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Original article

Risk of infections during the first year of life after *in utero* exposure to drugs acting on immunity: A population-based cohort study

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ABSTRACT

The aim of the study was to evaluate the association between *in utero* exposure to drugs that potentially exhibit immunosuppressive activity and occurrence of infections during the first year of life.

We conducted a cohort study on the prescription data of pregnant women and their children registered in EFEMERIS cohort (France), during a one-year period. We classified *in utero* child exposure according to the number of reimbursements for immunosuppressive drugs during pregnancy. The number of infectious episodes during the first year of life was estimated through the number of anti-infective drugs dispensed. The association was estimated by a quasi-Poisson regression with adjustment for confounders.

The study population consisted of 9614 children, 3141 of whom had been exposed to immunosuppressive drugs during pregnancy. The most frequently immunosuppressive drugs prescribed were corticosteroids. The mean number of infectious episodes during the first year after birth gradually increased with the number of immunosuppressive drugs dispensed during pregnancy (from 2.38 in controls to 3.88 in the most exposed group). After adjustment for potential confounders, *in utero* exposure to immunosuppressive drugs was significantly associated with the number of infectious episodes during the first year of life ($RR_{3ormoreexposuresVS0} = 1.35$, 95% CI 1.24–1.46).

Intrauterine exposure to potentially immunosuppressive drugs could be associated with an increased susceptibility to infections in early childhood.

1. Introduction

Studies performed in France and abroad have found a high number of drugs prescribed to pregnant women [1,2]. Corticosteroids and other immunosuppressive drugs are often unavoidable as first-line treatments for inflammatory diseases, autoimmune disorders or transplantations. As pregnant women are thus exposed to such drugs, we wanted to address the issue of their effect on the infant's immunity.

In each of the Goodman and Gilman's four major classes of immunosuppressive drugs [3], drugs are known to cross the placental membrane: glucocorticoids [4,5], calcineurin inhibitors [6,7], antiproliferative agents (*e.g.* azathioprine [8]), antimetabolites and biological therapies (*e.g.* most IgG-type medications including TNFα inhibitors [9]).

The immune system sets up early on during embryogenesis and requires several years to mature. Hence, the newborn's immune system is still immature, explaining their particular sensitivity to infections [10,11].

However, data regarding the possible risk of infections in infants after *in utero* exposure to immunosuppressive drugs are still controversial. Some authors assert that *in utero* use of glucocorticoids does not increase the risk of infections or immunosuppression in newborns [12]. And yet this subject has not been widely studied. Data exist regarding other drugs for a moderate number of children of mothers exposed during pregnancy for severe pathologies (prevention of organ rejection, auto-immune diseases). One study did not find any significant difference in the biological immunity parameters of children exposed during pregnancy to immunosuppressive drugs compared with unexposed controls. However the number of children exposed was low and the primary endpoint

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based on intermediate criteria [13]. One alarming case was reported regarding a 4-month-old infant who died of disseminated tuberculosis after vaccination with the BCG vaccine. He had been exposed *in utero* to infliximab, a monoclonal antibody prescribed to his mother for Crohn's disease [14]. Our hypothesis, based on the pharmacodynamics of immunosuppressive drugs, was that when a pregnant woman takes drugs that may lower immunity, her infant may have a greater risk of infection leading to a higher number of infectious episodes after birth.

We carried out a cohort study to assess the association between *in utero* exposure to immunosuppressive drugs and the occurrence of infections during the child's first year of life.

2. Methods

This is a historical cohort study about infants born to women of the EFEMERIS cohort covering one year [15]. It was carried out using data on drug reimbursements from the first day of intrauterine life until the child's first birthday. This study required cross-tabulating two databases: the EFEMERIS database (*in utero* exposure) and data from the records of French health insurance system [Caisse Primaire d'Assurance Maladie (CPAM) of Haute-Garonne, southwest France] (drug exposure during the first year of life).

In France, CPAM systematically and prospectively records all care and drugs reimbursed to people covered by the general health insurance system (80% of the population). Conditions whose seriousness and/or chronic nature require extended or costly treatment are recorded and called long-term disorders (LTD).

The study was approved by the French Data Protection Agency (CNIL, DR-2013-060).

2.1. Study population

Were included in the study, children who were the result of a live birth between July 1, 2010 and June 30, 2011 and who were administratively covered by their mother's health insurance system. Children for whom no data was found for themselves or for their mother or for whom their mother refused to participate to EFEMERIS were excluded. Children who died before the age of one year could not be monitored for the same period of time as the others and were then analyzed separately.

2.2. Variables and data sources

2.2.1. *Infants'* in utero *exposure to drugs*

EFEMERIS is a French database of all reimbursed drugs that are prescribed and dispensed during pregnancy and the pregnancy outcomes [15]. EFEMERIS data are anonymized. A string of single characters based on the mother's last name, first name and date of birth is created and is behind a single identifier. The EFEMERIS variables used were: the single identifier, age, exact pregnancy start date based on the first-trimester ultrasound, delivery date, LTD and drugs reimbursed during pregnancy: ATC classification, form, and dispensation date.

2.2.2. *Infants' exposure to drugs after birth*

Drug reimbursement data for children during the first year of life were gathered from CPAM. They were anonymized in the same way as the EFEMERIS data, making it possible to create the same single identifier as the mother's. The gathered data were: the single identifier, the infant's date of birth, birth order, sex, death, data concerning pharmaceutical acts: the prescriber's specialty, ATC code for the reimbursed drugs, dispensation date and number of dispensed units.

2.2.3. *Infants' health condition after birth*

The newborns' characteristics (weight, length, and Apgar score at birth), the notion of breastfeeding (usually gathered at release from the maternity ward) and the number of days of hospitalization during the first three months of the infant's life were also extracted from EFEMERIS.

Data from EFEMERIS and CPAM databases were then cross-tabulated to study the effects of *in utero* exposure to immunosuppressive drugs on the occurrence of infections during the first year of life.

2.3. Study size

Reimbursement data for the children's treatments were gathered for a one-year period. The number of pregnant women exposed at least once to immunosuppressive drugs during this period was estimated at approximately 2000.

2.4. Definitions

2.4.1. *Outcome: occurrence of infections during infancy*

The main outcome was the number of infectious episodes occurring during the infants' first year of life. This number was estimated by counting the number of different dates on which anti-infective drugs were dispensed to the infants during their first year of life. The anti-infective drugs (and their respective ATC codes) considered as markers for infections were: anti-infectives and antiseptics for local oral treatment (A01AB); intestinal anti-infectives (A07A); antifungals, antibiotics and chemotherapeutics for dermatological use (D01, D06); antibacterials, antimycotics, antiinfectives, antimycobacterials, and antivirals for systemic use (J01–J05); immune sera and immunoglobulins (J06); antiparasitic products, insecticides and repellents (P), mupirocin (R01AX06), antiseptics and antibiotics throat preparations (R02A); ophthalmological and otological antiinfectives alone or in combination (S01A, S01C, S02A, S02C).

2.4.2. In utero *exposure to immunosuppressive drugs*

Drugs that could impair the immune system (immunosuppressive drugs) were identified through their ATC codes: antineoplastic agents (L01), immunosuppressants (L04), corticosteroids for systemic use (H02), corticosteroids acting locally (A07EA), nasal preparations of corticosteroids (R01AD), glucocorticoids for obstructive airway diseases, inhalants (R03BA), dexchlorpheniramine + betamethasone (R06AB52), and omalizumab (R03DX05).

Infants were categorized into 4 groups depending on their level of *in utero* exposure: 0, 1, 2 and 3-or-more exposures. Each group corresponds to the number of different dates on which immunosuppressive drugs were dispensed to the mother during pregnancy.

2.5. Statistical analysis

SAS software (Version 9.4) was used for statistical analysis.

2.5.1. *Descriptive analysis*

Qualitative variables were expressed as percentages and quantitative variables as means (+/− SD) and extreme values.

We used Pearson's chi-squared test to compare categorical variables between groups, and the Student *t*-test, Wilcoxon or Kruskal-Wallis non-parametric tests to compare quantitative variables as appropriate. Significance was determined by a p value lower than 0.05.

2.5.2. *Multivariable analysis*

We performed a quasi-Poisson regression model due to the existence of overdispersion. All quantitative variables were categorized. Variables significantly associated with *in utero* exposure to