Management and prevention strategies for premature birth complications

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Abstract

Infection is more common at early gestational ages and is associated with major neonatal mortality and morbidity. Abnormal genital tract microflora in early pregnancy predicts late miscarriage and early birth. As a result, many clinicians think that any antibiotic given at any time in pregnancy to any woman at risk of will cause more harm than good. Recent evidence from molecular-based techniques has demonstrated that pre-birth is not a single entity but a syndrome of different sub-types with different etiologies, different microbial communities, and different responses to antibiotics and, in all likelihood, different subsequent phenotypical outcomes from normal term birth to late miscarriage. This manuscript presents those data, the background and attempts to explain the confusion using new information from culture-independent molecular-based techniques. It also gives guidance on the structure of future antibiotic intervention studies.

Keywords: Prebirth, infection, handicap, variation

Introduction

Complications and the disturbance of normal development may result from factors that influence prenatal development and the etiology of preterm birth, but the extent to which this happens is often unknown [1]. The complications of preterm birth arise from immature organ systems that are not yet prepared to support life in the extrauterine environment. The risk of acute neonatal illness decreases with gestational age, reflecting the fragility and immaturity of the brain, lungs, immune system, kidneys, skin, eyes, and gastrointestinal system. In general, more immature preterm infants require more life support. There is controversy about how infants at the border of viability should be managed[2]. Neonatologists may vary in terms of how conservative they are with regard to treatment of these infants and some may regard treatment of infants at these very early gestational ages as experimental. Infants born preterm are more likely than infants born full term to die during the neonatal period and infancy, and mortality rates increase proportionally with decreasing gestational age or birth weight. Dramatic declines in infant and neonatal mortality and gestational-age specific mortality over the last several decades have been attributed to improvements in obstetric and neonatal intensive care, especially for infants born preterm and small for gestational age[3]. The United States ranked 28th of 37 industrialized nations in infant mortality in 2001 and has a higher rate of low birth weight. Although increasing preterm birth rates and racial and ethnic disparities in the rates of preterm birth have been implicated, methodological factors are contributors to these differences[4]. As pregnancy progresses, the genital tract microflora becomes progressively more benign such that by term; the vaginal microflora poses no significant threat to the fetus as it passes through the birth canal. In contrast, a positive result from screening in the second trimester is associated with a 2.0- to 6.9-fold increased risk of an adverse outcome[5]. Due to the polymicrobial nature of vaginal microflora, the definition of what is normal or abnormal genital tract microflora is very difficult. Normal vaginal microflora is assumed to be present in the absence of disease. Disease results from the interplay between microbial virulence, numerical dominance, and the innate and adaptive immune response of the host. Disease is assumed to be absent if the woman is asymptomatic, and there are no clinical signs of vaginal infectious morbidity. Abnormal vaginal microflora may occur (a) because of a sexually transmitted infection; (b) colonization by an organism which is not normally a constituent part of the vaginal microbial community such as *Haemophilus influenzae*, or *Listeria monocytogenes*; (c) due to increased virulence or overgrowth of an organism that is normally a constituent part of the vaginal microflora[6].

Antibiotics for the prevention of contamination

We know that abnormal vaginal colonization in early pregnancy is predictive of prebirth. The Centers for Disease Control and Prevention do not recommend erythromycin or coamoxiclav for the treatment[7]. Their recommendation is to use either metronidazole or clindamycin, orally or vaginally. Metronidazole and other

nitro-imidazoles are inactive *in vitro* against BV-associated organisms such as *M. hominis*, *G. vaginalis*, *Ureaplasma urealyticum*. Molecular-based studies have indicated a far greater diversity of microorganisms associated with birth variety than has been evident from culture-dependent techniques. In contrast, in other subtypes where anaerobic organisms are not dominant, metronidazole may be less effective [8]. Finally, clindamycin may be active against both metronidazole-sensitive sub-types but also against a wider range of BV sub-types with different microbial communities. It should be noted that while *M. hominis* is extremely sensitive to clindamycin, *U. urealyticum* is only weakly sensitive to clindamycin [9]. Vaginal administration is the most direct and efficient route of administration of antibiotic to the site of the heaviest bacterial load. More data are now available on azithromycin and a new antibiotic, solithromycin, that may be considered candidate antibiotics in future intervention studies.

Environmental effect with genetic susceptibility

Woman may possess the gene polymorphism to mount a damaging inflammatory response, but if she does not have environmental exposure then damage may not occur. However, when both susceptibility and exposu re are present, the risk of an adverse outcome will be increased, and this is known as the gene–environmental interaction. That response may be appropriate resulting in tissue repair and healing [10-13]. Alternatively, the response may be exaggerated resulting in tissue damage from increased production and release of proinflammatory cytokines. Accordingly, the earlier the gestational age at which clindamycin is administered to women with objective evidence of risk of infection [4].

Complications of premature birth

Developmental immaturity affects a wide range of organ systems. This section describes the short-term complications of preterm birth in terms of fetal development as well as injury to fragile organ systems during the perinatal and neonatal periods [5]. Many of these complications have lifelong consequences for the health, growth, and development of infants born preterm. Although some randomized, controlled trials demonstrate the safety and effectiveness of a few treatments for neonates, most standard NICU treatments and interventions have not been adequately investigated [14]. The role that defining and treating the complications resulting from preterm birth plays in the health and neurodevelopmental outcomes of children born preterm argues for more long-term outcome studies and more rigorous studies of new therapies and medications before they are widely adopted. The primary function of the lung is gas exchange i.e., they inhale oxygen and exhale carbon dioxide [15]. Fetal breathing movements begin as early as 10 weeks of gestation, and the breathing of amniotic fluid in and out is essential for the stimulation of lung development. Fetal breathing movements tend to be erratic and occur only 30 to 40 percent of the time up to 30 weeks of gestation [16]. The failure of fetal breathing movements or a lack of amniotic fluid that can be breathed in and out results in underdeveloped lungs (i.e., pulmonary hypoplasia), which can be incompatible with extrauterine life. By approximately 30 to 32 weeks of gestation, the lungs make surfactant, a soaplike substance that helps keep the air sacs alveoli open [17]. Infants born before 28 to 30 weeks gestation lack alveoli and breath with their terminal bronchioles and primitive air sacs. After delivery, the breathing pattern generally becomes more regular and continuous, but immature regulatory systems can lead to brief episodes of not breathing [18].

Respiratory syndrome

Respiratory failure because of fatigue, apnea, hypoxia, or an air leak from alveolar injury results from stiff lungs that need high pressures for ventilation. The provision of exogenous surfactant through an endotracheal tube improves pulmonary gas exchange and reduces mortality, air leak and chronic lung disease but does not influence neurodevelopmental or long-term pulmonary outcomes [19]. Positive-pressure ventilation, high oxygen concentrations, infection, and other inflammatory triggers all contribute to lung injury; but the primary cause of BPD/CLD is lung immaturity. Especially for infants born at less than 28 to 30 weeks of gestation, the lung tissue is very fragile and the injured lung tissue tends to trap air, collapse, or fill with mucus and other fluids, which further compromise lung growth and development [20].

Apnea syndrome

Another complication of preterm birth is apnea, in which infants may stop breathing for 20 seconds or more, sometimes accompanied by a slow heart rate (bradycardia). Immaturity of the control of breathing is the major cause of apnea and bradycardia, although sometimes preterm infants have obstructive apnea [21]. They require constant monitoring but generally respond quickly to stimulation (or in the case of obstructive apnea, repositioning). They may occasionally need to be given some positive-pressure breaths to get them breathing again. There is no agreement as to what constitutes pathologic apnea or the threshold of apnea that requires

treatment[22]. Apnea generally resolves as the preterm infant matures. Occasionally, preterm infants continue to have apnea beyond term, and some are discharged on home apnea monitors. The long-term beneficial effects of the treatment of apnea in preterm infants in an NICU have not been demonstrated.

Conclusion

The interactions between the fetal and the maternal immune systems during pregnancy are complex. Carefully regulated changes in the fetal immune system are programmed to retain the pregnancy and reduce the likelihood of being attacked by the maternal immune system. Many of the mother's antibodies cross the placenta to protect the growing fetus beginning at 20 weeks of gestation, but most transfer during the third trimester[22]. Abnormalities of this delicate and complex interplay between the fetal and the maternal immune systems and infections can result in fetal compromise, maternal or fetal death, or preterm birth. Although the mechanism is not well understood, many data support the association between subclinical infection and preterm birth [23-25]. Preterm infants have immature immune systems that are inefficient at fighting off the bacteria, viruses, and other organisms that can cause infections. The most serious manifestations of infections with these agents commonly seen in preterm infants include pneumonia, sepsis, meningitis, and urinary tract infections. Fetal blood loss, fetomaternal hemorrhage, and hemolysis can all result in congenital anemia, but the most common hematologic complication in preterm infants is anemia of prematurity. Anemia of prematurity is an exaggeration of the physiological anemia of infancy because of suppressed hematopoiesis for 6 to 12 weeks after birth and is earlier in onset and symptomatic[26]. Its causes are multifactorial and include blood loss from frequent blood sampling, the shorter survival of red blood cells in preterm infants, a suboptimal response to anemia, and a greater need for red blood cells with growth. Kangaroo care provides skin-to-skin care by placing the naked preterm infant in an upright position between the mother's breasts and allows unlimited breast-feeding[27-29]. This concept of caring for preterm infants originated in Bogota, Colombia, as a low-cost way to assist preterm infants with temperature regulation, nutrition, and stimulation. The high rates of neurological injury in preterm infants highlight the need for better neuroprotective strategies and postnatal interventions that support the extrauterine neuromaturation and neurodevelopment of preterm infants [30].

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