Microbial aetiology of acute rhinosinusitis during pregnancy*

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Abstract

Background: Pregnancy as an immunosuppressive condition and with the associated tendency for mucosal oedema can predispose women to acute rhinosinusitis. Our hypothesis was that pregnancy enhances opportunistic sinus infections.

Methodology: We retrospectively collected data on pregnant women with acute rhinosinusitis treated at the Department of Otorhinolaryngology, Helsinki University Hospital, Finland in 2010-2015. Maxillary puncture was performed on all patients, and patients with purulent sinus secretions and bacterial culture were included in the study. Clinical data on patients and microbial findings of bacterial cultures were recorded and compared with those of non-pregnant controls.

Results: Ninety-five pregnant patients and 91 controls were included. The bacterial cultures of pregnant patients revealed bacterial growth more often than control patients' specimens (78.9% vs. 54.9%). The most common bacterial findings (pregnant vs. control patients) were *Streptococcus pneumoniae* 43.2% vs. 20.9%, *Haemophilus influenzae* 22.1% vs. 16.5%, and *Moraxella catarrhalis* 10.5% vs. 2.2%. *S. pneumoniae* was the most frequent finding in all trimesters, and the proportion of *S. pneumoniae* sinusitis was highest during the last trimester of pregnancy.

Conclusions: The pathogens of acute rhinosinusitis in pregnant patients are the same as in non-pregnant patients, however, the proportions differ; during pregnancy *S. pneumoniae* infection is more frequent.

Key words: maxillary sinus, paranasal sinus diseases, pregnancy, sinusitis, *Streptococcus pneumoniae*

Introduction

Pregnancy as an immunosuppressive condition and with the associated tendency for mucosal oedema can predispose women to acute rhinosinusitis (ARS) [1,2]. During pregnancy changes in maternal immunity are required to prevent the foetus from being rejected by the mother's immune system [3]. The placenta produces progesterone, prostaglandin E2, and interleukins (IL) 4 and 10, which inhibit the T helper (Th) 1 response of maternal immune defence. In addition, both $CD4^+$ and $CD8^+$ T cells in the peripheral blood down-regulate Th1 cytokines (e.g. IFN-gamma and IL-2) and up-regulate Th2 cytokines (e.g. IL-4). Thus, the maternal immune system shifts towards Th2-type immunity [4]. It is unclear whether these changes affect the incidence of sinus infections and change the distribution of pathogens.

Very few studies on rhinosinusitis during pregnancy have been conducted. Based on previous research, pathogens causing sinusitis during pregnancy appear to be more or less the same as in non-pregnant patients [5]. Treatment of rhinosinusitis during pregnancy is based on the same recommendations as treatment of rhinosinusitis in non-pregnant patients, with the exception of doxycycline, which should be avoided during pregnancy [6]. The frequency of bacterial sinusitis has been reported to increase sixfold during pregnancy [5]. According to a study by Sorri et

al. in 1980, classic symptoms and clinical signs of sinusitis are absent in almost half of pregnant women with documented purulent sinusitis [7].

According to Finnish clinical practice guidelines on rhinosinusitis, maxillary puncture is recommended if symptoms are intense or prolonged despite adequate treatment or if the patient is pregnant. Maxillary puncture enables removal of sinus secretions, relieving symptoms and providing a sample for bacterial and fungal culture [8].

This study was performed to examine the bacterial aetiology of ARS during pregnancy and to compare it with that of non-pregnant patients. When aetiology of the infection is known, treatment can be targeted appropriately to ensure efficient treatment and to avoid use of broad-spectrum antimicrobials, which is especially desirable during pregnancy.

Materials and methods

Patients

We retrospectively collected data on female patients aged 18-45 years with ARS treated at the Department of Otorhinolaryngology, Helsinki University Hospital (HUH), Helsinki, Finland in 2010-2015. ICD-10 codes J01.0 (ARS) and J01.4 (acute pansinusitis) were used for patient inclusion. Patients with sinus symptoms for less than 12 weeks and patients with clear exacerbation of chronic rhinosinusitis were first identified. From these patients, women who were pregnant at the time of diagnosis were selected for the study. This study was based on hospital and patient records without any ethical issues and an institutional research permission was granted.

Maxillary puncture was performed on all patients, and only patients with purulent secretions and bacterial culture were included in the study. Primarily, the bacterial culture taken on the first visit to the study clinic was included in the analyses. If that culture did not reveal a pathogen, but the culture performed in primary health care before referring the patient to the study clinic did, the earlier culture was included instead. In addition, if the first culture at the study clinic was negative, and another sample was taken within a month during the same infection episode, the result of the latter culture was included in the analysis. Recorded clinical data on the patients included age, diagnosis, date of first visit, pregnancy week, smoking status, allergies, number of previous sinus infections, and possible previous sinus surgery. Long-term conditions, especially asthma and other lower airway diseases and immunosuppressive illnesses, and medication were registered. Possible simultaneous pneumonia, the results of bacterial and fungal cultures, and antimicrobial treatment prior to maxillary puncture were documented.

Sinus infection was considered to be of dental origin if it could be verified by imaging or if root canal therapy or dental extraction was subsequently performed.

Control patients

We collected clinical data on non-pregnant patients treated at the Department of Otorhinolaryngology, HUH, Helsinki, Finland in 2013. Control patients were selected from the same age group and with the same ICD-10 codes and inclusion criteria as pregnant patients. Patients with organ transplant, human immunodeficiency virus, cancer, or vasculitis with nasal manifestations were excluded.

Microbial findings

The sample for microbial diagnostics was taken by maxillary puncture. The samples were analysed according to routine culture techniques for diagnostic puncture samples at Helsinki University Hospital Laboratory Services (HUSLAB). The results were recorded from the hospital laboratory database.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA). Statistical differences between categorical variables were calculated using Chi-square test or Fisher's exact test. If the information in question was missing, the patient was excluded from analysis. Mantel-Haenszel's test was used in analysis of possible confounding factors. A two-sided p value <0.05 was considered statistically significant.

Results

Ninety-five pregnant patients (median age 32 years, range 22-41 years) and 91 control patients (median age 30 years, range 22-41 years) met the inclusion criteria. The control group included 59 females and 32 males. Clinical data of the patients are presented in Table 1.

Treatment prior to maxillary puncture

The use of antimicrobial medication was more common in control patients than in pregnant subjects (Figure 1). At the time of maxillary puncture, the use of antimicrobial medication was equally common in both groups (p=0.85). During the last two weeks prior to maxillary puncture control patients had finished antimicrobial treatment more often than pregnant patients (p=0.04).

Microbiological findings

Bacterial culture was performed on all maxillary puncture specimens. Samples were taken year-round and the seasonal distribution of the number of samples was comparable between the groups (data not shown).

The cultures of six pregnant patients at the Department of Otorhinolaryngology, HUH, revealed no bacterial growth. In these

Table 1. Clinical data of pregnant and control patients with acute rhinosinusitis.

			Pregnant (N=95)	Controls (N=91)	
			N (%)	N (%)	p value
Demographics	Sex	Women	95 (100.0)	59 (64.8)	<0.001
		Men	0 (0)	32 (35.2)	
	Age (years)	Mean	32	31	
		Median	32	30	
		Range	22 - 41	22 - 41	
Diagnosis	J01.0 (Acute sinusitis)		90 (94.7)	63 (69.2)	<0.001
	J01.4 (Acute pansinusitis)		5 (5.3)	28 (30.8)	<0.001
Radiological imaging			15 (15.7)	77 (84.6)	<0.001
Patient history	Previous sinusitis		43 (72.9)*	26 (44.8)*	0.002
		N/A	36 (37.8)	33 (36.2)	
	Nasal polyposis		2 (2.1)	2 (2.2)	
	Smoking at time of diagnosis		3 (4.3)*	21 (25.0)*	<0.001
		N/A	26 (27.4)	7 (8.0)	
	Allergy		40 (57.1)*	31 (35.6)*	0.007
		N/A	25 (26.3)	4 (4.4)	
	Asthma		10 (10.5)	12 (13.2)	
	Immunosuppressive disease or medication		8 (8.4)	2 (2.2)	
	Simultaneous pneumonia		0 (0)	8 (8.8)	0.003

Correlations between groups were analysed with Chi-square test or Fisher's exact test. Significant differences between the groups are indicated. A two-sided P value <0.05 was considered statistically significant. * % of patients whose patient records included the information on the parameter in question. N/A, not available.

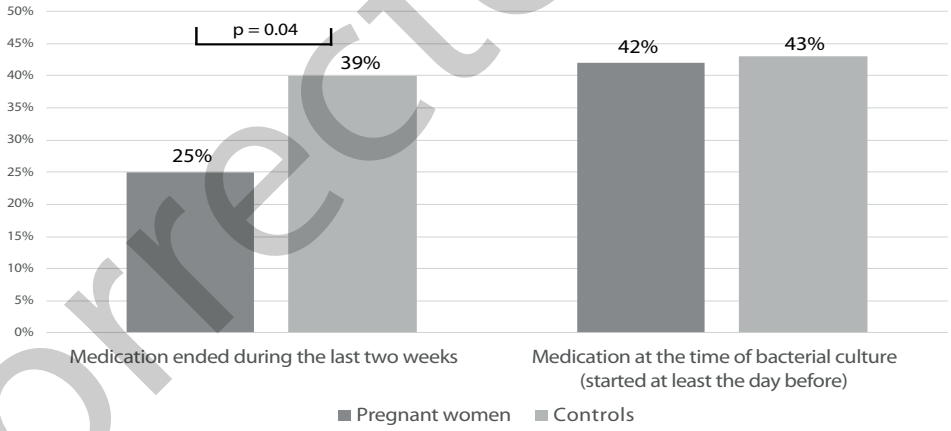

Figure 1. Antimicrobial medication during the last two weeks preceding maxillary puncture and at the time of maxillary puncture among pregnant patients and controls. A significant difference between the groups is indicated. A two-sided P value <0.05 was considered statistically significant.

cases, maxillary puncture had been performed previously at the outpatient clinic, and in all of these cases, *Streptococcus pneumoniae* growth was found. None of the control patients underwent maxillary puncture and had bacterial cultures taken before treatment at the study clinic. In three control patients and one pregnant patient, the first bacterial culture was negative, but the second culture revealed microbial growth. Fungal culture was performed on two controls and one pregnant patient.

The microbiological findings of both groups are shown in Table 2. Only bacteria considered probable ARS pathogens were taken into account, whereas cultures with apathogenic bacteria were considered negative. In all cases where the apathogenic bacteria comprised a single finding, bacterial growth was scarce.

A potential pathogen was found more often in pregnant patients' specimens than in the specimens of controls (p<0.001). The most frequent pathogens among pregnant patients were *S.*

Table 2. Microbial findings in pregnant women and control patients with acute rhinosinusitis.

		Pregnant (N=95)	Controls (N=91)	
		N (%)	N (%)	p value
Aerobic	*Streptococcus pneumoniae*	41 (43.2)	19 (20.9)	0.001
	Haemophilus influenzae	21 (22.1)	15 (16.5)	
	Moraxella catarrhalis	10 (10.5)	2 (2.2)	0.033
	Staphylococcus aureus	2 (2.1)	4 (4.4)	
	Streptococcus anginosus -group	3 (3.2)	6 (6.6)	
	Streptococcus pyogenes	0 (0)	2 (2.2)	
	Viridans group streptococci*	1 (1.1)	0 (0)	
	Eschericia coli	2 (2.1)	2 (2.2)	
	Enterobacter species*	2 (2.1)	0 (0)	
	*Haemophilus parainfluenzae**	1 (1.1)	0 (0)	
	Acinetobacter species	0 (0)	1 (1.1)	
	*Klebsiella pneumoniae**	0 (0)	1 (1.1)	
Summary	Aerobic bacteria	73 (76.8)	46 (50.5)	<0.001
Anaerobic	Non-specified anaerobic Gram-negative rods	5 (5.3)	9 (9.9)	
	Prevotella species*	0 (0)	3 (3.3)	
	*Fusobacterium necrophorum**	0 (0)	1 (1.1)	
	*Fusobacterium nucleatum**	1 (1.1)	0 (0)	
	Veillonella species*	1 (1.1)	0 (0)	
	Propionibacterium species	1 (1.1)	1 (1.1)	
	*Parvimonas micra**	1 (1.1)	1 (1.1)	
	Anaerobic mixed flora	1 (1.1)	1 (1.1)	
Summary	Anaerobic bacteria	6 (6.3)	13 (14.3)	
Summary	Aerobic and/or anerobic bacteria	75 (78.9)	50 (54.9)	<0.001

Correlations between groups were analysed with Chi-square test or Fisher's exact test. Significant differences between the groups are indicated. A two-sided P value <0.05 was considered statistically significant. *not seen as a single finding in bacterial culture.

pneumoniae, Haemophilus influenzae, and *Moraxella catarrhalis*; one of these bacteria was found in 70.5% (n = 67) of pregnant patients' specimens and in 38.5% (n = 35) of controls' specimens (p<0.001). The difference between groups arose from the difference in *S. pneumoniae* growth, which was more frequent in pregnant patients. When *S. pneumoniae* growth was excluded from the analysis, the statistical difference disappeared (whole group without *S. pneumoniae*, p=0.41).

M. catarrhalis was also found more often in pregnant patients (p=0.03). When patients with previous sinus surgery and/or a condition predisposing to infections were excluded (pregnant patients n = 16, control patients n = 3), the difference between groups was lost (p=0.11). All fungal cultures (n = 3) were negative.

Antimicrobial therapy and microbial findings

The use of antimicrobial medication among pregnant patients had an influence on the frequency of *S. pneumoniae* growth. If no antibiotics were used during the last two weeks before the maxillary puncture, 58.3% (n = 21) had *S. pneumoniae* in the culture, whereas of patients with antibiotics at the time of maxillary puncture, but no antibiotic therapy that had ceased during the previous two weeks, 41.9% (n = 13) had *S. pneumoniae* growth. If antimicrobial therapy was finished during the preceding two weeks, but no antibiotics were used at the time of maxillary puncture, 23.5% (n = 4) of the specimens revealed *S. pneumoniae*. None of the patients with antibiotic treatment at the time of maxillary puncture and who had finished antibiotic therapy during the preceding two weeks had *S. pneumoniae* (p=0.02).

The use of antimicrobial therapy prior to maxillary puncture was

Table 3. Antibiotic resistance pattern of *Streptococcus pneumoniae* in maxillary sinus puncture samples (n = 60) compared with the national data on pus samples (year 2013) reported by the Finnish Institute for Health and Welfare [9].

	Sensitive (%)		Intermediate (%)		Resistant (%)	
	Study Data*	National Data	Study Data*	National Data	Study Data*	National Data
Penicillin	85.0 (51/60)	85.9	13.3 (8/60)	13.0	1.7 (1/60)	1.1
Tetracycline	87.7 (50/57)	87.5	0 (0/57)	0.7	12.3 (7/57)	11.8
Erythromycin	82.1 (46/56)	79.3	0 (0/56)	0.4	17.9 (10/56)	20.4
Clindamycin	89.5 (51/57)	89.8	0 (0/57)	0	10.5 (6/57)	10.3
Trimethoprim-sulfa	84.2 (48/57)	83.7	1.8 (1/57)	2.1	14.0 (8/57)	14.2

* a portion of samples with known antibiotic resistance pattern. Resistance information was available from all control patients' samples (n=19) but missing from a portion of pregnant patients' samples (n=41).

more common in the control group (p=0.04). When differences between antimicrobial therapy were taken into account, pregnancy was an independent risk factor for *S. pneumoniae* (OR 2.38; 95% CI 1.15 – 4.90).

All patients with simultaneous pneumonia (n = 8, all control patients) had antimicrobial therapy at the time of maxillary puncture. When patients with simultaneous pneumonia were excluded, the difference between the groups regarding sinusitis with *S. pneumoniae* remained significant (p=0.002).

Concerning antibiotic resistance pattern of *S. pneumoniae*, no statistical difference between pregnant and control patients was found (p=0.117). Resistance pattern of *S. pneumoniae* in this study was comparable with the national data (year 2013) reported by the Finnish Institute for Health and Welfare [9]. Resistance information was available from all control patients' samples (n=19) but missing from four pregnant patients (n=41) concerning some of the five reported antibiotics (Table 3).

Pregnancy trimester, seasonality, and sinusitis

Most of the ARS during pregnancy was diagnosed during the second trimester, and the predominant bacterial finding in sinus secretions through all trimesters was *S. pneumoniae* (Figure 2). Furthermore, *S. pneumoniae* was found more often during the third trimester than during the first and second trimesters combined (59.4% vs. 34.9%; p=0.02), but for other pathogens no difference between the trimesters emerged. *S. pneumoniae* was the most common finding in pregnant patients year-round (data not shown).

Conditions predisposing to infection and microbial findings

Of pregnant patients, 8.4% (n = 8), in contrast to 2.2% (n = 2) of control patients, had a chronic illness predisposing to infections or immunosuppressive medication (p=0.10). Three of these pregnant patients had rheumatic disease and one had type I diabetes mellitus. Three of these patients had *M. catarrhalis* in bacterial culture, one had microbial finding suggestive of sinusitis of dental origin, and the rest (n = 4) had a negative bacterial culture. One of the control patients had rheumatic disease. None of the control patients with a condition predisposing to infection had bacterial growth in culture. Two of the pregnant patients had received pneumococcal vaccination, and they both had *M. catarrhalis*.

Smoking, gender, and microbial findings

Smoking was more common in the control group (p<0.001) (Table 1). Three of the pregnant patients were smokers; two of them had odontogenic sinusitis and one had sinusitis caused by *H. influenzae*. In the control group, 25.0% (n = 21) were smokers; men smoked more often than women (40.0% vs. 16.7%, p=0.02). Neither smoking status nor gender was a confounding factor in analysis concerning *S. pneumoniae* sinusitis.

Sinusitis of dental origin

Two pregnant and three control patients had ARS of dental origin (p=0.68). Two of the patients with odontogenic sinusitis had anaerobic microbial findings, two mixed anaerobic and aerobic microbial findings, and one aerobic microbial finding. The most common bacteria in odontogenic ARS were *Streptococcus anginosus* (n = 3) and anaerobic Gram-negative rod (n = 3). Smoking was a predisposing factor for odontogenic ARS (test of heterogeneity, p=0.009), whereas pregnancy was not an independent risk factor.

Discussion

The major pathogens causing ARS during pregnancy were found to be the same as in non-pregnant patients: *S. pneumoniae, H. influenzae,* and *M. catarrhalis*. However, pregnancy seems to change the proportions. In pregnant patients with bacterial growth, the proportions of the four most frequent bacteria were *S. pneumoniae* 54.7%, *H. influenzae* 28.0%, *M. catarrhalis* 13.3%,

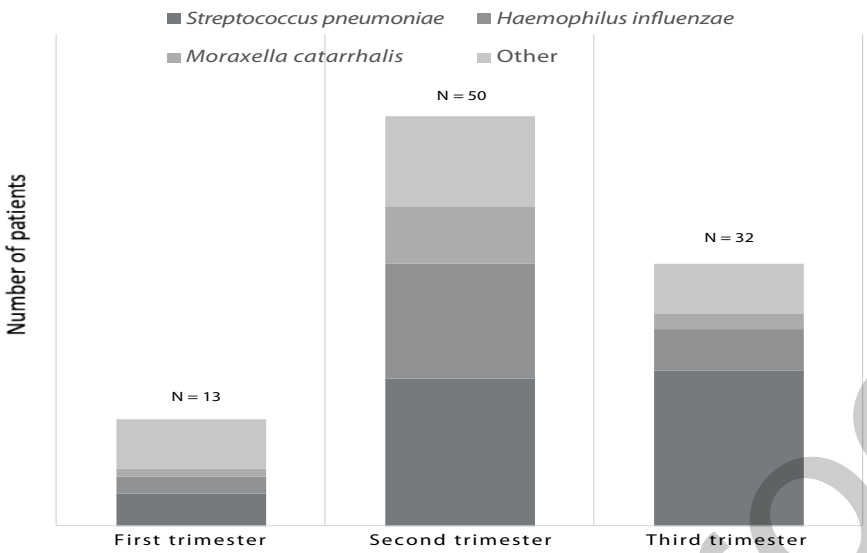

Figure 2. Pregnancy trimesters and pathogens in acute rhinosinusitis (ARS). Most of the ARS during pregnancy was diagnosed during the second trimester, and the most frequent single bacterial finding in sinus secretions through all trimesters was *S. pneumoniae*.

and *S. aureus* 2.7%. The corresponding proportions among control patients were 38.0%, 30.0%, 4.0%, and 8.0%. Thus, *S. pneumoniae* dominates more clearly during pregnancy, whereas *S. aureus* is a rather infrequent finding. According to a meta-analysis by Payne et al. (2007), the bacterial culture rates in ARS were 32.7% for *S. pneumoniae*, 31.6% for *H. influenzae*, 8.8% for *M. catarrhalis*, and 10.1% for *S. aureus* [10].

Pregnancy was an independent risk factor for ARS caused by *S. pneumococcus*. The overall proportion of positive bacterial cultures among pregnant patients (78.9%) was also high compared with previous studies [10-12]. In a systematic review and meta-analysis by Smith et al. [12], 61.0% of sinus secretion specimens taken by maxillary puncture were positive [12]. In a study of 224 male army conscripts with ARS, 81.5% of bacterial cultures were positive, however, patients having had antibiotics during the preceding two weeks were excluded [13].

The distribution of ARS between the trimesters corresponds to a study by Sorri et al. [7] in which the incidence of sinusitis was also highest during the second trimester [7]. In our study, the incidence of sinus infections was lowest during the first trimester. *S. pneumoniae* was the most frequent pathogen during all trimesters, but its proportion was highest during the third trimester.

The clear dominance of *S. pneumoniae* in pregnant patients was somewhat surprising. According to our study, pregnancy as an immunosuppressive condition does not seem to predispose patients to sinus infections by opportunistic pathogens. The changes in immune defense during pregnancy may explain the dominance of *S. pneumoniae* as an ARS pathogen, especially during the third trimester. In Th1/Th17-mediated autoimmune diseases, like rheumatoid arthritis and multiple sclerosis, symptoms tend to be relieved during pregnancy, being especially mild during the third trimester [14,15]. This may be related to a change in T-cell-mediated immune response towards Th2-type cytokine responses during pregnancy [3,16]. Pregnancy may favour *S. pneumoniae* colonization and infection because Th1/Th17-mediated immune responses have been shown to be associated with control of *S. pneumoniae* in mucosal membranes [17,18]. In this study, the incidence of *S. pneumoniae* sinusitis was highest during the third trimester, i.e. at the same time as the activity of the aforementioned autoimmune diseases was lowest.

This study has a few limitations warranting attention. The retrospective nature of the study must be seen as a limitation, as the study data are limited to the information available in the medical records. Furthermore, the study population was treated in a tertiary hospital so the patients may have had more intense symptoms than the patients treated in primary health care, and this may be reflected in the microbial findings.

Conclusion

The bacteria of ARS during pregnancy are the same as in non-pregnant patients, but the proportions differ; during pregnancy *S. pneumoniae* infections clearly predominate over *H. influenza* and *M. catarrhalis*. The antimicrobial treatment of ARS during pregnancy does not need to differ from that of non-pregnant patients, with the exception of doxycycline, but the treatment must cover *S. pneumoniae*. Pneumonia seems to be rare in connection with ARS during pregnancy.

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Authorship contribution

Supervised the study: KB, HV. Designed the analytic plan: KB, HV, HR-B. Contributed to study design: KB, HV, HR-B. Obtained funding: KB. Enrolled patients and collected data at the study sites: HR-B, AW-L. Created and managed the database: HR-B, KB, HV, AW-L, LKM. Analyzed and/or interpreted the data: HR-B, AW-L, KB, LKM, HV. Acted as supervisor for data analysis and/or interpretation: KB, HV. Drafted the initial manuscript: LKM, HR-B. Reviewed and/or revised the manuscript: LKM, HR-B, HV, AW-L, KB. Approved the final manuscript: LKM, HR-B, HV, AW-L, KB

Conflict of interest

None.

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