Current Concepts on Respiratory Distress Syndrome in the Newborn (Hyaline Membrane Disease)

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ABSTRACT

Respiratory distress syndrome continues to be a major cause of neonatal morbidity and mortality. The etiology, clinical diagnosis, pathogenesis, treatment, and prognosis remain controversial. Despite this, a rational program of management is possible and slow but persistent improvement in mortality appears to result from its use. These aspects of respiratory distress syndrome (RDS) or hyaline membrane disease (HMD) are discussed in detail. Still, prevention remains the more reasonable goal. Since this depends largely on prevention of prematurity, every effort must be spent in attempts to reduce the rate of premature birth.

IDIOPATHIC RESPIRATORY DISTRESS SYNDROME or hyaline membrane disease is a major cause of death in the newborn. It has been estimated to occur in 0.5 to 1.0 per cent of all deliveries[1] and accounts for 35 to 45 per cent of all premature neonatal deaths.[2] The disease shows no predilection for race, geographic location or social standard. There is a greater proportion of male infants affected, the ratio approximating 3:2 in several series.[3, 4]

Etiologic Factors

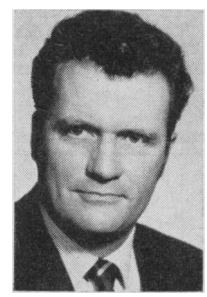
Premature birth appears to be the most important etiologic factor in hyaline membrane disease (HMD). Incidence at term birth is less than one per cent, rising progressively as length of gestation decreases. The highest incidence, approximately 25 per cent, occurs in infants weighing less than 1000 grams and/or delivered before the 31st week of gestation.[5] Intrauterine asphyxia is also considered to be a cardinal factor, although its effect seems to depend on gestational maturity. Thus, immature lamb fetuses developed hyaline membrane disease in the absence of discernible maternal or fetal acid-base changes.[6] Older premature lambs developed the disease only when the ewes were subjected to asphyxia. At term, asphyxia rarely resulted in hyaline membrane formation. While similar data for human infants are not available, clinical experience supports interaction of prematurity and asphyxia.

The role of caesarean section in the etiology of HMD has been controversial for many years. Some investigators have implicated this mode of delivery irrespective of the reason for the operation.[7, 8] Others believed it to be relevant only in the presence of third trimester bleeding or fetal asphyxia.[9, 10, 11] Now the British Perinatal Mortality Survey has rather conclusively shown an increased incidence of HMD following caesarean section even when electively performed and (though in reduced incidence) after a trial of labor.[4, 5, 12] In this same study the effect of maternal third trimester bleeding and of maternal anemia appeared to be significant factors also, although somewhat less critical than prematurity or caesarean section.

The effect of maternal diabetes is less certain. The literature affords this condition an etiologic role.[13] However, most series have not adequately accounted for the effect of prematurity and/or caesarean section, which are frequently associated in diabetic pregnancy. Still, it is possible that there may be a direct effect of maternal diabetes. More data is needed before this relationship can be properly evaluated.

Diagnosis and Clinical Course

A cardinal feature of this disease is the early onset of symptoms. More than half of the affected infants have difficulty in establishing respiration at birth.[14] Further, most infants show signs of the disease immediately after birth if observed and examined carefully.[1, 15] Finally, if an infant breathes normally for



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the first six to eight hours, he will not have hyaline membrane disease.[2] The clinical signs include the following: grunting or whining (when the infant is not crying), sternal and subcostal retractions, often with "see-saw" respiration[16] (the abdomen protrudes on inspiration, while the chest wall retracts), nasal flaring, rapid respirations (usually greater than 70/min.), cyanosis in room air, or in oxygen in severe cases, and low body temperature. The respiratory rate may, however, be normal or even depressed in the most severe cases and is an unfavorable sign. Breath sounds are decreased indicating poor air entry, and fine rales may be heard. Peripheral edema is present and systematic blood pressure is reduced. Cyanosis which persists despite high oxygen breathing and/or persistent hypothermia indicate severe disease and are generally poor prognostic signs.

Laboratory Data

Most chemistry determinations are neither of diagnostic nor of prognostic value. A venous hematocrit is useful to rule out severe blood loss. Bilirubin determinations should be obtained at intervals as infants with acidosis and hypothermia have a greater risk for kernicterus and at lower bilirubin levels than would otherwise be expected. Blood gas values are the most vital laboratory aids, allowing evaluation both of severity and of management, in addition to helping confirm the diagnosis. Finally a chest radiograph should always be obtained, first because the clinical diagnosis will often be confirmed and secondly, to rule out other causes of respiratory difficulty (pneumothorax, congenital diaphragmatic hernia, etc.)

Pathogenesis

Many theories have been proposed to explain the pathogenesis of hyaline membrane disease. Most have been rejected. Only three command much attention at present. The first of these focuses on the defect in the fibrinolytic enzyme system that occurs in premature infants. An inhibitor of plasminogen activator is released from the placenta into the fetal circulation. This results in an inability to dissolve intra-alveolar fibrin, secondary to fibrinolysin deficiency. The hypothesis presumes an initial capillary leak, loss of pulmonary surfactant due to inhibition by fibrinogen, and hyaline membrane formation.[17] This has provoked suggestions that fibrinolysins might be useful in therapy. Clinical trials have been suggestive,[18] but statistical significance of the value of this therapy is still lacking.

A second theory suggests that deficiency of alveolar lining layer or surfactant is the critical event. Evidence which supports this theory includes the following. a) The disease is not found in stillborn infants (surface forces could not act before air breathing[1]). b) The timing of onset of symptoms shortly after birth and the frequent brief interval of apparently normal respiration fit with the theory that surfactant production (the half-life is 12-16 hours) is inhibited during or shortly before birth. The onset of symptoms thus coincides with consumption of the surfactant synthesized previous to the intrauterine asphyxia.[19] c) Further, HMD is progressively more common with decreasing maturity. Surfactant production decreases with decreasing maturity and is poorly synthesized prior to 28 weeks gestation. If this is the primary defect, then the cyclic pathogenesis begins with "surfactant deficiency" in Fig. 1

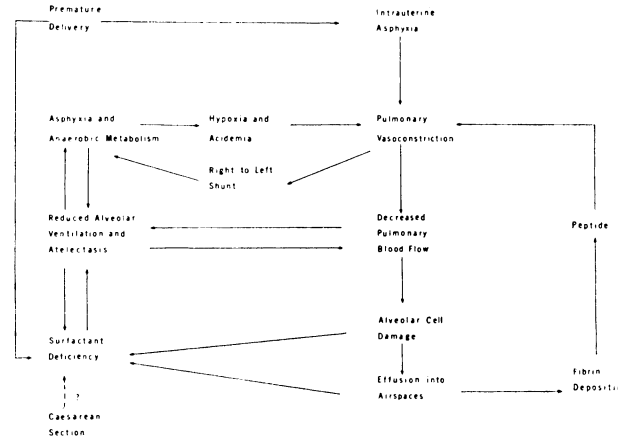

Fig. 1 Mechanisms Operative in the Pathogenesis of the Respiratory Distress Syndrome.

The third theory concerning pathogenesis of hyaline membrane disease states that the primary event is pulmonary vasoconstriction[20] and that the rest of the syndrome follows. (Fig. 1). The cycle would begin with intrauterine asphyxia which produces increased pulmonary vascular resistance leading to shunting of most of the cardiac output away from the lungs. Supporting evidence includes:

a) Fetal asphyxia, common in this disease, produces a marked increase in pulmonary vascular resistance.
b) Post-mortem perfusion studies in HMD lungs exhibit marked pulmonary vasoconstriction.
c) Increased effective pulmonary blood flow, gas exchange and clinical improvement follows therapy which dilates pulmonary arterioles.[20, 21]

It is not yet clear which of these mechanism is of primary important although the hypoperfusion theory has much merit. As can be seen from Fig. 1, however, each of the above mechanisms is probably involved as part of the pathogenesis and tends to contribute to the self-perpetuating cyclic pattern, unless it is interrupted by preventive and/or therapeutic measures. Prematurity probably affects this cycle both in relation to asphyxia production and deficient synthesis of surfactant. The point of impact of caesarean section is less clear, but there is a suggestion that it may relate to surfactant production.

The importance of other factors such as decreased blood volume, disturbed autonomic regulation and the role of serum protein levels, etc., remain uncertain. Certainly, infants with severe RDS exhibit a clinical picture identical with hypovolemic shock. Data in the literature however, indicate no difference in plasma volume between premature infants with and without RDS.[22] Nevertheless there is some doubt concerning the validity of plasma volume measure-

ments using albumin space techniques in RDS and so the question remains open. Autonomic imbalance is certainly present in RDS. The uncertainty concerns whether it is etiologic or merely an effect. The significance of serum protein levels in pathogenesis is as yet unproven.

Pathology

In cases uncomplicated by intracranial hemorrhage the pathology is restricted to the lung. At autopsy the lungs are airless and liverlike with no increase in water content. On microscopic examination the most striking finding is that only the terminal bronchioles and, variably, alveolar ducts contain air while the rest of the lung is airless. The specific lesions noted vary with the duration of life. If the infant survives less than 4 to 6 hours no membranes are seen. Epithelial cells are damaged and may be desquamated in the lumina of terminal bronchioles. The basement membranes may be disrupted. Infants dying between 6 and 48 hours of life show membrane formation in terminal bronchioles in addition to the above lesions. There may be pulmonary hemorrhages present also. The pulmonary arterioles exhibit thick muscular walls and small lumina, like those of fetal lungs. After 72 hours of life, death is usually due to a complication rather than HMD alone. At this time the membranes will be fragmented, macrophages may be seen and reparative cellular proliferation will be present. The membrane has been shown to contain iron-containing compounds, hemoglobin-like material and fibrin, proving the circulatory origin of this material.

Prevention

The prevention of prematurity, avoidance of unnecessary caesarean section and careful management of the diabetic mother are important in prevention of RDS. Further, prevention of maternal acidosis, hypoxia and hypotension are also important. Chilling and hypoxia of the infant in the delivery room or nursery result in pulmonary vasoconstriction. Both should be avoided. Late clamping of the umbilical cord (after two inspirations) is probably helpful in the prevention of RDS.

Treatment

Treatment recommended for RDS tends to reflect the physician's opinion regarding pathogenesis of the syndrome. No specific regimen has been proven to be statistically superior. Until this situation changes rational treatment should aim to minimize the risk to the infant from the disease without introducing additional hazard. Table I outlines such an approach.

If this regimen does not produce results quickly, then additional therapy will be needed. Several specific points are worth emphasis. Maintenance of body temperature has been mentioned several times. On occasion it is not possible to keep small premature infants warm with conventional incubators. Radiant heaters are very helpful if the oxygen requirements can be maintained by means of an oxygen hood. Where automatic servocare incubators are available these often work rather well. Where they are not, wrapping the infant's extremities in cellophane and/or wrapping the infant's body may be necessary. The use of albumin, fresh frozen plasma and blood transfusions (including exchange transfusions) has been reported to be helpful. Though provision of each of these is based on observational or scientific data, the evidence is slight and further verification is needed before considering this form of therapy routinely.

Oxygen, it must be remembered, can be dangerous, as well as therapeutic. It is essential to use as little oxygen as will achieve the desired arterial Po_2. This must be checked frequently and as long as the infant is on enriched oxygen breathing. Retrolental fibroplasia remains a distinct threat in premature infants given oxygen therapy. Further, there is some evidence that high oxygen concentrations can be toxic to bronchial epithelium.[23] Consequently premature infants should be weaned from the oxygen as rapidly as their wellbeing will allow. Increased environmental concentration of oxygen is needed if cyanosis persists after the above therapy. This requires repeated arterial blood sampling for pH, Po_2 and Pco_2. The most practical manner to achieve this is by placing a catheter in the umbilical artery with its tip extending into the descending thoracic aorta. Oxygen and bicarbonate can then be regulated to achieve the desired Po_2 (50 to 90 mm Hg) and pH (7.30-7.35). Caloric requirements may also be given by this catheter.

Only if this program fails, and there are adequate trained personnel available on a 24-hour basis, should respirator therapy be entertained. While this latter form of therapy has been shown to be effective, it is not an approach to be undertaken lightly and is best carried out in a specially equipped and staffed intensive care nursery. Criteria used to initiate respirator care under these circumstances include:

1) $P_aO_2 < 40$ mm Hg or
2) pH < 7.20 or
3) $PaCo_2 > 70$ mm Hg

} in 100 percent oxygen

Table I. Minimal Risk Therapy for Respiration Distress Syndrome. (Adapted from Klaus[1])

Treatment Provided	Benefit Sought
1. Avoid maternal acidosis, hypoxia and hypotension.	Prevention of fetal and neonatal asphyxia.
2. Avoid cooling and hypoxic of the infant in the delivery room.	Prevention of metabolic acidosis and pulmonary vasconstriction.
3. Treat neonatal hypoxia, or asphyxia promptly, (both with bag and mask ventilation, and with $NaHCO_3$).	Reduce metabolic acidosis, induce pulmonary vasodilation, minimize or avoid brain damage, increase cardiac output.
4. Maintain body temperature (axillary) at 36.5°C ($\pm$ 0.5°C), i.e. in the neutral thermal range.	Reduce oxygen requirements to a minimum.
5. Maintain hydration with intravenous fluids and glucose.	Supply metabolic needs and minimize hyperbilirubinemia.

Prognosis

Prognosis depends on many variables including gestational age, weight, blood gas values, age at beginning therapy, among others. One of the most useful prognostic signs is the Po_2 while breathing 100 percent oxygen — if it is above 100 mm Hg, the prognosis is good, if below, poor. Mortality rates vary according to criteria for selection of cases, and since these are rather variable, generalized mortality rates are probably not meaningful. It can be said, however, that with the above or similar regimens, more severely affected newborn infants are surviving RDS than was the case before their adoption. Since the largest single factor in production of this syndrome remains prematurity, significant reductions in morbidity and mortality await effective programs for prevention of premature birth.

Summary

Respiratory distress syndrome continues to be a major cause of neonatal morbidity and mortality. The etiology, clinical diagnosis, pathogenesis, treatment, and prognosis remain controversial. Despite this, a rational program of management is possible and slow but persistent improvement in mortality appears to result from its use. Still, prevention remains the more reasonable goal. Since this depends largely on prevention of prematurity, every effort must be spent in attempts to reduce the rate of premature birth. ◄

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