Minimizing the risk of respiratory distress syndrome

Ian Morris

Roshan Adappa

Abstract

Respiratory distress syndrome, or hyaline membrane disease, remains one of the most significant causes of neonatal morbidity and mortality, despite advances in perinatal care. It is a condition predominantly affecting premature infants, with an incidence inversely related to gestational age. Whilst many infants will improve within a few days, more severely affected babies are at risk of developing chronic lung disease, and a range of extrapulmonary complications. Minimizing the risk of respiratory distress syndrome requires a combination of preventative strategies prior to and in the immediate aftermath of delivery and a balanced approach to treatment of established disease. The use of antenatal steroids and pulmonary surfactant have revolutionized perinatal medicine, however a number of controversies still exist for both treatments such as optimal dosing, timing, and repeat courses. This article reviews the current evidence for these treatments, as well as over viewing the other essential antenatal and perinatal concerns faced when managing an infant at risk of respiratory distress syndrome.

Keywords antenatal steroids; bronchopulmonary dysplasia; chronic lung disease; hyaline membrane disease; respiratory distress syndrome; surfactant

Introduction

Respiratory distress syndrome (RDS), or hyaline membrane disease, remains a significant cause of neonatal morbidity and mortality, despite greater understanding of its pathophysiology and advances in perinatal care. It occurs almost exclusively in premature infants, with an incidence and severity inversely related to gestational age and birth weight. RDS complicates 1% of all births, but the incidence rises to 50% at 30 weeks gestation, 75% at 28 weeks and 90% at 26 weeks. At gestations below this, RDS is almost universal.

The classic natural history of RDS sees the development of respiratory distress either at birth or shortly afterwards with clinical deterioration over the first 48–72 hours of life. Providing that appropriate and timely medical support is instigated, subsequent improvement is then seen. Without intervention, and/or in the most severe cases, death can ensue as a result of progressive hypoxia and respiratory failure.

Ian Morris *MBBS (Hons) MRCPCH is Neonatal Registrar in the Neonatal Intensive Care Unit, Department of Child Health, University Hospital Wales, Cardiff, UK. Conflicts of interest: none declared.*

Roshan Adappa *MBBS MRCP MD is Neonatal Consultant in the Neonatal Intensive Care Unit, Department of Child Health, University Hospital Wales, Cardiff, UK. Conflicts of interest: none declared.*

Pathophysiology

Typical signs observed in an infant with RDS include grunting, cyanosis, tachypnoea, and chest wall retraction. Plain chest radiograph images show a characteristic ground glass appearance, air bronchograms and diminished lung volume. These observations are a result of a complex pathological process (Figure 1) beginning with inadequate (deficient and immature) surfactant production, leading to the formation of hyaline membranes within hours of birth. In more mature babies, and those with milder disease, endogenous surfactant production commences within a few days, leading to recovery. For the remainder, recovery is slower and an inflammatory response ensues with subsequent risk of chronic lung disease (CLD). Extrapulmonary complications such as intraventricular haemorrhage (IVH), patent ductus arteriosus, sepsis, retinopathy of prematurity and neurological impairment are also observed.

Prevention strategies

Several groups have an increased risk (males, multiple births, infants of diabetic mothers, caesarean section deliveries) but most infants developing RDS are born prematurely, and there is often prior warning of impending delivery. The potential exists for obstetric, midwifery and neonatal teams to initiate strategies to prevent RDS, or minimize its severity.

Antenatal management

The greatest determinant of RDS incidence and severity is gestational age, therefore the implementation of strategies to prevent premature delivery is of paramount importance. Provision of quality antenatal care and promotion of healthy maternal lifestyle cannot be overstated. Teenage pregnancy, social deprivation, poor nutrition and poor antenatal care attendance are all associated with premature delivery and adverse neonatal outcome. Behavioural influences such as alcohol, smoking or recreational drug use are further risk factors.

Timing of planned caesarean section: the risk of respiratory distress is increased following caesarean section deliveries and is multi-factorial in origin.

Surfactant production and lung fluid clearance are enhanced by the onset of labour and triggered by β-adrenergic agents and prostaglandins. Advancing gestation increases the ratio of lecithin to sphingomyelin concentration in amniotic fluid, increases the concentration of surfactant protein A and increases endogenous glucocorticoid production. These changes are delayed or diminished in infants who develop RDS. To a lesser degree, the physical process of labour also aids removal of lung fluid by compressing the chest. Consideration should therefore be given to the necessity and timing of planned caesarean section (CS) delivery.

Although the incidence of RDS in babies born after 36 weeks is low (2–3/1000), most occur in infants born by planned CS. A significant decrease in RDS and other respiratory morbidity is

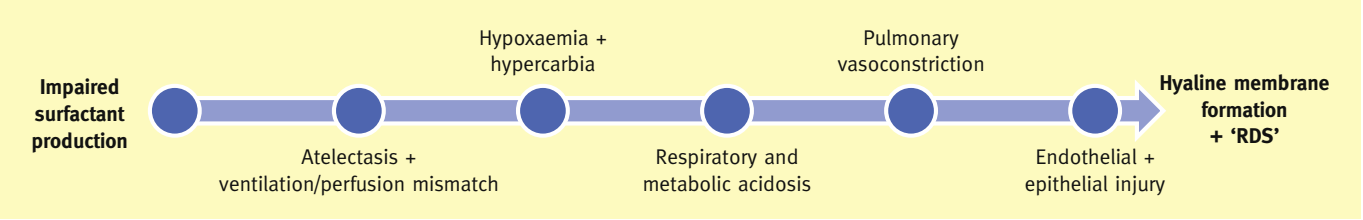

Figure 1 Simplified pathological process in RDS.

also seen with each completed gestational week until 39 + 0. The National Collaborating Centre for Women's and Children's Health and Royal college of Obstetrics and Gynaecology therefore recommend that planned CS should not be carried out before 39 weeks.

Antibiotics: antibiotics may delay delivery for women who enter labour prematurely. Activation of both innate and acquired immune systems, and increased proinflammatory cytokine levels are seen in labour, and can be prematurely triggered by infection. Infection may contribute to more than half of all cases of RDS in the most extremely premature infants.

The ORACLE trial of antibiotics for spontaneous preterm labour, and a Cochrane review assessing prophylactic antibiotics for inhibiting labour with intact membranes, found no evidence of reduced neonatal morbidity. Therefore, the use of antibiotics in asymptomatic women in preterm labour is not supported.

The use of antibiotics for premature labour accompanied by rupture of membranes is less clear. Studies suggest that neonatal sepsis, intracerebral haemorrhage, and the need for oxygen and surfactant therapy are all reduced. However, mortality and longer term morbidity figures remain unchanged. The *choice* of antibiotic is controversial, but evidence of a correlation between the use of co-amoxiclav and necrotizing enterocolitis has led to recommendations for the use of erythromycin instead.

On the whole, there is no evidence that the use of antibiotics in preterm labour or preterm rupture of membranes reduces the risk of RDS.

Tocolytics: tocolytics can delay premature delivery, but there is no evidence that they reduce perinatal or neonatal mortality, or neonatal morbidity including RDS. Advocates cite a benefit of delaying delivery to allow the opportunity for women to be offered antenatal steroids and transferred to a unit with tertiary neonatal facilities. This greatly diminishes morbidity and mortality of extremely premature infants. In some instances such as cases of advanced labour or where there is evidence of intrauterine infection or placental abruption, tocolysis may be inappropriate. The Royal College of Obstetricians and Gynaecologists (RCOG) currently recommend case-by-case decisions, following a discussion of the available evidence with the mother.

Antenatal corticosteroids: the development and widespread use of antenatal corticosteroids prior to premature delivery have had a substantial impact upon neonatal morbidity and mortality. The most recent Cochrane review showed an overall reduction in RDS and neonatal death, with the greatest benefit observed in infants born between 1 and 7 days after receiving corticosteroids. Infants born outside of this window had only a non-significant trend towards risk reduction.

Additionally, there appear to be added benefits of reductions in cases of IVH, necrotizing enterocolitis and early onset sepsis. Whilst antenatal corticosteroids do not confer any direct benefit to the mother, there are no apparent significant adverse effects either. Caution should be exercised with maternal systemic infection or overt chorioamnionitis however; the use of antenatal steroids in women at risk of preterm birth is advocated as routine practice.

Whilst the advantages of corticosteroids are clear, several controversies remain; including the choice of drug, optimal dose, treatment window and the value of repeat dosing.

Preparation and dose — A 2006 Cochrane review of betamethasone versus dexamethasone, suggested that whilst both drugs significantly reduced RDS, a greater reduction was observed with betamethasone. A more recent review in 2008 found no differences in neonatal outcomes, apart from a lower incidence of IVH with dexamethasone. No firm conclusions have been drawn regarding optimal route or precise regimes for administration, but latest RCOG guidelines suggest betamethasone 12 mg given intramuscularly in two doses, or dexamethasone 6 mg given intramuscularly in four doses, should be the standard practices.

Which gestations — in maternally corticosteroid-treated infants, combined foetal and neonatal death is significantly reduced in those born between 28 and 36 weeks, and RDS is significantly reduced in infants born between 28 and 34 weeks gestation.

There is a paucity of data for the use of steroids in pregnancies below 26 weeks, with no clear evidence of a reduction in RDS. However, there is evidence to suggest a reduction in other neonatal outcomes and longer term neurodevelopment, and so the use of steroids from 24 weeks is generally supported.

Below 24 weeks, less agreement exists. A 2008 study of infants born at 23 weeks, showed a reduced risk of death in the infants receiving a full course of antenatal steroids compared to those receiving none. The decision to offer steroids at these most extreme gestations is one taken at a senior level, on a case-by-case basis.

The ASTECS research team, looking at the effects of antenatal steroids for elective CS at term, found a decrease in NICU admission, overall respiratory morbidity, and RDS in the group randomized to antenatal steroids. Whilst elective CS below 39 + 0 weeks gestation should not be routine practice, the RCOG recommend the use of antenatal steroids until 38 + 6 weeks where a CS is planned. For all other modes of delivery, the administration of antenatal steroids for pregnancies over 34 + 6 weeks is not supported.