

# Complications of the 2009 influenza A/H1N1 pandemic in pregnant women in The Netherlands: a national cohort study

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The 2009 influenza A/H1N1 pandemic caused an increase in complications in pregnant women. To be well prepared for a next pandemic, we investigated the obstetric and maternal complications of this pandemic. In our national cohort of 59 pregnant women who were admitted to the hospital, no major complications apart from preterm birth and admission to the neonatal intensive care unit were observed. Although the small

size of this study precludes us drawing any definitive conclusions, comparing our results with those in other countries suggests that the influenza A/H1N1 pandemic had a relatively benign course in pregnant women in The Netherlands.

**Keywords** H1N1, infection, influenza, pandemic, pregnancy.

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## Introduction

Both during and after the 2009 influenza A/H1N1 pandemic, several authors have reported worldwide an increased risk of complications in pregnant women with 2009 influenza A/H1N1 infection, like pneumonia, preterm birth or even maternal death. Previous flu pandemics showed the identical increased risks.<sup>1</sup>

Although in August 2010 the World Health Organization announced the disease to be post-pandemic, viral mutations possibly representing the start of an antigenic drift have already been reported.<sup>2</sup> To be well prepared for a next influenza pandemic, we investigated maternal and neonatal outcomes of pregnant women infected by this novel influenza virus and who were admitted to the hospital during the 2009 influenza A/H1N1 pandemic in The Netherlands.

## Methods

All patients admitted to Dutch hospitals with the suspicion or diagnosis 2009 influenza A/H1N1 infection had (and still have) to be reported to the regional health authorities (Gemeentelijke Gezondheidsdienst, GGD) during the pandemic. These local health authorities reported to the

national health authority (Rijksinstituut voor Volksgezondheid en Milieu). This institute registers nationwide all admitted patients infected with 2009 influenza A/H1N1 virus.

We asked the national health authority for names and e-mail addresses of all GGD physicians that reported pregnant or just delivered patients in the period June till December 2009. All these physicians were asked for the names of hospitals in their region that had reported pregnant patients with confirmed 2009 influenza A/H1N1 virus infections. All reporting hospitals were asked to give, anonymously, the following information about the registered patients: age, gravidity/parity, gestational age (GA) at admission, length of hospital stay, pre-existing diseases including obesity, antiviral medication, intensive care unit (ICU) admission, ventilation support, administration of steroids to enhance foetal lung maturity, GA at birth, neonatal weight, Apgar scores after 1 and 5 minutes, neonatal intensive care unit (NICU) admission and embryonic, foetal or neonatal mortality. When physicians or hospitals did not respond initially, they were recalled twice. When regional health authorities could not provide us with adequate information, we sent all laboratories for microbiology in that specific region, a letter to ask them if they encountered positive 2009 influenza A/H1N1 cultures in pregnant

patients and, if so, the names of the hospitals from where the virus cultures came from.

One-sided Fisher's Exact test was used to analyse the differences in complications between the women who were treated or untreated with antiviral medication. Statistical analysis was performed using SPSS PASW, version 17.0.2, IBM, Armonk, NY, USA.

The local medical ethical committee waived the need for informed consent because of the retrospective and anonymous character of this study.

## Results

Sixty-nine pregnant or just delivered patients with 2009 influenza A/H1N1 infection were reported to the national health authority. Seventeen patients were additionally reported by the contacted hospitals and laboratories. From this total of 86 patients, data of 67 patients (78%) could be retrieved. Seven patients appeared not to have been admitted and one patient proved to be not pregnant. The remaining 59 patients were eligible for further analysis. From eight patients, data could not be completely retrieved because of referral to another hospital or midwife, but their data were as much as possible included in the analysis.

Mean age of the admitted patients was 29.7 years (SD 6.0; range 18–45). Sixteen patients (27.6%) were nulliparous and 42 (72.4%) multiparous. All patients had singleton pregnancies. At admission, GA of six patients (10.2%) was <16 weeks, of 11 patients (18.6%) between 16 and 28 weeks and of 40 patients (67.8%) more than 28 weeks. Two patients (3.4%) were admitted 3 and 7 days after delivery (Figure 1). Median hospital stay was 3 days (range

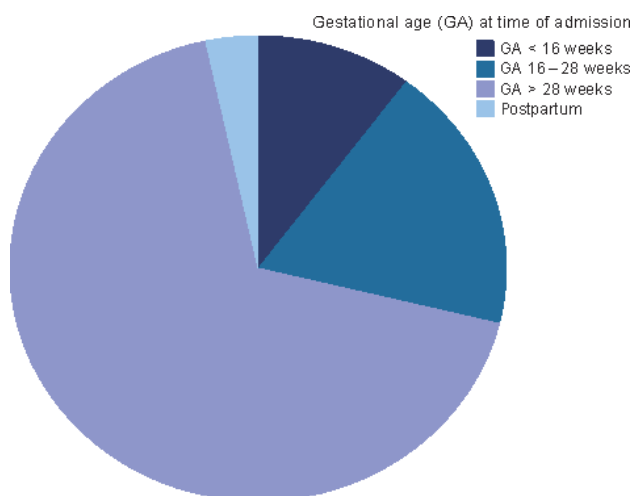


Figure 1. Gestational age (GA) at time of admission.

1–30 days). Fourteen patients (23.7%) had a history of physical comorbidity, most of them asthma. Only 43 (75.4%) patients were treated with antiviral medication (all oseltamavir), including the six patients that had to be admitted to an ICU for mechanical ventilation. Among the 52 patients not admitted to ICU, no major differences in complications were seen between treated and untreated patients (Table 1).

None of the six patients who were admitted to ICU had a history of comorbidity. Five were admitted before 37 weeks of gestation (range 30–36 weeks) and all delivered pre-term, one patient was admitted 3 days post-partum.

Three patients (5.2%) were treated with steroids to enhance foetal lung maturation. No small-for-GA neonates were born, but 11 patients (20.4%) gave birth pre-term. Three neonates (5.8%) were born with an Apgar score <4 after 1 minute, and two (3.7%) had an Apgar score <7 after 5 minutes. Fourteen newborns (26.4%) had to be admitted to NICU, but none died.

## Discussion

We investigated pregnancy outcomes and complications of all pregnant women infected by 2009 influenza A/H1N1 in The Netherlands, who were admitted to hospital. Due to the nationwide obligatory reporting system of infected cases, we could retrieve the majority of these patients. However, almost 20% additional patients were reported to us by the contacted hospitals or laboratories for microbiology; the reporting system appeared not to be flawless. Moreover, almost 20% of all patients could not be retrieved and our data set only contains admitted patients. Therefore, we only obtained data from the more severely affected patients. Another limitation of our study is the small sample size due to the fact that The Netherlands is a small country.

Most women in our study were admitted from 28 weeks GA onwards. This could be due to concerns about the foetal

Table 1. Number of patients treated or untreated with antiviral medication and maternal and neonatal outcome

Complications	Treated patients	Untreated patients	P
Steroid use	1/36	1/13	0.48
Pre-term birth	3/32	3/9	0.16
Small for gestational age	0/35	0/11	n/a
Apgar <4 after 1 minute	1/33	0/11	0.76
Apgar <7 after 5 minutes	0/36	0/11	n/a
NICU admission	4/31	4/7	0.08

NICU, neonatal intensive care unit.

condition, but more likely as result of the decreased pulmonary capacity caused by diaphragmatic elevation and decreased chest wall compliance.<sup>3</sup> The same applies to patients with co-existing morbidity like asthma, which was the most reported co-existing disease. This is consistent with other reported data.<sup>4</sup>

Pre-term birth is a recognised complication of 2009 influenza A/H1N1 infection.<sup>4</sup> From 2000 to 2007, the overall pre-term birth risk in The Netherlands was 7.7% and in singleton pregnancies 6.0%.<sup>5</sup> Our increased pre-term birth rate may be a reflection of the more severely affected patients being admitted and consequently the need for induction of labour to improve maternal respiration. It is also possible that these patients were admitted with the diagnosis of pre-term delivery, but appeared later to be also infected with 2009 influenza A/H1N1.

Mosby *et al.* reviewed all publications on 2009 influenza A/H1N1 infection in relation to pregnancy until August 2010. Worldwide, pregnant women accounted for 6.3% of all admissions and 5.9% of ICU admissions.<sup>4</sup> Similar figures were found in The Netherlands: of all hospitalisations until the end of 2009 caused by 2009 influenza A/H1N1 infection, 6.2% of all admissions and 5.4% of ICU-admissions were pregnant women.<sup>6</sup> Approximately one percentage of the Dutch population was pregnant at that moment,<sup>4,6</sup> so pregnancy appears to be a major risk factor for complications.

Comparisons can be made with the LEMMoN study. This study investigated nationwide severe maternal morbidity in The Netherlands for a 2 year period during which 371 021 women delivered. ICU admission was observed in 847 women (2.4 of 1000 deliveries). Respiratory problems appeared to be a relatively uncommon reason for ICU admission in pregnant patients (8%, equals 0.19 of 1000 deliveries) as opposed to major obstetric haemorrhage (47%) and hypertensive disorders of pregnancy (33%).<sup>7</sup> From June till December 2009 (grossly covering the pandemic in The Netherlands<sup>6</sup>), 110 059 children (<http://statline.cbs.nl/statweb>, accessed 12 May 2011) were born and six women were admitted to ICU because of 2009 influenza A/H1N1 infection, which equals 0.05 of 1000 life born children. Considering possible increased awareness caused by the pandemic, it may be concluded that 2009 influenza A/H1N1 barely increased the risk for ICU admission in pregnant women. Moreover, we did not encounter any maternal mortality.

The differences between ICU admissions of pregnant women with 2009 influenza A/H1N1 infection in the United Kingdom, Australia and New Zealand were investigated by Knight *et al.*<sup>8</sup> Women who got infected had a higher risk to be admitted in the southern hemisphere, where the peak of the pandemic was earlier than in the northern hemisphere. Primary (vaccination) and secondary

(early treatment with antiviral medication) prevention could have caused this difference.

Vaccination became available in The Netherlands in November 2009, at the peak of the Dutch pandemic. Pregnant women in the second or third trimester were considered as a risk group and were offered vaccination. Due to the retrospective character of the study and the fact that vaccination was carried out by the general practitioner instead of the obstetrician or midwife, we could not retrieve information about vaccination. On the other hand, due to the relatively late availability, vaccination is probably only a relatively small mitigating factor for morbidity.

Regarding antiviral medication, Dutch national guidelines appointed the use of neuraminidase inhibitors within 48 hours of the onset of febrile complications. Apart from ICU admission, we did not see any differences between the women who were treated with oseltamavir and the women who remained untreated, although information on the timing of its use was not available. However, this reflects recent doubts that have been arisen about the effectiveness of neuraminidase inhibitors and the limited evidence for its use.<sup>9</sup>

Although we could not find evidence for a positive effect of vaccination nor medication, our data are in concert with the findings of Knight *et al.*, as The Netherlands is situated at the northern hemisphere.

The perinatal outcomes of 2009 influenza A/H1N1 in the United Kingdom, a country geographically close to The Netherlands, were reported by Pierce *et al.*<sup>10</sup> They found in their cohort study, 10 deaths among 256 infants: an increased risk of perinatal mortality in infected women compared with an uninfected comparison cohort. In our Dutch cohort, no foetal or neonatal mortality occurred.

Although our sample size is not big, which could have led to insufficient power to detect more differences, we conclude that based on our findings that, despite its risks, the 2009 influenza A/H1N1 epidemic had a relatively benign course in pregnant women in The Netherlands.

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