Infection-Related Morbidities in the Mother, Fetus and Neonate

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ABSTRACT

Only partially understood host defense mechanisms operate against infections affecting maternal and fetal morbidity. Subclinical ascending infections through the lower female genital tract are predominant worldwide. Important micronutrient deficiencies may prevail in low-income countries where these infections are more common than in high-income countries. Important morbidities related to poor perinatal outcome both for the mother and for the fetus and newborn comprise preterm birth, prelabor rupture of membranes, placental abruption (predelivery detachment of the placenta), postpartum sepsis and maternal anemia. In the fetus, sepsis and intrauterine growth retardation are suspected to be consequences of ascending maternal infections. In the newborn, septicemia and respiratory disorders as well as some neurological disorders seem to be consequences of such ascending genital infections in the pregnant woman. It is concluded that much more attention should be given to efforts to elucidate the host defense mechanisms and antimicrobial barriers from the vagina through the cervix, fetal membranes and amniotic fluid including the early fetal immunocompetence in the second and the third trimester of pregnancy. J. Nutr. 133: 1656S–1660S, 2003.

KEY WORDS: maternal morbidity • fetal disease • chorioamnionitis

Infections associated with pregnancy and childbirth have caused concern for women and their caregivers for centuries. Much attention therefore has been focused on understanding these infections. Although the clinical approach to infections has improved markedly in the past few years, infections continue to pose a problem in pregnancy, particularly in low-income countries (1–4).

There is a surprising lack of documentation in the scientific literature regarding nutrition factors that may protect against or enhance infections affecting the pregnant woman. A thorough search in available databases testifies to the fact that information linking micronutrients to infections in pregnancy is scarce.

Infections are implicated in the pathogenesis of miscarriage, preterm labor and prelabor rupture of membranes, all of which are common events (4). Miscarriage is common worldwide and is the outcome of approximately 15% of all clinically diagnosed pregnancies. If syphilis and certain vaginal infections are common, this figure may reach significantly higher levels, including an increase in miscarriage in the second trimester. Preterm labor may occur in 10–20% of pregnancies in low-income countries whereas prelabor rupture of membranes and postpartum septicemia may occur in 5–10% in such settings. All these in turn are associated with neonatal infections and morbidity. Both the direct effect of the infection and the maternal immune response contribute to these eventualities (3,4). For example, infections that trigger T-helper-1 response can lead to the release of cytokines such as interferon (IFNγ), tumor necrosis factor (TNF-α) and interleukin (IL)-2 with activation of killer cells and initiation of preterm labor (3).

Systemic infections and genital infections due to many different microorganisms including mycoplasmas, Chlamydia trachomatis and Trichomonas vaginalis are reportedly involved in initiating preterm labor (3,5–9). A wide variety of bacteria present in the normal vaginal flora of pregnant women such as anaerobes and Escherichia coli can also cause ascending infections, usually after rupture of membranes, resulting in intraamniotic infection (IAI) (10). Chorioamnionitis resulting from such infections can lead to preterm labor and maternal and fetal morbidity (10). Antibiotics have been shown to prolong pregnancy in women with preterm prelabor rupture of membranes (3). Recent data show that Candida sp. may also be important in causing preterm labor and neonatal morbidity. IAI due to bacteria in the vaginal flora not only initiate labor but can also cause infections such as septicemia and meningitis in the newborn (10,11).

Several host defense mechanisms operate against ascending infections; these include vaginal acidity, cervical mucus, intact membranes and antibacterial activity of amniotic fluid (12,13). One study in India demonstrated that all samples of amniotic fluid inhibited Candida albicans and Clostridium

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3 Abbreviations used: CRP, C-reactive protein; IAI, intraamniotic infection; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.
These cytokines include IL-2, IL-6, IL-8 and IFN-γ. The inhibitory activity could be due to polymorphonuclear leucocytes, lysozyme, beta lystin, transferrin, immunoglobulins and other bacterial inhibitory factors such as polypeptide-zinc complexes in amniotic fluid (10).

IAI is difficult to diagnose on the basis of any single criterion and so diagnosis depends on a set of criteria, the most important clinically being maternal fever and tachycardia and fetal tachycardia (10). The use of laboratory methods for diagnosis is still not practical. The infection may be polymicrobial, but collecting amniotic fluid samples without contamination with normal vaginal flora is cumbersome and may require invasive procedures. Also, after membrane rupture many bacteria may enter the amniotic cavity without having caused the rupture. Because of these circumstances, cultures are not usually attempted, especially in low-income countries. Recent literature shows that detection and estimation of surrogate markers such as C-reactive protein (CRP), cytokines and fetal fibronectin help in diagnosing IAI and in predicting and diagnosing early-onset neonatal infections (15–18).

Levels of CRP rise when there is a microbial infection or an inflammation without microbes (19). Studies in pregnant women showed that CRP is elevated at the onset of labor even in normal pregnancies and reaches very high levels during the immediate postpartum period (20). Whether CRP levels are higher than normal in subclinical infections is not clear and the usefulness of this marker to diagnose IAI remains to be established. However, several studies have shown the usefulness of CRP to predict and diagnose neonatal infections (16–18).

Diagnosis of neonatal septicemia remains a major challenge. Sepsis can develop in infants with and without risk factors. Clinical signs are nonspecific and the laboratory criteria are also not fully reliable. Although a combination of clinical and laboratory criteria are required to make a diagnosis, antibiotic treatment is often initiated on the basis of clinical suspicion alone. Because an infected neonate can have a negative blood culture, the initiation of antibiotic therapy without supporting hard evidence of infection is currently justified; in addition, results from blood culture are not available until several days after the harvesting of blood for culture. Treatment on the basis of clinical symptoms alone leads to considerable overuse of antibiotics in the nurseries. Although laboratory data may not be of much use in preventing initiation of therapy, such data could at least help in stopping unwarranted use of antibiotics.

The tests currently used to diagnose neonatal infections include total and differential counts, absolute neutrophil count and the ratio of immature to total white cells. The sensitivity and specificity of these tests are low. In recent years, CRP estimation has been found to be useful in diagnosis. One of the pitfalls is that, as mentioned, CRP can be positive when there is no infection (i.e., the positive predictive value is very low). To make the predictive values better, a more appropriate cutoff level has to be established. Consensus on the cutoff level does not exist at present. In true infection, the test may become positive after 12 h, so estimation of CRP at presentation may not be of much value in diagnosis. Serial determinations may be required and may have a better predictive value than static single estimates (21). This test may be valuable for making decisions about discontinuing therapy. The test can be done using automated systems and a latex agglutination test, which is widely available in developing countries.

Over the years several proinflammatory cytokines have been tested for their use in diagnosing IAI and neonatal infections. These cytokines include IL-2, IL-6, IL-8 and IFN-γ. Maternal, cord and neonatal blood IL-6 levels have been found to correlate with chorioamnionitis and neonatal sepsis (16–18).

IL-6 stimulates the production of CRP. Therefore, IL-6 levels should rise before CRP levels rise. Several studies have confirmed that IL-6 is an early and sensitive marker of sepsis in newborns and in adults. IL-6 levels are found to be better predictors of mild sepsis (22). Combined use of IL-6 and CRP is found to give better predictive values than the use of either alone. However, more studies in different settings are required to confirm these findings and to evaluate their applicability as routine diagnostic tests.

TNF-α is responsible for organ injury. Although the levels of this cytokine also increase in infection, this is a less sensitive marker than IL-6. Combined use again increases sensitivity (22). IL-1β is a soluble protein released by macrophages in response to infection and inflammation. With IL-6 and TNF-α it also can initiate acute phase responses such as fever and synthesis of acute phase hepatic proteins such as CRP. However, estimation of levels of this cytokine in infections has yielded conflicting results and it is not considered important for diagnosis (22). Another widely studied marker is fetal fibronectin. Elevated levels of fetal fibronectin in vaginal fluids is highly predictive for preterm labor. This marker is detected with the use of monoclonal antibodies (19,20).

**Maternal morbidity**

The panorama of maternal morbidities vary from one low-income setting to another. We have seen levels of syphilis infection of 15–20% in countries such as Mozambique (23) while some subsets of women of reproductive age in the same country have syphilis seropositivity >60% (24). In India our studies have shown that syphilis seropositivity reaches prevalence levels of a few percent (25). Drawing conclusions about the effect of infectious maternal morbidity on pregnancy outcome can therefore be expected to be extremely different in different low-income settings.

**Preterm birth.** Precisely defining what we mean by preterm birth is important. Preterm birth occurs before 37 completed weeks or 259 completed days of gestation. It is a leading cause of infant death and several contributing mechanisms to this morbidity have been identified over the past 10 y (26). It is obvious that several pathways are involved in the pathogenesis of preterm birth, which may explain why it has proved so difficult to predict and prevent. Too early activation of the fetal hypothalamic-pituitary-adrenal axis may result from maternal psychosocial or fetal physiological stress. Such physiological fetal stress may in turn be a consequence of microbial invasion of fetal membranes, amniotic fluid and the fetus itself. This mechanism is considered to account for about one-third of preterm births (26,27). The critical mediator of stress-induced preterm birth appears to be corticotropin-releasing hormone, which is also expressed by several cell types in the placenta, chorion, amnion and uterine decidua (26,27). The concentration of corticotropin-releasing hormone rises during the second half of pregnancy and has been observed to be highest during labor (28). It stimulates the production of prostaglandins by cells in the amnion, chorion and decidua (26,27). Prostaglandins also stimulate the release of corticotropin-releasing hormone in the placenta, fetal membranes and decidua (26,27).

Ascending genital infections are generally considered to contribute to about half of preterm births, particularly those before gestational age 30 wk (26,27). IAI’s are known to be associated with activation of IL-1β and TNF-α in the genital tract. These cytokines stimulate prostaglandin synthesis in the fetal
membranes and decidua and appear to inhibit prostaglandin breakdown (26,27,29). Both cytokines enhance the expression of matrix metalloproteinases and IL-8 in the chorion, decidua and cervix. The ensuing increased expression leads to degradation of the extracellular matrix of the fetal membranes and the cervix (26,30). TNF and matrix metalloproteinases also promote programmed death of amniotic cells (26,30). The combined effect of these mechanisms may provoke preterm birth.

A number of studies have shown a correlation between vaginal infections and preterm birth. Bacterial vaginosis in early pregnancy is associated with increased risk of both preterm birth and prelabor rupture of membranes (31). Asymptomatic bacteriuria and symptomatic lower genital infections, including bacterial vaginosis, trichomoniasis, gonorrhea and chlamydia infection, are associated with preterm delivery (32). On the basis of current evidence, pregnant women who note a vaginal discharge are recommended to be tested for bacterial vaginosis, trichomonas infection, gonorrhea and chlamydia infection (32).

Because results of antibiotic trials for the treatment of preterm labor have been inconsistent, it has been argued that antibiotics should be used only for protecting the neonate from group B streptococcal sepsis in the absence of reasonable evidence that antimicrobial therapy significantly prolongs pregnancy in the setting of preterm labor (32). In practice, however, particularly in low-income countries, blind antibiotic therapy under these conditions is seldom possible. A fetus being infected by ascending maternal genital infection may thrive better outside the mother's body in middle- and high-income countries with fair neonatal care resources. In low-income settings the low-birth-weight neonate will have a poor chance of survival whether left inside or outside uterus. In selected cases (precious babies) giving the mother antibiotics to save the life of the fetus might be indicated.

An increasing body of evidence indicates that candida infection in the vagina is associated with preterm birth (33). Early colonization of the genital tract with infectious agents in the second trimester may also be associated with preterm birth (34). Midgestation miscarriage was found to be associated with presence of group B streptococci (34). In the search for potential infectious agents active in the second trimester, Lu et al. (35) tried to investigate the role of Mycoplasma genitalium but could not substantiate that its occurrence in the vagina at that gestational age is significantly associated with subsequent preterm birth.

Most methods for predicting preterm birth require expensive technology. One possible exception suggested by Saling et al. (36) is a simple, efficient and inexpensive program for preventing preterm birth. The program consists of regular measurement of the vaginal pH with appropriate therapeutic measures when a disturbance of the vaginal milieu is diagnosed. Saling et al. argue that the rate of very small low-birth-weight infants could be reduced from 7.8% in the immediate previous pregnancy to 1.3% in subsequent pregnancies. However, this simple approach has not been studied further and more systematic investigation is needed.

Prelabor rupture of membranes. The term “prelabor” should be used rather than “premature” or “preterm” because the latter two relate neither to gestational age nor to the weight of the fetus or neonate. The membrane rupture itself should be characterized as preterm (occurring before 259 completed days) or term (occurring after 259 completed days).

Several studies have shown that in patients with prelabor rupture of membranes in the preterm period, prophylactic antibiotics are of value in prolonging the latent period between rupture and onset of labor and in reducing the incidence of maternal and neonatal infection (32). The most extensively tested antibiotic regimen used for prophylaxis includes erythromycin either alone or with ampicillin (32). There is no evidence that antibiotic therapy prevents prelabor rupture of membranes. Bacterial vaginosis in early pregnancy has been found to be associated with prelabor rupture of membranes in the preterm period (31).

Considerable attention has been given to ILs as predictors of prelabor rupture of membranes. Lewis et al. (37) found that IL-6 in maternal plasma was a predictor of neonatal infectious complications in patients with prelabor rupture of membranes even when the data were stratified for patients receiving and not receiving corticosteroids. The neonatal infectious complications examined included respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, IAI, presumed neonatal sepsis, neonatal sepsis and congenital pneumonia.

Reactive oxygen species, which are generated by the body’s response to diverse insults such as infection, have also attracted attention. Such insults may activate collagenolytic enzymes and impair fetal membrane integrity (38). This impairment is then inhibited by antioxidants like vitamin E and possibly vitamin C (38). Damage by reactive oxygen species that impairs fetal membrane integrity and reduces midgestation levels of vitamin C is associated with prelabor rupture of membranes in the preterm period (38). Vitamins E and C can be safely and effectively absorbed and delivered to gestational tissues, which opens the possibility of intervention trials (38).

Placental abruption. No clear evidence indicates that placental abruption has an infectious origin but evidence is increasing that it occurs in more than half of preterm births (26). Decidual tissues are rich in factors that initiate hemostasis (26,39); after a hemorrhage, membrane-bound tissue factor from the decidual cells forms a complex with activated factor VII to activate factor X, which in turn generates thrombin. The binding of thrombin to its receptor enhances the production of enzymes that break down the decidual and fetal membranes (39). Thrombin has also been found to bind to myometrial receptors, resulting in the stimulation of uterine contractions (39,40).

Dynamic uterine dysfunction, uterine atony or uterine inertia. Some anecdotal evidence suggests that infection may play a role in dynamic uterine dysfunction (dysfunctional myometrial activity). It has been argued that chorioamnionitis, reflecting intrauterine infection, is associated with prolonged labor. It can also be argued that a prolonged labor may increase contamination (e.g., by repeated palpation of the cervix) more than a shorter labor. However, no systematic studies are available to clarify this issue. If serological markers for intrauterine infection can be found, it would be possible to test the hypothesis of such infection as a cause of prolonged labor.

Postpartum hemorrhage. In analogy with what has been said regarding dynamic uterine dysfunction and uterine atony postpartum with ensuing hemorrhage, anecdotal evidence has suggested that uterine inertia is associated with infection. There have been no studies, however, substantiating the interesting relationship between chorioamnionitis and subsequent uterine atony. Such studies are highly desirable and should be carried out.

Retained placenta. A search of databases (Medline, Cochrane) yielded no findings on any infection-related etiology of interest in this condition.

Postpartum sepsis. Studies in Mozambique showed that postpartum sepsis after vaginal (41,42) and caesarean (43) delivery is associated with specific infections. The most interesting finding here is that almost half of women presenting with
postpartum sepsis give birth to low-birth-weight infants (42), suggesting that subclinical infection is an important factor for postpartum sepsis. The belief that such sepsis is predominantly caused by unhygienic handling of the delivering woman is obviously not correct. Rather, it seems as if intrauterine subclinical infection may provoke preterm birth (with an ensuing low-birth-weight neonate) with a risk of neonatal sepsis, leaving behind an infected cavity with subsequent postpartum sepsis (42). It is striking that studies have not been able to distinguish an intrauterine microbial growth pattern clearly related to postpartum sepsis (41). Nonbacterial agents may be responsible for a substantial percentage of cases with postpartum sepsis.

**Mastitis.** Mastitis, subclinical and clinical, is a potential risk factor for mother-to-child transmission of HIV. This route of transmission of infectious agents is presumably underestimated and should be given more attention, not only in the context of HIV transmission.

**Anemia.** Recent evidence indicates that signs of inflammation or infection are prevalent in women with anemia. In Malawi it was found that CRP concentrations were notably high in more than half of anemic women with no nutritional deficiencies and in more than 70% of anemic women who were iron replete by bone marrow assessment (44). Anemia may thus be a maternal morbidity sign indicating inflammation or infection of unknown origin.

**Fetal morbidity**

**Fetal sepsis.** Studies on cord blood in women with clinical suspicion of having infants subject to IAI have shown that cord blood cytokines may predict neonatal outcome. Cord blood from neonates with intrauterine infections had more IFN-γ-producing CD3+T cells than did cord blood from uninfected neonates (45). The percentage of these cells in the infected neonates correlated with a duration of membrane rupture before the onset of labor but not with the level of CRP. The infected neonate born the longest time after membrane rupture had an increased percentage of IL-4-producing CD3+T cells. The result suggests that the increase of cord blood IFN-γ and IL-4-producing T cells is part of the immune system’s reaction to perinatal intrauterine infections (45).

**Intrauterine growth retardation.** Most of the literature available linking infection with intrauterine growth retardation focuses on malaria. Some evidence shows that cytomegalovirus infections may play a role in this context. Cytomegalovirus immunoglobulins were given to pregnant women with primary infections may play a role in this context. Cytomegalovirus infection and the development of neonatal intrauterine growth retardation, possibly by the ventricular leukomalacia with subsequent cerebral palsy (48,50). The intraventricular hemorrhage is thought to be mediated through the generation of proinflammatory cytokines by the fetus.

**Neonatal neurological disorders**

Hitti et al. (49) also saw a number of severe neurological sequelae, such as intraventricular hemorrhage and multiple organ dysfunction. Similar results were shown in other studies and evidence now exists of a relationship between intrauterine infection and the development of neonatal intraventricular hemorrhage, possibly by the ventricular leukomalacia with subsequent cerebral palsy (48,50). The intraventricular hemorrhage is thought to be mediated through the generation of proinflammatory cytokines by the fetus.

**Conclusion**

Only partially understood host defense mechanisms operate against infections affecting maternal and fetal morbidity. Subclinical ascending infections through the lower female genital tract are predominant worldwide. Important micronutrient deficiencies may prevail in low-income countries where these infections are much more common than in high-income countries. Proinflammatory cytokines have been tested for their use in diagnosing such infections, and promising leads indicate that affordable kits may soon be available for serological diagnosis of the mother. Important morbidities related to poor perinatal outcome both for the mother and the fetus and newborn comprise preterm birth, prelabor rupture of membranes, placental abruption, postpartum sepsis and maternal anemia. Fetal sepsis and intrauterine growth retardation are suspected to be consequences of ascending maternal infections. Neonatal sepsis and neonatal respiratory disorders as well as some neurological disorders seem to be consequences in the newborn of such ascending genital infections in the pregnant woman. Much more attention should be given to efforts to elucidate:

- the host defense mechanisms;
- antimicrobial barriers from the vagina through the cervix, the fetal membranes and the amniotic fluid; and
- early fetal immunocompetence in the second and the third trimester of pregnancy.

**LITERATURE CITED**
