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Brief report

Adverse events in pregnant women with the tetravalent influenza vaccine obtained from cell cultures

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ABSTRACT

Influenza vaccination in pregnant women shows a clear benefit/risk ratio. Influenza vaccines are currently being developed using new platforms. It is essential to analyse the safety of these new vaccines in this population group, underrepresented in clinical trials.

In the 2019–2020 season, a vaccine obtained in cell culture was recommended to pregnant women in two autonomous communities. Information is collected from the vaccination and pharmacovigilance centres of both communities.

The reporting rate of adverse events (AEs) after vaccination in pregnant women was 4.02/100,000 doses administered, and in non-pregnant women aged 18–64 years it was 5.9/100,000 doses administered. The rate of AE reported was 8.04 and 17.74 respectively. No spontaneous abortions, prematurity or foetal malformations were reported.

This analysis suggests the safety in pregnant women of the influenza vaccine obtained from cell cultures.

Acontecimientos adversos en embarazadas con la vacuna tetravalente contra la gripe obtenida de cultivos celulares

Palabras clave:
Seguridad de los medicamentos
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Farmacoepidemiología
Vacunas contra la gripe
Sistemas de notificación de reacciones adversas a los medicamentos
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RESUMEN

La vacunación de la gripe en embarazadas muestra una clara relación beneficio/riesgo. En la actualidad se están desarrollando vacunas frente a la gripe utilizando nuevas plataformas. Es imprescindible analizar la seguridad de estas nuevas vacunas en este grupo poblacional, infrarrepresentado en los ensayos clínicos.

En la temporada 2019–2020 se aconsejó una vacuna obtenida en cultivo celular a las embarazadas en dos comunidades autónomas. Se recoge información de los centros de vacunación y de farmacovigilancia de ambas comunidades.

La tasa de notificación de casos de acontecimientos adversos (AA) tras la vacunación en embarazadas fue de 4,02/100.000 dosis administradas, y en mujeres de 18 a 64 años no embarazadas de 5,9/100.000 dosis administradas. La tasa de AA notificados fue de 8,04 y 17,74 respectivamente. No se notificaron abortos espontáneos, prematuridad o malformaciones fetales.

Este análisis sugiere la seguridad en embarazadas de la vacuna de la gripe obtenida de cultivos celulares.

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Introduction

Any authorised medicinal product undergoes an exhaustive quality, effectiveness and safety analysis. However, once it is placed on the market and used in the general population, these aspects must continue to be evaluated. The safety analysis of seasonal influenza vaccines is a requirement of the European Medicines Agency. This makes it possible to detect any variation in reactogenicity or allergic reactions, if they occur. It must also be carried out by age or risk groups.

Influenza morbidity and mortality in pregnancy is similar to that of other risk groups[1]. In the first trimester of pregnancy, influenza has been associated with an increase in heart malformations, cleft lip and neural tube defects, and during the second and third trimesters with a greater number of miscarriages and premature births[1]. The vaccine is safe and effective in pregnant women and is therefore indicated in Spain in any trimester of pregnancy. The vaccination of pregnant women provides a triple beneficial effect: protection of the mother, the newborn and the infant in the first few months of life, with a 20% reduction (incidence rate ratio [IRR]: 0.80; 95% CI: 0.66–0.99) in cases of severe pneumonia in children of vaccinated mothers (56% protection; IRR: 0.44; 95% CI: 0.23–0.84, during the circulation of influenza)[1].

The influenza vaccine is usually obtained from embryonated eggs, a platform that has certain drawbacks, since it is laborious, production is limited as it depends on the number of embryonated eggs available, and in addition there are strains of virus that affect humans and do not grow well in eggs. For this reason, the World Health Organization recommends the development of alternative platforms[2], such as the production of vaccines from viral cultures in mammalian cells. These new platforms would also facilitate and speed up the production of vaccines in the event of an influenza pandemic.

Flucelvax, a virus vaccine grown in MDCK, Madin-Darby canine kidney cells, is marketed in Spain and has an adequate immunogenicity and safety profile[3]. It was recommended to pregnant women in the 2019–2020 season in four autonomous communities (ACs). This group of women is not represented in clinical trials, hence post-authorisation information on effectiveness and safety must be increased. Safety is of the utmost importance in this more susceptible group.

Methods

The Sistema Español de Farmacovigilancia de Medicamentos de uso Humano [Spanish pharmacovigilance system for medicinal products for human use] (SEFV-H), coordinated by the AEMPS [Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines and Medical Devices)], and made up of the regional pharmacovigilance centres of the different ACs collects, evaluates and processes all the information on suspected adverse drug reactions (SADRs). Its purpose is to identify previously unknown risks or changes in known risks once a medicinal product is authorised for marketing.

The SEFV-H is based on the system of spontaneous reporting of SADRs carried out by health professionals and by the general population via the www.notificaram.es website. Health professionals can also report SADRs through the channels that each autonomous community makes available to them, such as computerised medical records or vaccination records.

In the case of vaccines, pharmacovigilance systems collect any adverse event (AE) temporarily associated with the vaccination and no causal relationship is necessary. In this way, the pharmacovigilance of vaccines differs from that of other medicines, an aspect that must be taken into account when this information is analysed.

For vaccines that have been on the market for a long time, the reporting of serious AEs and all those not included in the summary of product characteristics is recommended.

The data in this analysis are from the 2019–2020 influenza vaccination season from 2 ACs: the Valencian Community and Galicia. For this purpose, all the AEs with an association with the quadrivalent cell culture vaccine reported during this period by health professionals and by patients were requested from the regional pharmacovigilance centres of the 2 ACs). The procedures established by the SEFV-H for requesting and processing anonymised information were followed.

Once the AE notification data had been received they were reviewed and analysed. Subsequently, the AE notification rate was calculated according to the number of vaccines administered. For this purpose, the vaccination coverage data were used. They were obtained from the vaccination registries of each autonomous community on request to the competent bodies.

As a result, this paper describes the AEs reported with this vaccine in pregnant women and in the group of women aged 16–64 years, as well as the reporting rate.

Results

During the season, 24,870 pregnant women were vaccinated with the quadrivalent cell culture seasonal vaccine: 7480 in Galicia and 17,390 in the Valencian Community. The number of non-pregnant women vaccinated was 219,861 (92,026 women in Galicia and 127,835 in the Valencian Community).

In Galicia, no AEs were reported in pregnant women or in women between 18 and 64 years of age. In the Valencian Community, 13 cases of AEs were reported in non-pregnant women between 18 and 64 years of age, vaccinated with Flucelvax. These cases reported 39 AEs, 92.3% of them considered non-serious. Those that occurred in three of the 13 women were considered serious, but the only one in a woman of childbearing age was a nerve injury due to the administration process.

In the group of pregnant women, after these doses, only one case of fever and arthralgia was reported following vaccination, yielding a Flucelvax AE case reporting rate in pregnant women of 4.02/100,000 doses administered, and of 5.9/100,000 doses administered in non-pregnant women 18–64 years of age. The AE reporting rates were 8.04 and 17.74, respectively. No miscarriages, prematurity or foetal malformations were reported.

Discussion

The quadrivalent influenza vaccine produced in cell culture, used in pregnant women in the 2019–2020 season, has shown similar safety to that of non-pregnant women of the same age group.

Pharmacovigilance systems, which are based on spontaneous reporting, make it possible to detect signs of unknown adverse effects, although they are not designed to analyse their frequency[4]. If any signs are detected, they are thoroughly evaluated by the regulatory agencies using other more solid epidemiological methods[5].

Being a passive reporting system, it has its limitations: reporting biases (over- or under-reporting), inconsistency in the quality of data or in the degree of exhaustiveness applied to obtain them. There is also a tendency to report AEs that are closest to administration in terms of time since no association is made with the more distant ones. For example, in VAERS (United States Vaccine Adverse Events Reporting System), most preterm births potentially associated with the influenza vaccine were reported in the trimester in which the vaccine was administered[6].

In vaccines used for a longer time, the most common situation is under-reporting, generally due to the lack of knowledge among

health professionals as to what to declare and how to declare it and their insecurity and indifference towards pharmacovigilance[7], hence the training of health workers and their awareness is a pending issue.

The vaccination of pregnant women is indicated for its safety and effectiveness in preventing serious infection in the woman and the newborn[8]. Regarding safety, a systematic review described that vaccinated women had a lower probability of stillbirth, both from the seasonal vaccine (relative risk [RR] 0.73; 95% confidence interval [95% CI]: 0.55–0.96); and from the H1N1pdm09 vaccine (RR: 0.69; 95% CI: 0.53–0.90). No association was found between the vaccine and miscarriages (RR: 0.91; 95% CI: 0.68–1.22)[9]. In addition, a review of declarations to VAERS regarding the cell culture influenza vaccine in pregnant women finds no difference compared to other influenza vaccines[6].

In conclusion, the quadrivalent influenza vaccine obtained in cell culture has not demonstrated safety issues and has a declaration rate similar to that of non-pregnant women from the same age group.

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Conflicts of interest

None.

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