominal circumference and estimation of fetal weight. (Measures that may be taken on ultrasound: BPD = biparietal diameter (cm) FAA = fetal abdominal area (cm_2) FL = femur length (cm) AC = abdominal circumference (cm)).

Various thresholds (2.5th, 3rd, 5th, 10th, 15th and 25th centiles and 1.0, 1.5 or 2.0 standard deviations below the population average) are used for various fetal measures. The commonly used threshold is the tenth centile for abdominal circumference and estimated birth weight. So, SGA fetuses have failed to achieve their growth potential (fetal growth restriction, FGR) or are constitutionally small. (See Green top Guideline RCOG).

Outcome is also influenced by birth weights with the ELBW having greater mortality and morbidity. SGA fetuses are at greater risk of stillbirth, birth hypoxia, neonatal complications impaired neurodevelopment and possibly type 2 (non-insulin-dependent) diabetes and hypertension in adult life. The reason that studies on SGA fetuses have shown poor perinatal outcome is likely to be the high incidence of true FGR in this group. However, the vast majority of term SGA infants have no appreciable morbidity or mortality.

Large for gestational age

We must not forget the large for dates neonate. AS with 'normally' small neonates, some are naturally large again due to parental makeup & constitution / genetic factors. A large neonate with a birth weight greater than the 90th centile may present as a result of maternal / gestational diabetes. Neonates from diabetic mothers can have very unstable blood sugars due to hyperinsulinaemia after delivery, immature Surfactant mechanisms as well as macrosomia along with other potentially serious issues relating to unstable, insulin dependent diabetes (e.g. cardiac disease, congenital malformations).

Assessing & differentiating the preterm and LBW neonate

It is important to recognise the difference between a neonate who is born early and one who is near term but is growth restricted / small. – (i.e. same weight but different gestations) in order to plan care most effectively. There may also be the situation where a neonate is preterm but large for dates so appearing much older in gestation. Similarly there may be neonates who are of similar gestations but very different weights. One must not assume gestation if the correct information in unknown about a neonate on admission as care may not then be appropriate. Not all mothers know their EDD or may deliver without any antenatal care and so exact information about dates and gestational age may be not readily available. For example, a neonate who is preterm but large in weight may look like a term neonate and so essential potential problems outlined above for the LGA neonate may be overlooked. The survival of a neonate who is ELBW will be influenced by their gestation and maturity and so knowing dates would help to make decisions and plan care about what is best for that neonate.

Tools do exist to assess neonates in view of assessing their gestational age – E.g. the Dubowitz tool assesses neonates on a range of criteria including neuro-muscular control, tone, presence of lanugo hair, skin appearance and many others. A similar and more recently cited tool is the Ballards score which uses the following criteria to score neonates on the extent of prematurity.

New Ballard Score Maturational Assessment of Gestational Age;
Over the course of gestation, babies develop a wide range of characteristics that can be measured through simple examination. As the baby develops muscle tone, distinct posture ensues, as well as measurable angles of resistance in key muscle groups. Physical characteristics are also key in determining gestational age. The eyes transform from being fused in very premature infants, to wide open in full-term babies. The skin and hair also give away important information in determining gestational age, as well as a host of other characteristics described in this site.

The New Ballard Score is a set of procedures developed by Dr. Jeanne L Ballard, MD to determine Gestational Age through neuromuscular and physical assessment of a newborn fetus.

Neuromuscular Maturity
Posture, Square Window, Arm Recoil, Popliteal Angle, Scarf Sign, Heel to Ear
Physical Maturity Skin, Lanugo, Plantar Surface, Breast, Eye/Ear, Genitals

For example, taking one of these elements for assessment – SKIN; the Ballards score assigns a score from -1 up to 5 from the following 7 categories..

Sticky, friable, transparent / gelatinous, red, translucent / smooth pink, visible veins / superficial peeling &/or rash, few veins / cracking, pale areas, rare veins / parchment, deep cracking, no vessels /leathery, cracked, wrinkled
http://www.ballardscore.com/Pages/mono_phys_skin.aspx

Lower scores indicate lower gestations while higher scores are for the mature neonate. This score for skin is then added to all other scores from all criteria listed to assess gestation.

Examples in relation to neonates using these criteria:
Very preterm neonates exhibit characteristic signs of immature gestation such as flat nipple, reduced / absent palmar and plantar creases, soft pinna of the ear lacking cartilage and lanugo hair is visible at around 24-28 weeks gestation up to weeks 32 and then starts to diminish towards the latter part of the last trimester. They will have floppy limbs and lie in a frog like posture with extended limbs. The cry and suck will be weak / absent. Their skin will be more transparent and opaque, with no keratin and reduced collagen taking a very red appearance.

Conversely, a LBW neonate who is near term but growth restricted will have raised nipple, presence of palmar and plantar creases, cartilaginous pinna, with probably no lanugo hair. They will have toned vigorous limbs and movement, a lusty cry and good sucking ability. The skin will be formed and keratin present with less plethoric appearance but it may be baggy / loose due to the lack of subcutaneous fat from growth restriction and compromise.

Another example is illustrated blow – Neonate in picture A is near term but only weighs 1.8kg (asymmetrical growth restriction due to maternal drug abuse in pregnancy) and the neonate in picture B is preterm (32 weeks) also weighing 1.8 kg

A **B**

An overview of the preterm and low birth weight neonate has been given including an overview of problems within these groups. Specific conditions will be covered in further depth in subsequent Units in Part 2. Finally, as with any previous neonate mentioned, it is essential to consider the impact of prematurity and growth restriction on the parents and family, particularly if the stay in hospital is lengthy, the outcome is uncertain and morbidity likely. Psycho-social care therefore must also be applied to this important group of vulnerable neonates and their families

KEY READING

ALL RCOG GREEN TOP GUIDELINES
http://www.rcog.org.uk/womens-health/guidelines

SUMMARY OF PROBLEMS OF THE PRETERM
http://www.nlm.nih.gov/medlineplus/ency/article/001562.htm
http://www.patient.co.uk/doctor/Premature-Babies-and-their-Problems.htm
http://emedicine.medscape.com/article/975909-overview
http://www.enotes.com/nursing-encyclopedia/premature-infants

GROWTH RESTRCITION / SGA
http://www.aafp.org/afp/980800ap/peleg.html
https://www.aarphealthcare.com/galecontent/intrauterine-growth-retardation-1
http://www.racgp.org.au/Content/NavigationMenu/Publications/AustralianFamilyPhys/2005Issues/SeptemberGrowth/200509sheridan.pdf
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3087156/
http://www.patient.co.uk/doctor/Small-for-Gestational-Age-(SGA)-Babies.htm
http://emedicine.medscape.com/article/261226-overview

BALLARD TOOL FOR ASSESSING GESTATIONAL AGE
http://www.ballardscore.com/
http://www.merckmanuals.com/professional/sec20/ch283/ch283a.html#v1076181

EPICURE
http://www.epicure.ac.uk

SIDS
http://www.infantgrapevine.co.uk/pdf/inf_022_itd.pdf

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Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews 2006, Issue 3. Art.

No.: CD004454. DOI: 10.1002/14651858.CD004454.pub2

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Royal College of Obstetricians and Gynaecologists (RCOG) Clinical Guidelines Antenatal corticosteroids to prevent respiratory distress syndrome (2004) http://www.rcog.org.uk/resources/Public/pdf/Antenatal_corticosteroids_No7.pdf

Royal College of Obstetricians and Gynaecologists (RCOG) Clinical Guidelines Tocolytic Drugs for women in preterm labour (2002) RCOG guideline number 1 (B)

Ruth VA (2008) Extra uterine Growth Restriction; A Review of the Literature Neonatal Network, 27, 3, 177-184

Royal College of Obstetricians and Gynaecologists (RCOG) Clinical Guidelines; Small-for-Gestational-Age Fetus, Investigation and Management (Green-top 31) (2002) http://www.rcog.org.uk/womens-health/investigation-and-management-small-gestational-age-fetus-green-top-31

Royal College of Obstetricians and Gynaecologists (RCOG) Clinical Guidelines; Antenatal Corticosteroids to Reduce Neonatal Morbidity (Green-top 7) (2010) http://www.rcog.org.uk/womens-health/clinical-guidance/antenatal-corticosteroids-prevent-respiratory-distress-syndrome-gree

Royal College of Obstetricians and Gynaecologists (RCOG) Clinical Guidelines; Cervical Cerclage – Green top 60 (2011) http://www.rcog.org.uk/womens-health/clinical-guidance/cervical-cerclage-green-top-60

Royal College of Obstetricians and Gynaecologists (RCOG) Clinical Guidelines; Preterm Labour, Tocolytic Drugs (Green-top 1B) http://www.rcog.org.uk/womens-health/clinical-guidance/tocolytic-drugs-women-preterm-labour-green-top-1b

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