

Increased Attack Rate of Meningococcal Disease in Children With a Pregnant Mother

Elske J. van Gils, MSc*; Job B. van Woensel, MD, PhD*; Arie van der Ende, PhD‡; and Taco W. Kuijpers, MD, PhD*

ABSTRACT. *Objective.* To investigate the relationship between meningococcal disease and family composition, especially pregnancy in mothers.

Methods. This was a retrospective matched case-control study. Case patients were children (aged 0–18 years) who had meningococcal disease and were admitted to our hospital from 1990 to 2002. Children who were admitted to 1 of the general pediatric wards of the hospital during the same period and did not have meningococcal disease served as control subjects. One control subject (matched according to gender, age, and year, and season of admission) was enrolled for each case patient. Parents of case patients and control subjects were asked to fill out a questionnaire on family composition, birth dates of siblings, and pregnancy at the time of hospital admission.

Results. A total of 88 matched case-control pairs were included. In the case group, 17 (19%) mothers reported having been pregnant at the time of hospitalization of their child, compared with 2 (2%) in the control group. Other family characteristics were not different. After adjustment for confounding factors, pregnancy of mothers remained a significant risk factor for meningococcal disease in children (odds ratio: 11.7; 95% confidence interval: 2.6–53.9).

Conclusions. Meningococcal disease in children was highly associated with pregnancy of the patient's mother during hospitalization. Mechanisms by which the presence of a pregnant mother in a family affects the attack rate of meningococcal disease in her children need additional investigation. *Pediatrics* 2005;115:e590–e593. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2291; *meningococcal disease, Neisseria meningitidis, pregnancy, risk factors.*

Meningococcal disease is caused by *Neisseria meningitidis* and characterized by high morbidity and mortality. In the Western world, the annual incidence is 1 to 5 cases per 100 000 population. The human nasopharynx is the only known reservoir of meningococci. Although up to 10% to 15% of the normal population carries meningococci in their nasopharynx, invasive disease is rare. Both

microbial (eg, virulence of the meningococcal strain) and host defense factors may affect the risk of occurrence of meningococcal disease.^{1,2}

The incidence of meningococcal disease is high in infants and young children up to the age of 5 years. Their relatively immature immune system may contribute to a higher susceptibility to the disease. In most people, carriage leads to a systemic protective antibody response and therefore is an immunizing process. Considering the low rate of ~2% of meningococcal carriage in infants and children, transmission from household members seems to play an important role in the acquisition of meningococcal disease in this age group. This assumption is supported by the relatively high carriage rates in household members who are related to an infant with meningococcal disease as opposed to the carriage rates in household members of an adult with meningococcal disease.³ Moreover, Frasch et al⁴ showed that, among household contacts of children with meningococcal disease, the mother was most likely to carry the disease isolate.

The age at which meningococcal disease peaks during childhood overlaps with the period of child-bearing and active family planning of the mother. To assess the involvement of risk factors within families and the role of household contacts, especially mothers, in the acquisition of meningococcal disease by children, we performed a retrospective case-control study. Because there is still a large threat of disease transmission irrespective the current vaccination strategies or serogroups, additional determination of risk factors for meningococcal carriage is relevant in the understanding and prevention of meningococcal disease in children. Thus, family composition, sibling number, and pregnancy were investigated as determinants in invasive meningococcal disease.

METHODS

Participants and Study Design

In this retrospective study, families of case patients and control subjects were contacted by telephone to participate in answering a short questionnaire. Case patients (aged 0–18 years) were defined as patients who were admitted to the Emma Children's hospital from 1990 to 2002 and had definite meningococcal disease by positive cultures for *N meningitidis* from blood, cerebrospinal fluid, and/or biopsies from skin lesions. The first 100 consecutive cases were contacted. Families with fatal meningococcal disease of the index child were excluded because of the emotional distress for the parents. A next case was contacted in case of no response.

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TABLE 1. Reasons for Hospitalization of Control Subjects

	<i>n</i> (%)
Surgery	28 (32)
Ears-nose-throat-related surgery	8 (9)
Cardiac problems	5 (6)
Infectious problems	11(13)
Neurologic problems	10 (11)
Respiratory problems	6 (7)
Diagnostic procedures	4 (4)
Gastrointestinal problems	5 (6)
Metabolic problems	1 (1)
Enuresis training	2 (2)
Intoxication	1 (1)
Other	7 (8)
Total	88 (100)

TABLE 2. Characteristics of Study Participants

	<i>n</i> (%)		<i>P</i> Value
	Case Patients (<i>n</i> = 88)	Control Subjects (<i>n</i> = 88)	
Age of patient at admission, median (IQR), y	3.7 (2.1–6.9)	3.8 (1.8–7.1)	.99
<1 y	13 (15)	6 (7)	
1–5 y	41 (46)	48 (54)	
5–10 y	20 (23)	22 (25)	
≥10 y	14 (16)	12 (14)	
Gender			1.00
Female	43 (49)	44 (50)	
Male	45 (51)	44 (50)	
Season of admission			.78
Winter	35 (40)	29 (33)	
Spring	17 (19)	21 (24)	
Summer	19 (22)	19 (22)	
Autumn	17 (19)	19 (22)	

IQR indicates interquartile range.

Identification of Matched Control Subjects

Control subjects, being children who were admitted to 1 of the general pediatric wards of the hospital during the same period and not having meningococcal disease, were identified from an electronic database. To each case patient, 1 control subject was matched by gender, year of birth (age in years for children >10 years), and year and season of hospitalization. Control subjects with a history of >5 admissions within 1 to 2 years were excluded because of the possible negative effect on family planning. Another control subject was selected in case of refusal or no response.

Questionnaire

The questionnaire contained questions on present family composition, birth dates of siblings, premature birth, abortion and miscarriage, mortality, and the medical history of the patients and the family regarding (infectious) disease. Pregnancy of the mother of the index case was defined as birth of a term child within 40 weeks, as well as memorized pregnancy during hospitalization of the index child, resulting in abortion or miscarriage.

Statistical Analysis

The statistical package SPSS for Windows (version 11.5.1) was used for data analysis. Characteristics of both groups were compared using the Pearson χ^2 test and *t* test for proportions and group means, respectively. Risk factors for meningococcal disease were examined using univariate analysis. Variables that were associated with meningococcal disease in univariate analysis and potential confounders (matching factors) were included in a multivariate model to obtain adjusted odds ratio estimates.

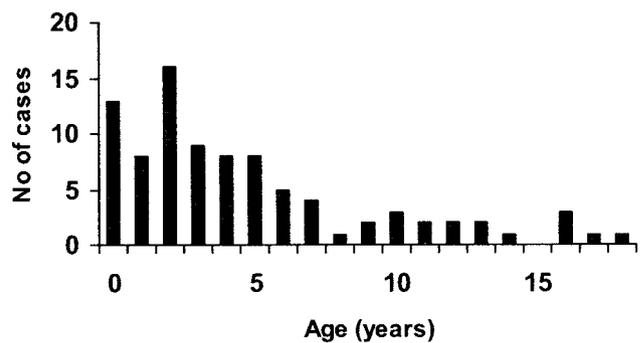


Fig 1. The number of cases according to age at admission.

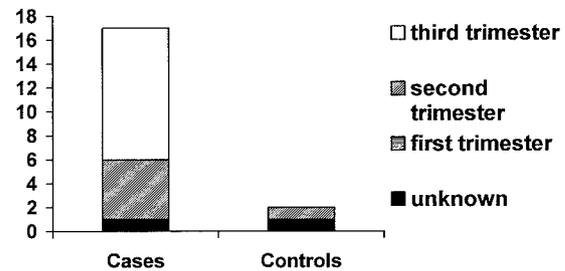


Fig 2. Duration of pregnancy in trimesters.

RESULTS AND DISCUSSION

Of the first 100 consecutive patients who had culture-proven meningococcal disease and were admitted to our hospital, 90 cases were included in our case-control study. Ten families gave imprecise information or refused for reasons not further explored. Case patients were hospitalized in the period 1993–2001. Because of the lack of matches for 2 case patients, 88 matched case-controls were used in the final analysis. The reasons for hospitalization of control subjects were various, eg, surgery, respiratory, and neurologic problems (Table 1). Characteristics of both groups are displayed in Table 2. Most of the meningococcal disease case patients were younger than 5 years (*n* = 54; 61%; Fig 1). Conforming to the literature, the incidence was highest in the winter (December 21 to March 21; *n* = 35; 40%).

In the case group, 17 (19%) mothers reported to have been pregnant at the time of hospitalization of their child, compared with 2 (2%) in the control group (odds ratio: 10.3; 95% confidence interval: 2.3–46.1; *P* = .002). Figure 2 shows the duration of pregnancy in trimesters. Two mothers (1 in each group) were pregnant during hospitalization of the child but had miscarriages later on. Therefore, the exact duration of pregnancy is unknown. No other significant univariate risk factors for meningococcal disease were identified (Table 3). After adjustment in multivariate analysis, pregnancy of the mother remained highly associated with meningococcal disease (odds ratio: 11.7; 95% confidence interval: 2.6–53.9; *P* = .002; Table 4).

To our knowledge, this is the first case-control study to reveal a strong association between pregnancy of the mother and the onset of meningococcal disease in 1 of her children. Limitations of our study are the retrospective character of our analysis and the

TABLE 3. Univariate Analysis of Risk Factors for Meningococcal Disease

Risk Factor	n (%)		Crude OR	95% CI	P Value
	Case Patients (n = 88)	Control Subjects (n = 88)			
Pregnancy of mother					
No	71 (81)	86 (98)	1.00		
Yes	17 (19)	2 (2)	10.3	2.3–46.1	.002
Season of admission					
Not winter	53 (60)	59 (67)	1.00		
Winter	35 (40)	29 (33)	1.30	0.7–2.5	.35
Gender					
Male	45 (51)	44 (50)	1.00		
Female	43 (49)	44 (50)	1.05	0.6–1.9	.88
Age					
≥5 y	34 (39)	34 (39)	1.00		
<5 y	54 (61)	54 (61)	1.00	0.5–1.8	1.00
No. of siblings					
≤2	77 (89)	79 (90)	1.00		
>2	10 (11)	9 (10)	1.10	0.4–3.0	.79
Unknown	1	0 (0)			
Patient ranking in family					
First child	34 (39)	45 (51)	1.00		
>First child	53 (61)	43 (49)	1.60	0.9–3.0	.11
Unknown	1	0 (0)			

OR indicates odds ratio; CI, confidence interval.

TABLE 4. Multivariate Analysis of Risk Factors for Disease

	Adjusted OR	95% CI	P Value
Pregnancy of mother	11.7	2.6–53.9	.002
Admission in winter	1.4	0.7–2.7	.31
Female gender	0.8	0.5–1.6	.67
Age <5 y	0.7	0.4–1.4	.35

OR indicates odds ratio; CI, confidence interval.

high mortality of 8.6% in the case group. This survival bias may be a confounding factor. However, it is hard to imagine how maternal pregnancy could have resulted in altered mortality rates during admission. Concerning incomplete memorization of pregnancy, we believe that the birth dates of siblings are sufficient proof of pregnancy during admission of either a case patient or control subject. Early pregnancy followed by spontaneous abortion may have been missed, but this is considered to be equal among both groups.

Other reported risk factors, such as smoking by parents⁵ or previous viral disease,⁶ were not taken into account. Considering the retrospective design, we believe that reliable data on these matters could not be obtained. Because women are advised against smoking during pregnancy, it is unlikely that this factor would account for the association established in our study. Moreover, the number of cases is relatively small, making statements about environmental factors of limited value.

Increased carriage rates of meningococci in household members were found to be related to young infant cases of meningococcal disease by Munford et al.³ However, the authors did not further substantiate an explanation for their findings. In another study on meningococcal carriage among household contacts of children with meningococcal disease, the mother was found to be more likely to carry the meningococcal isolate.⁴ This is an interesting observation in the context of our finding that maternal

pregnancy was highly correlated with meningococcal disease. Increased colonization of the vagina by bacteria during pregnancy has been reported.⁷ However, little information is available on nasopharyngeal carriage and changes herein as a consequence of prolonged hormonal adaptations of the nonurogenital mucosa during pregnancy. To the best of our knowledge, the only study related to the issue raised by our study is from Winkler et al,⁸ who found an association between the levels of sex hormones (as reflected by the karyopyknotic index [KI] on colposcopic smears) and nasal carriage rates *Staphylococcus aureus*. Decreasing nasal patency was determined during pregnancy, coinciding with the rise in the serum concentration of female sex hormones, returning to normal postpartum.⁹ This finding may be of relevance to microbial colonization and disease transmission as suggested by our observations on pregnancy and increased meningococcal attack rate in children. Taken together with our findings, the lack of information on the association between nasopharyngeal carriage and hormonal changes warrants additional study.

We hypothesize that alterations in the mucosal barrier and epithelial binding capacity in the nasopharynx may affect meningococcal carriage during pregnancy. Possibly, the increased meningococcal carriage rates, prolonged carriage duration, and/or altered virulence of the meningococcal strain under pregnant conditions of the mothers may contribute to an increased risk for meningococcal transmission.

CONCLUSIONS

We found a strong and significant association between pregnancy in mothers and concomitant meningococcal disease in a child within the same family. Determining the precise mechanism(s) by which the presence of a pregnant mother in a family affects the attack rate of meningococcal disease in her children requires additional prospective investigation.

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REFERENCES

1. Emonts M, Hazelzet JA, de Groot R, Hermans PW. Host genetic determinants of *Neisseria meningitidis* infections. *Lancet Infect Dis*. 2003;3:565-577
2. Townsend R, Goodwin L, Stevanin TM, et al. Invasion by *Neisseria meningitidis* varies widely between clones and among nasopharyngeal mucosae derived from adult human hosts. *Microbiology*. 2002;148:1467-1474
3. Munford RS, de Moraes JS, Taunay Ade E, Fraser DW, Feldman RA. Spread of meningococcal infection in within households. *Lancet*. 1974;303:1275-1278
4. Frasch CE, Mocca LF. Strains of *Neisseria meningitidis* isolated from patients and their close contacts. *Infect Immun*. 1982;37:155-159
5. Fischer M, Hedberg K, Cardoso P, et al. Tobacco smoke as a risk factor for meningococcal disease. *Pediatr Infect Dis J*. 1997;16:979-983
6. Moore PS, Hierholzer J, DeWitt W, et al. Respiratory viruses and mycoplasma as cofactors for epidemic group A meningococcal meningitis. *JAMA*. 1990;264:1271-1275
7. Galask RP. Vaginal colonization by bacteria and yeast. *Am J Obstet Gynecol*. 1988;158:993-995
8. Winkler J, Block C, Leibovici L, Faktor J, Pitlik SD. Nasal carriage of *Staphylococcus aureus*: correlation with hormonal status in women. *J Infect Dis*. 1990;162:1400-1402
9. Philpott CM, Conboy P, Al-Azzawi F, Murty G. Nasal physiological changes during pregnancy. *Clin Otolaryngol*. 2004;29:343-351

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