Clinical Aspects of Infections as a Cause of Prematurity: "A Continuum of Risk"

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One of several high priorities in clinical obstetrical research is the determination of the proportion of preterm deliveries caused by infection. If infection can be shown with a high degree of certainty to be a significant cause, and if the mechanisms are understood, a safe therapeutic scheme can be proposed to reduce the incidence of preterm birth.

Most infections have a prodromal phase: this premonitory phase is now referred to as a preclinical or "silent" infection. In order to understand more clearly the role of infection in clinical obstetrics, we must begin at an early stage. This chapter will focus on the continuum of risk from the silent stage of infection to the symptomatic phases, from the point of view of a clinical disease and from a mechanistic point of view.

SUBCLINICAL INFECTIONS

The major debate today is about whether infection precedes and initiates preterm labor and/or premature rupture of the membranes, or whether it is an associated event. Several years ago our group considered clinical infections as a significant contributor only at later stages in the pathophysiology of preterm labor (1). Figure 1 indicates that clinical infections occur during the symptomatic stages (Stage III A and B) of preterm labor. What is the current evidence for the role of subclinical infections (Stage II) in increasing the likelihood of preterm delivery or premature rupture of the membranes? We shall explore the risk factors associated with infection which are present before and during pregnancy.

Role of Infection Prior to Pregnancy

Only recently has prepregnant genital tract infection been considered an early cause of asymptomatic bacterial colonization of the uterine cavity. Toth et al. (2)
FIG. 1. A hypothesis for the multifactorial etiology of preterm labor. Stages I and II are considered silent or asymptomatic, whereas Stages III A and B are associated with clinical symptoms (1).
TABLE 1. Risk factors for infection

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<tr>
<td>History of septic abortion (2)</td>
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<td>History of pelvic inflammatory disease (3)</td>
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<td>History of intrauterine contraceptive device (3)</td>
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<td>Multiple sex partners (3)</td>
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<td>Presence of antisperm antibodies (3)</td>
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<td>History of pregnancy loss (3)</td>
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<td>Pregnancy</td>
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<tr>
<td>Maternal age (3,4)</td>
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<td>Number of pathogenic bacterial species at first visit (3)</td>
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<td>History of pregnancy loss (3)</td>
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<td>Asymptomatic bacteriuria (5-7)</td>
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<td>Sickle cell trait (8)</td>
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<td>Low social class (4,9)</td>
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<td>High parity (4)</td>
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Reference numbers in parentheses.

in 1986, reported a significant association between antibiotic therapy for septic abortions and subsequent pregnancy outcomes. They proposed that a subclinical infection persists in the endometrium and during a subsequent pregnancy, with its concomitant immune suppression, there is a persistence of the infection with a high probability of its evolution into a clinically important condition.

Risk Factors

If pre preg nancy events are important, then what information is available on the role of risk factors in identifying patients at risk? More recently, Toth et al. (3) identified four significant risk factors associated with preterm birth and premature rupture of the membranes (Table 1). When these risk factors were entered into a logistic regression analysis, maternal age, numbers of pathogenic bacterial species, and history of pregnancy loss were still found to be significant. Their conclusion was that preexisting infection of the uterine cavity is a predisposing factor in preterm delivery.

Asymptomatic Bacteriuria During Pregnancy

The average incidence of asymptomatic bacteriuria in pregnancy is 5.1%, with a range of 3.8–9.7% (10). The incidence is similar in the pregnant and nonpregnant population; however, in pregnancy the incidence of symptomatic urinary tract infection is approximately three times that of the nonpregnant population (11,12). The increased risk of developing symptomatic infection in pregnancy is probably secondary to the urinary tract changes that occur, leading to stasis. It is also possible that some bacteria, such as the coliform bacilli, grow more rapidly in the urine of pregnant women than in that of nonpregnant controls (13).
Risk of Pyelonephritis

The risk of asymptomatic bacteriuria is considerable. Untreated women have on the average a 30% (range is 23–42%) risk of developing acute pyelonephritis, whereas the general incidence is <2% (10). Women who are treated have a risk of developing acute pyelonephritis of less than 5% (5).

Risk of Preterm Labor and Low Birth Weight

Kass (5) in 1962 was the first to note a very high prevalence of prematurity and perinatal mortality in infants of bacteriuric women (5). This was quickly reconfirmed by Kincaid-Smith and Bullen (6) in Australia in 1965. Kass also showed that both of these risks were significantly diminished when the bacteriuria was treated, although this was not confirmed by Kincaid-Smith and Bullen. These studies resulted in a considerable interest in the early diagnosis of asymptomatic bacteriuria. Between 1960 and 1971 there were 19 studies on the subject, of which only six showed a significant relationship between asymptomatic bacteriuria and the incidence of preterm delivery and low birth weight (7). Recently, Romero et al. (7) applied meta-analysis to examine the relationships between asymptomatic bacteriuria and preterm delivery and low birth weight. They classified reports according to study design into cohort studies and randomized treatment trials. Meta-analysis of cohort studies showed that untreated asymptomatic bacteriuria significantly increases the rates of both preterm delivery and low birth weight. The analysis of clinical trials showed that antibiotic treatment significantly reduced the risk of low birth weight. This careful analysis of the available clinical trials clearly indicates that antibiotic treatment of asymptomatic bacteriuria is effective in reducing the occurrence of low birth weight. The pathogens most frequently isolated from bacteriuric women are listed in Table 2. The species in this list are different from those identified by Toth et al. (3) in the cervix in first trimester pregnancies.

Risk Factors

Factors associated with a high incidence of asymptomatic bacteriuria are shown in Table 1 (8,9,14,15).

CLINICAL INFECTIONS

Vaginal-Cervical Colonization During Pregnancy

Very little is known about the time course between colonization of pathogens and the appearance of clinical symptoms meeting criteria for the diagnosis of vaginitis and the occurrence of preterm labor or premature rupture of the membranes (3,16).
INFECTIONS AS A CAUSE OF PREMATURITY

TABLE 2. Most frequently isolated pathogens in clinical infections

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<tr>
<td>Escherichia coli</td>
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<td>Klebsiella pneumoniae</td>
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<td>Proteus mirabilis</td>
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<td>Pseudomonas aeruginosa</td>
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<td>Enterobacter cloacae</td>
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<td>Enterobacter aerogenes</td>
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<td>Staphylococcus saprophyticus</td>
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<td>Enteroceococcus</td>
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<td>Group B β-hemolytic streptococcus</td>
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<td>Peptococcus spp.</td>
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<td>Peptostreptococcus spp.</td>
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<td>Clostridium</td>
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<td>Bacteroides spp.</td>
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<td>Gardnerella</td>
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<td>Gonococcus</td>
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<td>Chlamydia</td>
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<td>Trichomonas</td>
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<td>Mycoplasma</td>
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<td>Ureaplasma</td>
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Minkoff et al. (16) carried out a prospective study of vaginal flora by culturing 250 apparently asymptomatic patients early in pregnancy and relating their outcome to the presence or absence of various organisms. They found that patients who had Trichomonas vaginalis or Bacteroides sp. were more likely subsequently to experience premature rupture of the membranes, and those with Ureaplasma urealyticum more frequently began preterm labor. These authors cautiously interpreted their results by stating that a positive culture early in pregnancy may be noncausal or indirectly causal. Subsequent follow-up screening of these patients would be necessary to find a true correlation between the presence of these organisms and preterm birth or premature rupture of the membranes. As can be determined from Table 2, the pathogens found in the cervix and vagina of asymptomatic women are different from those of bacteriuric women but similar to those implicated in vaginitis, cervicitis, and preterm labor.

Vaginitis-Cervicitis

Vaginal discharge is the most frequent gynecologic complaint and it accounts for 7% of all patient visits to the obstetrician gynecologist (17). The diagnostic categories of vaginitis are: nonspecific, 40–50%; candidiasis, 20–30%; and trichomoniases, 20–30%. In the normal nonsymptomatic patient there is a large number of microorganisms, many of which have pathogenic potential. However, the presence of lactobacilli is vital for restructuring the growth of other bacteria, primarily by maintaining
a low vaginal pH. The mechanisms causing a change in the complex interrelationship between microorganisms is not well understood. Symptomatic vaginitis is most often secondary to an overgrowth of Candida albicans and Gardnerella vaginalis and also of sexually transmitted organisms such as Trichomonas or Neisseria gonorrhoeae. Cervicitis is considered to be an entity distinct from vaginitis (17). Approximately 25% of patients with vaginal discharge have cervicitis. The only known specific causes of cervicitis are Neisseria gonorrhoeae, Chlamydia trachomatis, and Mycoplasma hominis. There is increasing evidence that cervical and vaginal infection may cause a significant proportion of preterm deliveries.

**Bacterial Vaginosis (Nonspecific Vaginitis)**

As noted above, this diagnosis is made in about 50% of patients who complain of vaginal discharge, the associated organisms being Gardnerella vaginalis and Bacteroides sp. A prospective study by Gravett et al. (18) showed a significant association between premature rupture of the membranes, preterm labor, and amniotic infection in women who met criteria for the diagnosis of bacterial vaginitis. Nineteen percent of 534 pregnant women were found to have bacterial vaginosis. These same investigators, in a matched case-control study of patients with subclinical amniotic fluid infections, found a fourfold increase in the risk of premature labor in patients with this diagnosis (19). Even though Minkoff et al. (16) found that 31.8% of 233 prenatal patients had clinical criteria for nonspecific vaginitis they did not find an association with preterm labor. However, they did find a significantly increased incidence of Bacteroides isolation in those who delivered preterm, which is correlated with bacterial vaginosis.

**Trichomonas Vaginalis**

Early studies did not associate trichomoniass with the risk of low birth weight (20). It is known that the organism may cause inflammation. Recently Minkoff found trichomonads in approximately 15% of prenatal patients, and these women were significantly more likely to have premature rupture of the membranes (16).

**Vaginal Candidiasis**

Candidiasis is the third most common vaginal infection during pregnancy and there is no apparent association with preterm birth or premature rupture of the membranes. The mechanisms by which the vagina is colonized with candida is not well understood. It appears that candida species are opportunistic pathogens that flourish only when the normal flora is altered. Progesterone receptors have been identified in the cytosol of Candida albicans which may explain the increased incidence of symptomatic disease observed in pregnancy (21). It is not known whether the recovery
of this organism in up to approximately one-third of patients has any clinical significance with reference to preterm birth.

**Chlamydia Trachomatis**

Cervical infection with *Chlamydia trachomatis* has been associated with preterm labor, premature rupture of the membranes, and low birth weight (18,22). However, some studies have not supported this association (23,24). The reasons for these different findings are not clear. From my review of these papers, the selection of patients by risk factors, the timing of the first culture, and the reassessment as to recurrence are all issues that determine the final associations between positive results and poor perinatal outcome.

**Neisseria Gonorrhoeae**

The incidence of gonococcal infection in pregnant women ranges from 2.5% to 7.3% (25,26). Handsfield *et al.* (25) were the first to direct our attention toward gonococcal infection as a cause of preterm delivery and premature rupture of the membranes. These investigators observed a significantly greater incidence of *Neisseria gonorrhoeae* isolated from orogastric aspirates in women with preterm labor and premature rupture of the membranes than in a group without these complications. Their findings were consistent with the concept of "amniotic infection syndrome" proposed by Blanc 14 years earlier (27). These studies formed the basis for initiating the study of infection as a cause of these two major complications in obstetrics.

**Mycoplasma Species**

The role of *Mycoplasma species* in poor pregnancy outcome has been reviewed by Romero and Mazor (28). The rate of isolation of *Mycoplasma hominis* from cervicovaginal fluid was found to vary between 5% and 49% whereas that of *M. urealyticum* was higher, at 44% to 81%. After a careful review of over 17 publications these investigations came to the conclusion that only one randomized clinical trial (29), in which colonized women were treated with erythromycin, was associated with a lower prevalence of low birth weight infants. A second study, by Kundsin *et al.* (30), suggested a positive association between histologic chorioamnionitis and the isolation of *Ureaplasma urealyticum* (30). Thus at best there is little to suggest that cervical-vaginal colonization with mycoplasmas is a significant cause of either low birth weight or prematurity (31).

**Cystitis/Pyelonephritis**

This is one area of the spectrum of clinical infections in pregnant women that has received little recent attention. The linkage between asymptomatic bacteriuria and
pyelonephritis is quite clear; little has been mentioned, however, about the likelihood of the occurrence of cystitis in patients who have asymptomatic bacteriuria (32).

Cystitis occurs in approximately 1.3–3.4% of pregnant patients (4,33). It is characterized by lower urinary tract symptoms (urinary urgency, frequency, dysuria, and suprapubic discomfort), the absence of systemic symptoms, and a positive urine culture. According to Harris and Gilstrap (33) cystitis in pregnancy is a distinct clinical syndrome different from both asymptomatic bacteriuria and pyelonephritis. Patients who develop cystitis have a 26% incidence of positive asymptomatic urine screens as compared to 80% of those who develop pyelonephritis. Likewise, the incidence of recurrence is only 17% compared to 33% for asymptomatic bacteriuria and 75% for pyelonephritis. It is very clear that cystitis may occur as a newly acquired complication of pregnancy, not highly associated with prior positive screening, and it has a low recurrence rate. The only reports associating cystitis with preterm labor or premature rupture of the membranes are by Mimouni et al. (34) in a group of insulin-dependent diabetic women. However, this study combined cystitis and vaginitis to form “urogenital infection” as the diagnostic category.

Acute pyelonephritis occurs in 1–2% of pregnant patients (32). Approximately 70–80% of patients who develop acute pyelonephritis during pregnancy have a prior history of asymptomatic bacteriuria. As noted earlier, the treatment of asymptomatic bacteriuria significantly reduces the risk of pyelonephritis. In the early 1960s Kass (5) showed that untreated women with asymptomatic bacteriuria had a high risk of developing pyelonephritis and when the condition was treated, not only was pyelonephritis prevented but the incidence of prematurity and low birth weight was also reduced. The association between preterm delivery and pyelonephritis is complex. It is most likely that the onset of preterm labor associated with pyelonephritis comes about by two different mechanisms, though these may be related. One mechanism is via the release of an endotoxin from bacteria in the bladder and kidney causing increased myometrial contractility (35). A second mechanism is via an associated ascending vaginal infection with necrosis of the decidua, release of lipases and prostaglandin production, also affecting uterine contractility (28). Thus in some cases preterm labor may not be caused directly by pyelonephritis. Gilstrap et al. (36) noted that delivery of low birth weight infants occurred exclusively in patients who had premature labor in association with acute pyelonephritis.

**Amnionitis, Clinical and Subclinical**

Maternal pyrexia has been the hallmark for the diagnosis of clinical chorioamnionitis; however, pyrexia is a late sign since infection within the amniotic cavity can be present with normal body temperature. The standard criteria used for the diagnosis of clinical amnionitis are maternal fever ≥37.8°C (100°F) plus two or more of the following: leukocytosis (≥15,000 per mm³ with a shift to the left in the differential), maternal pulse >100 beats per min, fetal tachycardia ≥160 beats per min, and/or uterine tenderness (37). At the present time subclinical amnionitis is defined
as the presence of a positive culture in the absence of the signs of clinical amnionitis (38). The combined incidence of these two clinical entities is between 0% and 25.8% (39). In 1977 Bobitt and Ledger were the first to provide evidence that amniotic fluid analysis in patients in preterm labor was positive for bacteria prior to the development of signs of maternal infection. This ushered in the concept of "subclinical" amnionitis (40,41). A subsequent study by Bobitt et al. (42) confirmed this finding and reported a 25% incidence of amniotic fluid infection in patients in preterm labor, and of these 75% were subclinical. These early reports led to several studies to determine the incidence of positive cultures (41–43). Wahbeh et al. (43) identified a subgroup of patients with extreme prematurity at highest risk of being colonized. This finding was consistent with the report from Naeye and Peters (44) whose analysis of the collaborative perinatal project data identified a peak incidence of amniotic fluid infections in the early pregnancy as a cause of perinatal deaths.

As more investigators begin to focus on subclinical intraamniotic infections, several important observations have been made. Hameed et al. (45) recognized that markers of infection (maternal C-reactive protein and amniotic fluid white cell count, gram stain, and culture) were significantly more common in cases that were refractory to tocolysis. These data indicated that the more difficult preterm labors may be due to infections that had reached the amniotic cavity. These data could support the concept that preterm labor due to milder infections in the decidual space or membranes, without invasion into the amniotic cavity, might be easier to inhibit with tocolytic therapy. Other studies have not been able to identify a high incidence of asymptomatic infections in women in preterm labor (46,47). The differences observed in these studies may be related to the differences used to define preterm labor, or to different population demographics, microbiologic techniques, and thresholds required for performing amniocentesis. This disparity between investigations makes it difficult to justify amniocentesis for microbiological evaluation of asymptomatic women with intact membranes and preterm labor.

There has been an ongoing controversy as to whether subclinical intra-amniotic infection or ascending type infection cause premature rupture of the membranes. There are some data to suggest that subclinical intra-amniotic infection can lead to premature rupture of the membranes. Leigh and Garite (48), who studied the value of amniocentesis in the management of premature labor with intact membranes, found that in all those who subsequently had premature rupture of the membranes positive cultures were present. In a study on the relationship between premature rupture of the membranes and fetal immunoglobulin production, Cederquist et al. (49) showed that fetuses from mothers with premature rupture of the membranes had significantly higher immunoglobulin levels than those of a control group. They found two patterns of infection. In a first group the peak immunoglobulin level occurred between 1 and 12 h after rupture of the membranes, while a second group peaked after 72 h. They hypothesized that in the first group the peak suggested that the infection was present before the membranes ruptured. There is thus considerable evidence to support the role of asymptomatic infection as a cause of preterm labor with and without premature rupture of the membranes. The pathogens identified in
these patients are similar to those cultured from the vagina and cervix of asymptomatic and symptomatic women (vaginitis-cervicitis) (Table 2).

THE PATHOPHYSIOLOGY OF INTRAUTERINE INFECTION

Currently little attention is being directed toward understanding the mechanisms by which infection reaches the amniotic cavity. Romero and Mazor (28) carefully described the pathways for intrauterine infection. They concluded that indirect evidence indicates that the most common pathway is the ascending route, as opposed to the hematogenous route, or retrograde seeding via the fallopian tubes, or accidental introduction during intrauterine procedures. However, the investigations cited did not attempt to pursue the mechanisms by which organisms ascend through the cervix. If progress is to be made in the prevention of preterm birth, then investigations into these mechanisms must be pursued, since specific interventions to reduce or prevent bacteria from entering the uterus would be more efficacious than treating asymptomatic or symptomatic infections with antimicrobial agents.

Ascending Route of Infection

The mechanism by which bacteria pass the cervical barrier from the vagina into the uterus is of primary importance. The factors involved have not been clearly described. After an extensive review of the literature, I can propose a possible mechanism. For pelvic inflammatory disease the mechanisms by which infectious agents may spread from the lower to the upper genital tract have been described by Keith et al. (50). Three potential mechanisms have been described: trichomonads as vectors, sperm as vectors, and passive transport.

Trichomonads and Sperm as Vectors

There are data to suggest that both trichomonads and sperm act as vectors in pelvic inflammatory disease (50). Whether they play an important role in ascending infection in pregnancy remains to be studied; however, there is indirect evidence to support the fact that sperm may act as a vector. Bacteria are known to attach to sperm at both high and low bacterial concentrations (51). Bacteria have also been shown to attach to and invade the chorioamniotic membranes (52). Naeye and Ross (53) studied a clinic population in South Africa and found that premature delivery was four times more frequent in patients who had coitus. They observed a peak frequency of chorioamnionitis limited to the extraplacental membranes when labor and delivery took place within 2 days of the last coitus. This was only true when coitus occurred without a condom. Orgasm may also play a role: spontaneous rupture of the membranes occurred twice as frequently when there was recent coitus with orgasm than in patients with coitus without orgasm.
Passive Transport of Pathogens

Interest in the role of this mechanism stems from the early observations of Beck (54) in 1874, who showed that the rapid transport of sperm into the cervix and uterus cannot be accounted for entirely by sperm motility. The concept of active suction by the uterus during coitus was proposed by Heape (55) in 1898. During the 1930s, numerous studies using various techniques were performed in animal models to study sperm transport. This subject was reviewed by Noyes et al. in (56) 1958, but a sucking action of the uterus could not be confirmed. In the same year, Hartman (57) reviewed the subject and proposed that sperm migration must be dependent upon the muscular action of the female genital tract.

A breakthrough in this area of investigation occurred in 1960 when Bickers (58) demonstrated in human subjects that, in the absence of uterine contractions, the ascent of sperm in the human uterus was impossible. After placing carbon particles in the vagina prior to abdominal hysterectomy, Egli and Newton (59) observed carbon particles in the tubes within 30 min when oxytocin was administered. They concluded that contractions of the uterus were important for transporting the carbon particles into the uterus. The precise mechanical relationships that allow the passage of substances into the uterus was not established until Fox et al. (60) using a radiotelemetry device, studied the interrelationship between vaginal and uterine pressures during and after coitus. They identified a final negative pressure following female orgasm that could effect a sucking action of cervical mucus and entrapped sperm into the uterus.

The common denominator from studies on sperm migration in the nonpregnant women appears to be uterine contractility. Could uterine activity, as an active transport mechanism in pregnant women, cause the aspiration of cervical mucus and potential pathogens into the lower uterine segment and set the stage for a subclinical infection and possibly for clinical infection? We are currently studying this active transport mechanism, which is most plausible since excessive uterine activity is thought to precede preterm labor and premature rupture of the membranes (61). It is well recognized that important physiologic and anatomic changes occur in the uterus with the onset of labor. Reynolds (62) has described an increase in uterine myometrial tension in the fundus that exceeds the tension in the lower uterine segment. The result is a thinning of the lower segment and a gathering in of the myometrium. Thus there may be a passive mechanical aspiration of tissue components into the uterus together with contaminated material, setting the stage for subclinical infection between the uterine wall and the chorioamniotic membranes. I have referred to this as a squeeze (contraction), pull (suction) action that occurs because the cervix is anchored to the pelvis by the various ligaments, producing a zone of adhesion to allow this anatomical change to take place (Fig. 2). In support of both active and passive changes in the uterus it has been recently shown by de Vries et al. (63), using endovaginal real-time ultrasound, that rhythmic myometrial contractions of the inner myometrial third in pregnant and nonpregnant women are the rule rather than the exception. The majority of the uterine activity was retrograde, with
FIG. 2. Mechanism for ascending route of intrauterine infection. In the normal quiescent phase the cervix is closed. During uterine contractions a squeeze-pull effect results in an "in suck" of pathogens into the cervix. During preterm labor the internal cervical os moves cephalad forming a contraction ring. This passive state allows bacteria to be moved up into the lower uterine segment. Note, progressive dilatation of the lower uterine segment, thickening of the myometrial layers in the fundus (active segment), and thinning of these layers in the lower passive segment (50).

the contraction wave moving from the cervix to the fundus. These investigators were concerned that insertion of the endovaginal probe may have caused the observed uterine activity. This is unlikely since a similar type of endometrial movement has been observed using transvesical real-time ultrasonography (64).

CONCLUSION

There is a growing body of evidence to suggest that infection is a significant contributor to poor pregnancy outcome. The current debate focuses on whether infection precedes and causes preterm labor and/or premature rupture of the membranes or whether it is only an associated event. The purpose of this chapter is twofold. First, I have attempted to assess our current understanding of genitourinary infections from the point of view of a continuum of risk. There are significant maternal factors that identify a population at greatest risk. This risk begins before pregnancy. We should therefore place particular emphasis on identifying patients at risk before they become pregnant, at a time when intervention may make a difference to the outcome of the future pregnancy. I have next focused on the importance of recognizing the complex
INFECTIONS AS A CAUSE OF PREMATURELY

problems imposed by asymptomatic infections. It is apparent that we must focus more attention on particular pathogens causing vaginal infection that are different from those causing cystitis and pyelonephritis. There does not appear to be a continuum of risk between the clinical diseases of the genital tract and those of the urinary system, because the pathogens that are associated with preterm birth in these two conditions are different. However since both are associated with premature labor there must be common factors in the pathogenesis.

Finally, I have focused on symptomatic and asymptomatic intrauterine infections. Published reports emphasize the ascending route for both of these infections. The mechanism by which bacteria enter the uterus and establish themselves during pregnancy has not, however, been discussed. I have proposed an active process whereby uterine contractions pull pathogenic bacteria retrogradely into the cervix and lower uterine segment. A second passive mechanism occurs whereby the anatomic changes in the lower uterine segment allow bacteria to move up into the decidual-chorionic space and eventually into the amniotic cavity, initiating the cascade of events leading to preterm delivery.

REFERENCES


**DISCUSSION**

**Dr. Marini:** What do you feel about variations in the membranes themselves? Are some more readily penetrated by bacteria than others?

**Dr. Hobel:** In women with premature rupture of the membranes the force required to rupture the membranes is considerably less than in control women without premature rupture. Thus the membranes are weaker, and I also think that the changes in the lower uterine segment in the presence of infection allow the membranes to rupture more easily. Changes in elastin and collagen occur in preterm labor and these changes presumably affect the membranes. Copper is an important element in collagen synthesis and women with premature rupture of the membranes have been found to have lower copper levels than controls. Thus there may be several reasons why some membranes are more vulnerable than others.

**Dr. Saling:** Electron microscopic examination of the membranes in cases of amnionitis shows structural damage and in these cases the frequency of premature rupture is as high as 40%, i.e., double the normal frequency of membrane rupture immediately before parturition.

**Dr. Marini:** A study by Naeye (1) showed that the frequency of sexual intercourse was related to premature delivery. Is this due to mechanical factors increasing the likelihood of bacterial penetration, or is it due to the sperm?
Dr. Hobel: Naeye's study clearly showed that when a condom was used the frequency of premature rupture of the membranes decreased. Thus the sperm appear to play an important role. He also showed that female orgasm increases the likelihood of premature labor.

In relation to obstetric examinations, I feel strongly that no attempt should be made to insert a finger into the cervix. The length of the cervical canal can be readily assessed by examining the posterior part of the cervix.

Dr. Marini: Do you think antibiotic treatment has a place in preventing premature labor?

Dr. Hobel: I have not been impressed by the results of studies in this area. Significant effects have been only borderline. The use of prophylactic antibiotics disturbs the vaginal flora which may itself be harmful. Treating patients when they are symptomatic is appropriate, but efforts should really be directed at preventing bacteria from getting into the lower uterine segment. I am interested in the possibility of preventing colonization by maintaining a low vaginal pH. We also need to know more about uterine motility and how to control it. Some women have retrograde uterine motility.

Dr. Saling: In certain specific cases antibiotic treatment can be helpful. We have observed cases in which C-reactive protein levels were raised in association with symptoms of premature labor, and where treatment with antibiotics resulted in a reduction in uterine activity. The problem is how long to continue treatment for. When we discontinue antibiotic treatment we renew the vaginal flora by application of Lactobacillus acidophilus preparations.

Dr. Hobel: We do not do that but it sounds like a good idea. I am sure that it is very important to try to re-establish the normal vaginal flora after treating with antibiotics. I believe in the use of antibiotics in preterm labor because I am convinced there is infection in the lower uterine segment in these cases which is very difficult to diagnose. I am also concerned about the risks to the newborn. I think intrauterine infection plays an important role in confusing our pediatricians about whether there is IRDS or pneumonia.

Dr. Eschenbach: You propose a hypothesis that includes both bacteria and uterine contractions. How would you establish which of these is the more important, or whether a combination of both is required to cause premature rupture of the membranes?

Dr. Hobel: We need to measure uterine activity, monitor vaginal flora, and devise some marker whereby we could study this phenomenon in the human. I was impressed by a paper written in the 1950s in which strips of endometrium obtained from women who had had cesarean sections at term were examined and most showed evidence of infection. I think infection of the uterine cavity is a common phenomenon, but in a small proportion of patients who deliver preterm this may be an overwhelming effect. This suggests that some women have a very low resistance to infection.

Dr. Saling: I think that the general immunologic state of high-risk patients is very important. Papiernik believes that the social state of the patient is a key factor. This is relevant since in people with poor social status the immunological situation is likely to be worse than in people with higher social status, and therefore ascending infection is more likely to have critical consequences.

Dr. Hobel: This makes biological sense. Another factor of interest is the importance of progesterone in stimulating cervical immunoglobulins, which appear to be important in preventing the entry of bacteria. It is possible that women with low progesterone levels may be particularly at risk. I have been impressed by the low frequency of vaginal infections in women who have been given progesterone suppositories because of repeated pregnancy losses at 16 to 20 weeks' gestation. It is possible that vaginal progesterone may prevent colonization with pathogens.

Dr. Marini: Although in most cases of prolonged rupture of the membranes, lung maturation
is accelerated, this is not always the case. Do you advocate the use of steroids to enhance lung maturation?

**Dr. Hobel:** When there is premature labor with very low fetal weight, Dr. Jobe, who does our neonatal pulmonary physiology work, is convinced that corticoids have a beneficial effect on elastin and reduce the risk of bronchopulmonary dysplasia.

**Dr. Saling:** We give one course of lung maturation therapy in every case of premature rupture of the membranes before 35 weeks' completed gestation. We do not repeat the course if delivery does not occur, because the fact of premature rupture of the membranes itself stimulates lung maturation.

**Dr. Eschenbach:** Romero has shown a relationship between amniotic fluid infection and respiratory distress in the neonate, but because amniotic fluid infection may be related to low gestational age this is perhaps not surprising. However we have also shown that babies whose placentas contained bacteria had higher rates of IRDS, even when controlling for gestational age. These data suggest that infection in this group may have consequences beyond prematurity alone. Do you have similar data?

**Dr. Hobel:** There are data to suggest that infection also plays a role in CNS bleeds in preterm infants. Now that we are focusing more on infections during labor, we have an opportunity to help the pediatricians by treating infection. For many years we never gave antibiotics during labor because the pediatricians told us they interfered with their cultures. I think this was a big mistake!

**REFERENCE**