Influenza-like illness and seasonal influenza vaccination during pregnancy: a flemish monocentric cohort study

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ABSTRACT

Background and purpose: Seasonal influenza vaccination is recommended during pregnancy, reducing the risk of severe influenza and potentially reducing neonatal complications. The impact of seasonal influenza vaccination on the incidence of influenza-like illness (ILI) during pregnancy was determined in this monocentric cohort study, since the literature on this subject remains unclear.

Methods: The primary outcome of this monocentric cohort study was the impact of seasonal influenza vaccination on the incidence of ILI during pregnancy. Several secondary maternal and neonatal outcomes were obtained using a patient questionnaire and data from electronic patient files. 493 patients were included.

Results: 62.5% of patients received seasonal influenza vaccination and 12.8% patients reported ILI. Maternal vaccination did not significantly reduce ILI during pregnancy (RR=0.80, 95%CI=0.50-1.27, p=0.35). Smokers were significantly less vaccinated, but no difference in ILI prevalence was found. Other maternal outcomes were not significantly influenced by vaccination or ILI. Lower educated patients reported more ILI and were less likely to receive vaccination. Neonatal outcomes were not influenced by maternal vaccination or ILI.

Conclusions: No significant association between vaccination and ILI was observed in this pregnant cohort. This could be attributed to multiple factors, mainly the low specificity of the ILI definition. A high number of pregnant patients received seasonal influenza vaccination.

KEYWORDS

General obstetrics; prenatal vaccination; ILI; flu; maternal medicine.

Introduction

In a 2012 position paper, the World Health Organization (WHO) recommended seasonal influenza vaccination at any stage of pregnancy due to the substantial risk of severe disease [1]. Although many national bodies concurred with the WHO advice to offer seasonal influenza vaccination to all pregnant patients, vaccination coverage is relatively poor in Western Europe, with a reported coverage of between 7% and 47.2% [2–4]. In Belgium the national guidelines adhere to the WHO recommendation to promote seasonal influenza vaccination in all stages of pregnancy. However, this statement is true only since the 2018-2019 season. Before that, vaccination was recommended only in the second and third trimester of pregnancy. With this shift of recommendation, we were interested to explore vaccination uptake and its potential influence in pregnancy.

Influenza-like illness (ILI) is a clinical case definition describing symptoms caused by influenza. The incidence in the literature of ILI during pregnancy ranges between 11% and 16%, however the exact incidence remains unknown [5,6]. Furthermore, no data exist about ILI incidence during pregnancy in Belgium.

In a pregnant population, it has been hypothesized that maternal influenza infection could be linked to adverse neonatal outcomes [7]. However, a WHO working group report did not show a higher incidence of preterm delivery or of small-for-gestational-age neonates after maternal influenza infection [7]. In a systematic review by Katz *et al.*, only nine publications reported on laboratory-confirmed maternal influenza disease, and only three of these reports concerned seasonal influenza. These findings indicate the need for further research [8].

The aim of this study is to provide insights into seasonal influenza vaccination and its impact on the incidence of ILI in a pregnant population. Furthermore, we examined the influence of both vaccination and ILI on adverse neonatal and maternal outcomes in a Western setting.

We hypothesize that maternal vaccination reduces the incidence of ILI and has a favorable impact on maternal and neonatal outcomes.

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Materials and Methods

This is a monocentric cohort study conducted in AZ Delta Roeselare, a secondary teaching hospital in Flanders, Belgium. In 2018, this center had a live birth rate of 1,406, compared with the Flemish live birth rate of 63,836 [9]. All Dutch-speaking patients over the age of 18 years attending our center were eligible. Patients were included after giving their informed consent using a questionnaire; additional data were extracted from patients' electronic files.

The primary outcome in this study is the influence of seasonal influenza vaccination on the incidence of ILI during pregnancy. Secondary maternal outcomes are hospital admissions related to ILI and maternal mortality. We also explored the influence of smoking, pulmonary disease and socio-economic status on vaccination coverage and on the incidence of ILI. Secondary neonatal outcomes are the influence of seasonal influenza vaccination on preterm delivery, birth weight, admission to a neonatal unit, and neonatal mortality.

Data on the incidence of ILI were obtained on a weekly basis from the website of the Belgian Institute for Health [10]. The epidemic threshold during the influenza season of interest was defined, in Belgium, as 157 general practitioner consultations because of ILI per 100,000 inhabitants per week [10]. The influenza epidemic period during this season ran from 21st January 2019 to 18th March 2019. In order to accommodate fluctuations in ILI incidence, patients were recruited in three different timeframes: before, during and after the influenza epidemic. Figure 1 provides an overview of the three different cohorts.

Patients were asked whether they had received the seasonal influenza vaccination during their current pregnancy. ILI was defined according to the European Centre for Disease Prevention and Control (ECDC) definition: (i) Sudden onset of symptoms; (ii) AND at least one of the following four systemic symptoms: fever or feverishness, malaise, headache, myalgia; (iii) AND at least one of the following three respiratory symptoms: cough, sore throat, shortness of breath. Preterm delivery was defined as delivery before 37 weeks. Neonatal admission was defined as an admission to the neonatal unit or neonatal intensive care unit, regardless of the reason for admission. Socio-economic status was acquired by asking patients to state their current occupation. These data were entered in the British Office for National Statistics Occupation Coding Tool, obtaining major group codes, according to the Standard Occupational Classification 2010 (SOC2010) Hierarchy [11].

Statistical analysis was conducted using SPSS (version 26; IBM, Armonk, NY, USA). The significance level was set at 0.05 for all tests. Student's T-test, Pearson's Chi-squared test, Fisher's Exact test and the Mann-Whitney U test were used, as appropriate. All tests were two-sided. Vaccination effectiveness was defined as 1 minus relative risk, according to Centers for Disease Control and Prevention (CDC) principles [12]. Selection and response bias were minimized by trying to enroll all patients who delivered at our center during their hospitalization. Patients with missing data were contacted; if no sufficient response could be obtained, the entry was removed from the final statistical analysis.

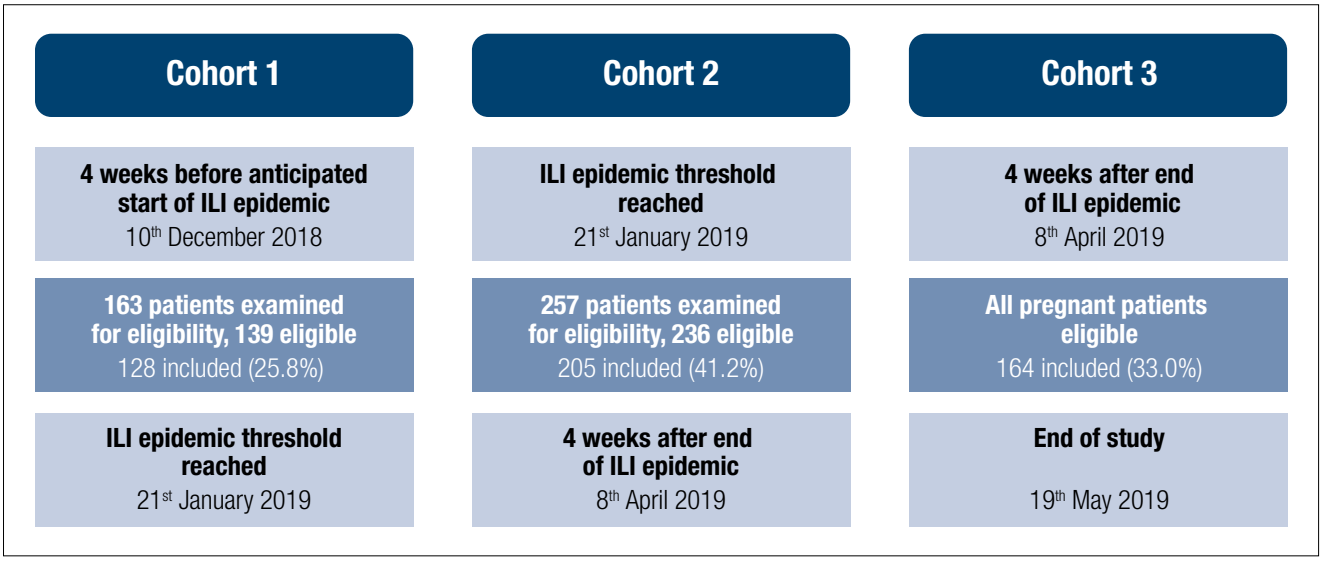
This study was reviewed and approved by the local review body of AZ Delta, according to ICH-good clinical practice principles and in line with the Declaration of Helsinki. Each individual provided written informed consent prior to participating.

Results

A total of 497 patients were included. An overview of the eligible and included patients is provided in Figure 1. The overall recruitment rate in cohorts 1 and 2 combined was 90.1%. When reviewing patient characteristics, gestational age, preterm delivery, birth weight and maternal or neonatal mortality, no significant differences were observed between the responders and the non-responders. After excluding four patients due to insufficient data about vaccination status or ILI occurrence, 493 patients were included in the final sample.

In total, 308 (62.5%) received seasonal influenza vaccination during their current pregnancy. Patient characteris-

Figure 1 Inclusion timeframes and patient selection. ILI = influenza-like illness.



tics are reported in Table 1. Smokers reported a significantly lower vaccination rate (p<0.01). The SOC2010 group could be retrieved for 447 patients, whereas non-working patients, such as housewives, students and unemployed patients could not be assigned a SOC2010 code. Patients in a higher-educated SOC2010 group showed significantly higher vaccination coverage (p<0.01) than patients in lower-educated SOC2010 groups. Fourteen (2.8%) patients had self-reported pulmonary disease. All but one of these patients reported asthma; the singleton (in the non-vaccinated group) had a history of pulmonary embolism.

The results for each primary and secondary outcome are summarized in Table 2. No significant association was observed between vaccination and incidence of ILI (relative risk=0.80, 95%CI=0.50-1.27; p=0.35). A vaccination effectiveness of 20.0% was observed. When excluding the pre-epidemic cohort (cohort 1), the association remained non-significant (relative risk=0.90, 95%CI=0.51-1.57; p=0.70) with a vaccination effectiveness of 10.3%. In the entire study population, only one (0.2%) patient was admitted to hospital because of an ILI-related cause, during the first trimester of pregnancy. This patient did not receive seasonal influenza vaccination.

ILI was reported during the current pregnancy by 63 (12.8%) patients. Of this group, 36 (57.1%) patients had received seasonal influenza vaccination. An ILI incidence rate of 2.73 per 1000 person days was observed in the complete cohort (2.74 per 1000 person days in the vaccinated group, 2.73 per 1000 person days in the unvaccinated group). No significant association (p=0.76) was found between the incidence of ILI and cigarette smoking during pregnancy, also when reviewing the number of cigarettes (p=0.78). Patients in a lower-educated SOC2010 group reported a significantly higher incidence of ILI compared with higher-educated groups (p=0.01).

In the ILI group, two (3.2%) patients had a preterm delivery, a rate not significantly different from the 26 (6.0%) patients without ILI (p=0.56). When examining the patients' gestational age at delivery, no significant difference between ILI and non-ILI patients was observed (p=0.16). Furthermore, no significant differences were found in birth weight (a mean of 3365g in the non-ILI group versus a mean of 3404g in the ILI group; p=0.56) or admission to a neonatal unit (18.8% in the non-ILI group versus 23.8% in the ILI group; p=0.35).

When excluding the pre-epidemic cohort (cohort 1), equivalent maternal and neonatal secondary outcomes were obtained. Finally, we could not examine the possible influence of seasonal influenza vaccination or ILI on maternal or neonatal mortality, since no such events occurred in this cohort.

Discussion

Maternal seasonal influenza vaccination appeared not to lower the incidence of ILI during pregnancy in this monocentric cohort study. In our cohort, we recorded a vaccination coverage of 62.5%. In comparison with the 47.2% coverage reported by Maertens et al. in a pregnant Flemish population,

Table 1 Patient characteristics.

N=493	NO SEASONAL INFLUENZA VACCINATION DURING PREGNANCY (N=185)		SEASONAL INFLUENZA VACCINATION DURING PREGNANCY (N=308)		*P*-VALUE
Age in years (mean, ±SD)	29.5	(±4.72)	29.4	(±3.99)	0.93
Parity before delivery (n,%)					
0	68	(36.8%)	135	(43.8%)	0.12
1	87	(47.0%)	131	(42.5%)	
2	20	(10.8%)	32	(10.4%)	
3	8	(4.3%)	9	(2.9%)	
4	2	(1.1%)	1	(0.3%)	
Cigarette smoking during pregnancy (n,%), n=492	26	(14.1%)	18	(5.8%)	<0.01
Pulmonary disease (n,%), n=492	6	(3.3%)	8	(2.6%)	0.67
SOC2010 group (n,%), n=447					
1	16	(9.9%)	16	(5.6%)	<0.01
2	45	(27.8%)	136	(47.7%)	
3	6	(3.7%)	17	(6.0%)	
4	45	(27.8%)	76	(26.7%)	
5	6	(3.7%)	4	(1.4%)	
6	4	(2.5%)	6	(2.1%)	
7	7	(4.3%)	3	(1.1%)	
8	2	(1.2%)	1	(0.4%)	
9	31	(19.1%)	26	(9.1%)	

Table 2 Primary and secondary outcomes.

N=493	NO SEASONAL INFLUENZA VACCINATION DURING PREGNANCY (N=185)		SEASONAL INFLUENZA VACCINATION DURING PREGNANCY (N=308)		RELATIVE RISK (95%CI)	*P*-VALUE
Reported ILI during pregnancy (n,%)	27	(14.6%)	36	(11.7%)	0.80 (0.50-1.27)	0.35
Preterm delivery (n,%)	7	(3.8%)	21	(6.8%)	1.80 (0.78-4.15)	0.16
Gestational age at delivery, in weeks (n,%)						
30	1	(0.5%)	0		/	0.58
34	0		3	(1.0%)		
35	2	(1.1%)	5	(1.6%)		
36	4	(2.2%)	13	(4.2%)		
37	7	(3.8%)	20	(6.5%)		
38	39	(21.1%)	55	(17.9%)		
39	49	(26.5%)	79	(25.6%)		
40	65	(35.1%)	96	(32.2%)		
41	18	(9.7%)	37	(21.0%)		
Birth weight, g (mean, ±SD)	3337	(±489)	3390	(±496)	/	0.25
Admission to neonatal unit (n,%)	38	(20.5%)	58	(18.8%)	0.92 (0.64-1.32)	0.64

ILI = influenza-like illness; CI = confidence interval

this number could indicate a higher uptake of vaccination during the influenza season considered in the present study [4]. In our institution, vaccination is promoted, although vaccines are administered only by primary health care providers.

We noted an ILI incidence of 12.8%, but without significant differences between the vaccinated versus the non-vaccinated cohort. This contra-intuitive finding could be affected by multiple factors. First, the purpose of vaccination in a pregnant population is to minimize severe influenza. ILI is a clinical case definition for all types of influenza, not only severe influenza. As such the potential benefits of vaccination on ILI itself is less recognized and possibly of lesser clinical significance [1]. Second, we defined ILI according to the ECDC definition. This definition has a high sensitivity, of 96.1%, with a low specificity, of 6.6% (receiver operating characteristic area under curve: 0.513) [13]. The low specificity is certainly a major factor influencing these findings. Third, the rate of ILI could be influenced by recall bias in individual patients.

Vaccination effectiveness (VE) was calculated, resulting in relative low numbers (20.0%, 10.3% when excluding the pre-epidemic cohort). In the literature, VE shows a very broad range, mainly due to inhomogeneous comparisons. VE in the general population is 27.24% (95%CI=15.6%-37.3%) [14]. In a pregnant population, VE ranges from 27% to 57% [15]. We attribute the low VE in this cohort to the use of a clinical case definition.

Vaccination is recommended due to its possible protection against severe influenza requiring hospitalization [1]. In the literature, a hospitalization rate during pregnancy of 2.54 per 10,000 woman-months is reported [16]. Pregnancy is indeed a risk factor for hospitalization related to influenza; a meta-analysis by Mertz et al. obtained an odds ratio of 2.44 (95% CI: 1.22-4.87) [7,17]. However, in the present cohort only one such case was recorded. This low incidence could be attributed to our cohort size. We also obtained information about active pulmonary disease, as this is a risk factor for severe influenza in pregnancy and increases the risk of influenza-related hospitalization [1,18]. Only 14 (2.8%) patients reported such a condition, in most cases asthma. These numbers are limited, making it difficult to reach conclusions, and indicating the need for further, large-scale research. We examined the potential impact of smoking status and lower educational level on vaccination coverage and the incidence of ILI. Smokers were significantly less frequently vaccinated but did not differ in ILI incidence. Patients with a lower educational level were also less likely to be vaccinated and reported a higher incidence of ILI in comparison with higher-educated SOC2010 groups. Smoking and a lower educational level are indeed risk factors for lower vaccination coverage [19].

When reviewing neonatal outcomes, no significant differences in vaccination status or the presence of ILI during pregnancy were noted. These findings support those of a systematic review by Fell et al., who explored preterm and small-for-gestational-age birth following maternal influenza but were unable to show a conclusive association [7,20].

The strengths of our study are the systematic inclusion of patients, at delivery, during the influenza season. Furthermore, we obtained a high recruitment rate of 90.1% (in cohorts 1 and 2), allowing us to achieve a good representation of the patient population. Patients were systematically asked about their oc-

cupation, and this allowed us to carry out a statistical analysis using the SOC2010 groups. No other studies focusing on ILI in pregnancy and using these groups could be found.

Due to the non-randomized, retrospective character of the study, the results could possibly be influenced by recall and confounding bias. A desirability bias cannot be excluded, since vaccination is recommended. Selection bias was minimized by including all pregnant patients, however non-Dutch-speaking patients could not be included, potentially excluding a low-resource population with immigrant backgrounds. The fact that the sample size did not allow the inclusion of large numbers of patients in each SOC2010 group underlines the need for population-based studies. Additionally, we did not perform laboratory testing or viral serological typing. Although this was not the initial intent, laboratory-confirmed cases might have provided us with additional insights. A correlation between laboratory-confirmed cases and ILI patients could also be of interest. Further research should be promoted, including both ILI and laboratory-confirmed cases.

In this monocentric cohort study, we reported a higher uptake of the seasonal influenza vaccine compared with what is reported in previous literature. We observed no significant difference in ILI incidence during pregnancy between the vaccinated and the non-vaccinated group. This could be attributed to multiple factors, mainly the low specificity of the ILI definition. Furthermore, seasonal influenza vaccination appears not to significantly alter various maternal and neonatal outcomes. Further prospective research should be conducted to fully appreciate the protective effect of seasonal influenza vaccination in pregnancy and its impact on clinical influenza-like illness.

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Conflict of Interest Statement: *The authors declare that there is no conflict of interest.*

Details of ethics approval: *This study has been reviewed and has been approved by the local review body of AZ Delta, according to ICH-GCP principles and in line with the Declaration of Helsinki. Written informed consent was obtained from each individual prior to participating in the study. Local study number: 18093 Belgian Clinical Trial Number: B117201838227.*