Arch Gynecol Obstet (1992) 251: 1–7

Archives of
Gynecology
and Obstetrics

Reviews

Intraamniotic infection with fusobacteria

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Received November 26, 1990/Accepted June 20, 1991

Summary. A literature search produced ten studies in which Fusobacterium was cultured from amniotic fluid in women with preterm labor and intact membranes or with preterm premature rupture of membranes (PROM). Fusobacterium was isolated in 9.9% (9/91) of positive amniotic fluid cultures in women with preterm PROM and in 28.3% (17/60) of positive amniotic fluid cultures in women presenting with preterm labor and intact membranes. Fusobacterium plays a previously unrecognized role in the pathogenesis of premature labor and delivery. Amniotic fluid culture for anaerobs, specifically Fusobacterium, is suggested for all women who present with premature labor and intact membranes and do not respond to tocolytic drugs.

Key words: Intraamniotic infection – Fusobacterium – Preterm labor – Premature rupture of membranes

Introduction

Intrauterine infection may be associated with preterm labor and delivery [11, 16, 18–20]. More than a decade ago, Bobitt and Ledger [2] were the first to present microbiological data suggesting that unrecognized amnionitis may be causally related to premature labor and delivery. Recently, a review of the available literature had found that the mean rate of positive amniotic fluid cultures in women with preterm labor and intact membranes was 13.5% (46/359) [18]. Moreover, in women presenting with preterm premature rupture of membranes (PROM), the prevalence of positive amniotic fluid cultures was significantly higher than in women with preterm labor and intact membranes, namely 28.5% (178/625) vs. 13.5% (46/359), respectively [18]. Indirect evidence suggests that microorganisms commonly gain access to the amniotic cavity from the vagina and cervix [18]. Indeed a large variety of vaginal organisms (commonly of the Fusobacterium species) have been identified in amniotic fluid of

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women with preterm labor and intact membranes and in women with preterm PROM. In a recent study, Fusobacterium was isolated from 5 out of 111 patients who delivered prematurely, positive amniotic fluid cultures being obtained in 21.6% (24 patients) [21].

The purpose of this communication is to review the literature for studies that examine the relationship between intraamniotic infection with Fusobacterium species and preterm labor and delivery.

Methods

We did a Medline search of the literature (1966 to 1989) for studies reporting intraamniotic colonization with Fusobacterium species and preterm labor and delivery. The studies described in this review were included only if amniotic fluid was obtained by transabdominal amniocentesis. We also did not include any study in which the method of amniotic fluid collection was not clearly stated [17]. Case reports were not included if they presented no data about prevalence of intraamniotic infection in the local population [6]. Data were extracted by two different authors and with a discrepancy in the interpretation of the results, a third investigator was consulted.

Results

We identified ten studies [5, 7, 8, 12, 20, 21, 25–28] in which Fusobacterium was cultured from amniotic fluid obtained by amniocentesis in women with preterm labor and intact membranes or with preterm PROM.

Table 1 displays the results of the three studies in women wirh preterm PROM [5, 7, 20]. The prevalence of positive amniotic fluid cultures was 26.1% (91/348). Fusobacterium was isolated in 9.9% (9/91) of the cases with positive amniotic fluid culture and in 2.6% from all cases (9/348). In three out of nine patients the type of Fusobacterium was not stated [5, 7].

Garite and Freeman [7] conducted a study on patients with preterm PROM and in 86 cases accurate bacterial cultures were available for analysis. In only one out of twenty patients with positive amniotic fluid culture was Fusobacterium identified. No specific details regarding the maternal and neonatal outcome of that pregnancy were reported.

Table 1. Intraamniotic infection with Fusobacterium in patients with preterm PROM

Author (reference)	Year	Gestational age (weeks)	No of Amniocenteses	Positive cultures		Fusobacterium		
				n	%	*n*	%	Type
Garite and Freeman [7]	1982	28–34	86	20	23.3	1	5.0	NS
Cotton et al. [5]	1984	27–36	41	6	14.6	2	33.3	NS
Romero et al. [20]	1988	25–32	221	65	29.4	6	9.2	sp.
Total			348	91	26.1	9	9.9	

NS = Not stated

In 1984, Cotton et al. [5] reported the results of 41 cases with preterm PROM in which an amniocentesis was performed to obtain fluid for culture and Gram stain. In two out of six patients with positive amniotic fluid cultures was Fusobacterium identified. In the first case, Fusobacterium grew with Bacteroides melanogenicus, Peptostreptococcus and Hemophilus vaginalis. The Gram stain examination revealed occasional Gram positive bacilli and Gram positive cocci in pairs without white blood cells. This patient had clinical chorioamnionitis and postpartum endometritis but no neonatal sepsis. In the second case, Bacteroides, Diphteroids and Fusobacterium grew. Gram staining showed occasional Gram positive coccobacilli, few Gram negative bacilli and few white blood cells. As with the previous case there was chorioamnionitis, postpartum endometritis and no neonatal sepsis.

Recently, Romero et al. [20] performed amniocentesis on 221 patients presenting with preterm PROM. From six out of 65 positive cultures was Fusobacterium isolated. In 4 of these cases Fusobacterium was the only microorganism identified. The microorganisms isolated from the other two cases were Streptococcus agalactiae in one case and Bacteroides fragilis and Mycoplasma hominis in the other. The colony count was more than 10^5 cfu/ml in two of the six cases.

Table 2 list the relevant details of the 7 studies in which Fusobacterium was isolated from amniotic fluid of women presenting with preterm labor and intact membranes [8, 12, 21, 25–28]. The overall prevalence of positive amniotic fluid

Table 2. Intraamniotic infection with Fusobacterium in patients with preterm labor and intact membranes

Author (reference)	Year	Gestational age (weeks)	No of Amniocenteses	Positive cultures		Fusobacterium		
				n	%	*n*	%	Type
Wallace-Herrik [26]	1981	26–34	25	1	4	1	100	sp.[a]
Wahbeh et al. [27]	1984	<35	33	7	21.2	3	42.9	nucl.[a] gonid. nucl.
Weible-Randall [28]	1985	24–34	35	1	2.9	1	100	nucl.
Leigh-Garite [12]	1986	<37	59	7	11.9	3	42.9	nucl. nucl. nucl.
Gravett et al. [8]	1986	<35	54	13	24	2	15.4	nucl. nucl.
Romero et al. [21]	1989	<36	264	24	9.1	5	20.8	sp.[b] sp.[b] sp. sp. sp.
Skoll et al. [25]	1989	20–35	127	7	5.5	2	28.6	sp. sp.
Total			597	60	10	17	28.3	

Other microorganisms isolated: [a] Bacteroides sp.; [b] Ureaplasma urealyticum

Table 3. Clinical data on the patients with intrauterine infection with Fusobacterium

Case no	Authors (reference)	Gestat. age	Gram stain	WBC	cfu/ml	Tocolysis	Maternal complications	Neonatal complications
1	Garite and Freeman [7]	NS	NS	NS	–		NS	NS
2	Cotton et al. [5]	27–36	Rare Gram pos. bacilli, rare Gram pos. cocci in pairs	None	–		Amnionitis Endometritis	None NS
3		NS	Rare Gram pos. coccobacilli, few Gram neg. bacilli	Few	–		Amnionitis Endometritis	None NS
4	Romero et al. [20]	25–32	NS		>10			
5		–	NS	20000				
6		–	NS	1000				
7		–	NS	–				
8		–	NS	–				
9		–	NS	–				
10	Wallace-Herrik [26]	28	NS	NS		Failed	None	Apgar score: 7/8, no sepsis, alive
11	Wahbeh et al. [27]	28	1+ Gram neg. rods	1+	>10	Not given	Chorioamnionitis	Alive, RDS, sepsis, suspected necrotizing enterocolitis
12		29	NS	1+		Failed	None	Alive, RDS, sepsis, suspected necrotizing enterocolitis
13		29	Negative	NS	<10	Failed	None	Alive, RDS, sepsis, suspected intraventricular hemorrhage
14	Weible-Randall [28]	NS	NS	Neutroph.	NS	NS	Puerperal fever	Transient tachypnea
15	Leigh-Garite [12]	31	Gram neg. bacilli	Few		Failed	Puerperal hemorrhage, sepsis, DIC, ARDS	HMD, PDA, A/B, CNS bleeding, jaundice
16		26	Gram neg. bacilli	Moderate		NS	None	HMD, pulmonary edema, CNS bleeding, A/B, jaundice
17		30	Gram neg. bacilli	Moderate		NS	Puerperal fever	Thrombocytopenia, granulocytopenia, jaundice
18	Gravett et al. [8]	28	Gram neg. rods	1+	Rare	Failed	Chorioamnionitis	None
19		35	Negative	1980	<10	Failed	Chorioamnionitis	None
20	Romero et al. [21]	NS	Positive	Negative	5000	Not given	NS	NS
21		NS	Positive	Positive	10	Not given	NS	NS
22		NS	Negative	Positive	>2500	NS	NS	NS
23		NS	Positive	Positive	+	Not given	NS	NS
24		NS	Positive	Positive	20	Not given	NS	NS
25	Skoll et al. [25]	20–35	NS	NS	NS	Given	NS	None
26		20–35	NS	NS	NS	Given	NS	None

RDS = respiratory distress syndrome; DIC = disseminated intravascular coagulation; ARDS = adult respiratory distress syndrome; HMD = hyaline membrane disease; PDA = patent ductus ateriosus; A/B = apnea/bradicardia; CNS = central nervous system; NS = not stated

cultures was 10% (60/597). In 17 out of the 60 cases (28.3%) with positive cultures was Fusobacterium isolated [8, 12, 21, 25–28]. The most common type was Fusobacterium nucleatum [47% (8/17)]. Eight patients grew F. species and one F. gonydiaformans. Seventeen of the intraamniotic infections were monomicrobial [76.4% (13/17)]. Remaining four polymicrobial, Ureaplasma urealyticum (two cases) and Bacteroides species (2 cases) being isolated.

Table 3 shows all the relevant clinical data available in the 26 women with Fusobacterium intraamniotic infection. The gestational ages at amniocentesis ranged from 20 to 35 weeks. The interval between amniocentesis often not clearly stated, ranged from the same day to the same week [20, 26–28]. The results of a Gram stain were available in 14 out of the 26 cases, and there was good correlation between Gram stain results and the white blood cells count. In only two studies [8, 21] was there a discordance between the results. Tocolysis was unsuccessful in 6 out of 8 reported cases. In the remaining cases there was no information about tocolysis. Three patients had clinical chorioamnionitis and three others had postpartum fever. Serious sepsis, disseminated intravascular coagulation and adult respiratory distress syndrome occurred in only one case [12].

Discussion

Several studies have emphasized the importance of anaerobic infection in the pathogenesis of premature labor [9–11, 13, 18–21]. Easterling and Garite [6] reported three cases of premature labour and occult amnionitis due to Fusobacterium infection and the purpose of the present study was to review the literature on this association.

Fusobacterium nucleatum is the most common species in human infection. Fusobacterium is a slow growing, anaerobic, Gram negative rod. It is an oropulmonary pathogen that rarely inhabits the cervix and vagina, but when not aggressively treated, can produce metastatic abscesses [22]. In a quantitative analysis of the vaginal flora performed on 118 specimens from 68 non pregnant women of reproductive age, Fusobacterium was isolated from 11 specimens (9%) [3]. Fusobacterium is generally less virulent than Bacteroides and usually appears in mixed infections. All strains of Fusobacterium are sensitive to treatment with high doses of Penicillin-G. Ampicillin is less effective, but Metronidazole and Clindamycin are both effective at low doses [3, 22].

Various observations indicate that the vagina harbors an average of 10^8–10^9 bacteria/g of secretions, anaerobes being most prevalent. The flora of vagina and cervix are similar [3, 14].

Fusobacterium seems to play a previously unrecognized role in the pathogenesis of premature labor. The presence of Fusobacterium in amniotic fluid cultures of patients with premature labor and intact membranes was significantly higher than in patients with preterm premature rupture of membranes, 28.3% (17/60) vs. 9.9% (9/91), respectively. Therefore, we suggest that amniotic fluid should be cultured for anaerobes, specifically for Fusobacterium, in all women presenting intact membranes and premature labor unresponsive to tocolysis.

As shown in Table 3, maternal morbidity in chorioamnionitis due to Fusobacterium is relatively low. Anaerobic infection of the amniotic cavity develops more than three weeks earlier than non-anaerobic infection [6], and those preterm infants, born to women with anaerobic amnionitis are subject to a greater degree of prematurity-associated morbidity [1].

The initiation of premature labor or PROM by intraamniotic infection has been the subject of recent investigation. Fusobacteria have a high phospholipase A_2 content and may precipitate labor by enhancing prostaglandin synthesis [4, 15, 23]. Recently another mechanism has been postulated involving Interleukin 1 and Tumor Necrosis Factor which may be produced in response to bacterial infection and can stimulate prostaglandin production by amnion and decidua [24]. Ascending microbiol invasion results in activation of the macrophage-monocyte system and secretion of cytokines and enzymes.

We found no perinatal mortality. However, several cases were complicated by perinatal morbidity (Table 3). The high rate of neonatal complications listed in Table 3 can mainly be attributed to low gestational age and birth weight rather than to neonatal infection. The reason for Fusobacterium infection is not known, but may reflect the virulence of this microorganism.

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