



NON-INTERVENTIONAL (NI) STUDY PROTOCOL SYNOPSIS

Study information

Title	Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry
Protocol number	C4591022
Date	14 April 2021
EU Post Authorization Study (PAS) register number	To be registered before the start of data collection
Active substance	COVID-19 mRNA Vaccine is single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2
Medicinal product	Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)
Research question and objectives	<p>Are the incidence rates of pregnancy and infant safety outcomes among pregnant women vaccinated with the Pfizer-BioNTech COVID 19 vaccine in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry (“OTIS Pregnancy Registry”) increased as compared with rates of these outcomes in pregnant women who did not receive the Pfizer-BioNTech COVID-19 vaccine?</p> <p><u>Primary Objective</u></p> <ul style="list-style-type: none"> To assess whether pregnant women in the OTIS Pregnancy Registry receiving the Pfizer-BioNTech COVID-19 vaccine experience increased risk of pregnancy and infant safety outcomes, including

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	<p>major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age.</p> <p><u>Secondary Objective</u></p> <ul style="list-style-type: none">• To characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among pregnant women in the OTIS Pregnancy Registry, including the proportion who completed the 2-dose vaccine schedule, the trimester of vaccine administration, and the distribution of time gaps between the first and second dose.
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1. RATIONALE AND BACKGROUND

Despite public health efforts, the incidence of coronavirus disease 2019 (COVID-19) due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has continued to rise. COVID-19 largely affects middle-aged persons with worsening clinical sequelae linked to increasing age and comorbid conditions (e.g., cardiovascular disease, diabetes, and chronic lung disease). As of 23 March 2021, over 29.8 million COVID-19 cases and 542,991 deaths have been reported in the United States (US) alone ([Johns Hopkins University, 2021](#)).

Pfizer and BioNTech have partnered to develop a novel messenger RiboNucleic Acid (mRNA) vaccine against SARS-CoV-2 for the prevention of COVID-19 (Candidate BNT162b2). On 11 December 2020, the US Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine for individuals 16 years of age and older.

Available data suggest that pregnant women who become infected with COVID-19 may be more likely to be hospitalized and may be at increased risk of preterm delivery ([MMWR, 2020](#)). The Pfizer-BioNTech COVID-19 vaccine is likely to be utilized by pregnant women when they and their healthcare providers believe that risk/benefit considerations favor its use, however, human pregnancy exposure data for the vaccine is lacking. While the current product labeling communicates that data are insufficient, Pfizer is conducting an ongoing Phase 2/3 clinical trial of the safety and immunogenicity of the Pfizer-BioNTech COVID-19 vaccine in pregnant women. Also, given the frequency of unplanned pregnancies, information regarding the safety of the COVID-19 vaccine in human pregnancy is essential from a public health perspective. Here, we provide a synopsis of the proposed study, which is intended to monitor rates of pregnancy and infant safety outcomes in pregnancies exposed to the Pfizer-BioNTech COVID-19 vaccine among women enrolled in an established North American pregnancy registry. This proposed non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is anticipated as a commitment to the FDA.

2. RESEARCH QUESTION AND OBJECTIVES

The research question for the study is: Are the incidence rates of pregnancy and infant safety outcomes among pregnant women vaccinated with the Pfizer-BioNTech COVID 19 vaccine in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry (“OTIS Pregnancy Registry”) increased as compared with rates of these outcomes in pregnant women who did not receive the Pfizer-BioNTech COVID-19 vaccine?

Primary objective

- To assess whether pregnant women in the OTIS Pregnancy Registry receiving the Pfizer-BioNTech COVID-19 vaccine experience increased risk of pregnancy and infant safety outcomes, including major congenital malformations, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age postnatal growth to one year of age.

Secondary objective

- To characterize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine among pregnant women in the OTIS Pregnancy Registry, including the proportion who completed the 2-dose vaccine schedule, the trimester of vaccine administration, and the distribution of time gaps between the first and second dose.

3. RESEARCH METHODS

3.1. Study design

This proposed study is a prospective, observational cohort study of pregnancy and infant safety outcomes in pregnant women with exposure to the Pfizer-BioNTech COVID-19 vaccine using data from the OTIS Pregnancy Registry. The comparator groups are 1) pregnant women who received an influenza or Tdap (i.e., tetanus, diphtheria, and acellular pertussis) vaccine during pregnancy and 2) pregnant women who received no vaccines during pregnancy.

3.2. Setting

The study population includes pregnant women aged 18 years or older residing in the US or Canada who are enrolled in the OTIS Pregnancy Registry during the study period 01 May 2021 – 30 April 2024. To participate in the study, women must provide consent indicating that they have been informed of all pertinent aspects of the study, including the conditions and requirements of the study such as the interview schedule and release of medical records.

The study will include three groups of participants followed for pregnancy and infant outcomes:

- **Pfizer-BioNTech COVID-19 Vaccine-Exposed**
 - Pregnant women with exposure to at least one dose of the Pfizer-BioNTech COVID-19 vaccine within one month prior to the first day of the last menstrual period (LMP) or during pregnancy
- **Influenza or TDAP Vaccine Exposed (Active Comparator)**
 - Pregnant women with exposure to an influenza or Tdap vaccine but no exposure to a COVID-19 vaccine within one month prior to the first day of LMP or during pregnancy
- **Vaccine Unexposed (Unexposed Comparator)**
 - Pregnant women who have not had exposure to any vaccine within one month prior to the first day of LMP or during pregnancy.

Women with a known pregnancy outcome at the time of study entry (e.g., positive prenatal diagnostic test results for a major congenital malformation prior to study entry) are not eligible for study entry.

3.3. Variables

Variables for the exposures, outcomes, demographics, and clinical characteristics of interest are included below. Data on these variables will be collected via maternal interview and medical record review per standard process within the registry infrastructure. Detailed operational definitions will be provided in the full protocol and the Statistical Analysis Plan (SAP).

3.3.1. Vaccine Exposures

- Pfizer-BioNTech COVID-19 vaccine (Exposure)
- Influenza and Tdap vaccines (Active Comparator)

3.3.2. Pregnancy and Infant Safety Outcomes

- Pregnancy Outcomes
 - Major congenital malformations
 - Spontaneous abortion/miscarriage
 - Stillbirth
 - Preterm delivery
 - Small for gestational age at birth
- Infant Outcome
 - Small for age postnatal growth to one year of age.

3.3.3. Demographic and Clinical Characteristics

- Demographic characteristics
 - Age
 - Race
 - Ethnicity
 - Geographic area of residence
 - Education
 - Socioeconomic category

- Clinical characteristics
 - Height
 - Pre-pregnancy body weight
 - Pre-pregnancy BMI
 - Number of prior pregnancies
 - Number of previous live birth or stillbirth deliveries
 - Number of previous pregnancies ending in spontaneous abortion
 - Number of previous pregnancies ending in elective termination
 - Gestational age at enrollment
 - Referral source
 - Prenatal vitamin, multivitamin, or folic acid use in pregnancy
 - Alcohol use in pregnancy
 - Tobacco use in pregnancy
 - Other vaccine exposure during pregnancy
 - Prenatal diagnostic tests prior to study enrollment
 - Prenatal diagnostic tests on or after study enrollment
 - Maternal pregnancy exposure to another known human teratogen
 - Comorbid maternal medical history
 - Covid-19 infection symptoms and/or positive test

3.4. Data Source

This study will use data that are collected as part of the OTIS Pregnancy Registry. The OTIS Pregnancy Registry was established in 1999 and is conducted by the OTIS Research Group, a network of university and health department based telephone information centers serving pregnant women and healthcare providers throughout the US and Canada ([Leen-Mitchell et al, 2000](#)). Pregnant women who call are recruited for the OTIS Pregnancy Registry, and the healthcare providers are requested to contact the OTIS Pregnancy Registry to provide patient referrals. Active recruitment strategies are also used, e.g., direct mailings to healthcare providers, website, and professional meetings.

As part of the registry protocol, data are collected using maternal interview(s), medical record review (obstetric, delivery hospital, pediatric, vaccine provider, and/or other specialty provider if applicable), and the pregnancy exposure diary (see [Table 1](#) Schedule of Follow-up).

3.4.1. Maternal Interviews

- **Intake/Enrollment Interview:** A structured maternal intake telephone interview is conducted at enrollment by a trained Research Associate from the OTIS Research Center. This interview includes questions on the following: pregnancy history; current health history; pre-pregnancy weight and height; socioeconomic and demographic information including maternal and paternal occupation, education and ethnicity; income category, current medication use, both prescription and over the counter; other environmental or occupational exposures, alcohol, tobacco, caffeine and illicit drug use; current pregnancy complications including illnesses; names and addresses of health care providers; and vaccine use.
- **Interim Interviews I and II:** Telephone interviews are conducted at 20-22 and 32-34 weeks' gestation (if enrolled at those times) by a trained Research Associate from the OTIS Research Center. This interview is intended to update records of pregnancy exposures (medications, vaccinations, vitamins, etc.), results of prenatal tests, and events of interest since last interview; to supplement this interview and improve recall, participants are given a pregnancy exposure diary after the Enrollment Interview to record related information.
- **Pregnancy Outcome Interview:** A structured telephone interview will be conducted at 0 to six weeks after the expected due date, or at an interim interview point if pregnancy has ended, by a trained Research Associate from the OTIS Research Center to elicit information based on type of birth:
 - For women with live born infants: date of delivery, hospital location and mode of delivery; sex, birth weight, length and head circumference; Apgar scores; description of delivery or birth complications including malformations; type and length of hospital stay for mother and infant; delivering physician's and infant physician's names and addresses; method of infant feeding; pregnancy weight gain; and additional exposures and results of prenatal tests occurring since the previous interview.
 - For women with spontaneous abortions: date and type of outcome; hospital location if applicable; prenatal diagnosis; pathology results if available; and additional exposures and results of prenatal tests occurring since the previous interview.
 - For women with stillborn infants: all of the above for women with spontaneous abortions, plus sex, delivery or birth complications including malformations, and autopsy results if available.

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3.4.2. Medical Records and General Pediatric Evaluation

The mother’s and infant’s medical records are captured at birth and again for the infant at 1 year of age. Medical records are reviewed by trained abstractors to confirm information self-reported by the participant related to vaccine exposure, outcomes, prenatal tests, and medical history. A standard physical evaluation form is also mailed to each pediatrician or other physician responsible for the care of each live born infant to complement the medical record which may not be complete. This form includes information on infant size at the time of the latest examination and an open-ended question about postnatal complications and congenital anomalies.

At one year of age, a second standard physical evaluation form is sent to the health care provider to request updated information on growth, and major congenital malformations.

Table 1. Timing of Cohort Enrollment, Interviews, Examinations, and Medical Records

	Any time In Pregnancy	20-22 Weeks’ Gestation ^b	32-34 Weeks’ Gestation ^c	0-6 Weeks Post-Delivery	0-12 Months Post-Delivery	1 Year Post-Delivery
Referral ^a	√					
Enrollment and Consent ^a	√					
Enrollment Interview ^a	√					
Interim Interview I		√				
Interim Interview II			√			
Pregnancy Outcome Interview and Request for Medical Records				√		
Medical Record Acquisition and Review					√	
Pediatric 1-Year Medical Records Request and Review						√

- a. Participants may enroll in the study any time during pregnancy.
- b. If subject is enrolled and Intake Interview is conducted after 18 weeks’ gestation, only one interim interview is conducted during pregnancy at 32-34 weeks gestation.
- c. If subject is enrolled and Intake Interview is conducted at 30 weeks’ gestation or after, no Interim Interview is collected.

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3.5. Study Size

The study will aim to enroll 1800 pregnant women in the cohort study over a 3-year recruitment period: 900 in the Pfizer-BioNTech COVID-19 vaccine group, 600 in the flu/Tdap vaccine group (active comparator), and 300 in the vaccine unexposed group (unexposed comparator).

The relative risk (RR) for safety endpoints between the exposed and comparator groups will be estimated as feasible (eg, sufficient case counts). The full protocol will include sample size and power calculations for the minimum detectable RRs with 80% power and two-sided alpha level of 0.05 for the range of background risks of the outcomes of interest.

3.6. Data Analysis

The distributions of demographic and baseline characteristics will be summarized within each exposure group. Birth prevalence rates and incidence rates will be calculated for the pregnancy and infant outcomes, respectively. For each outcome, risk estimates will be described separately for each cohort and, where feasible, will be compared between the Pfizer-BioNTech COVID-19 vaccine-exposed group and 1) the influenza/Tdap vaccinated cohort and 2) the unvaccinated cohort using methods to control potential confounding. Descriptive statistics will be used to summarize utilization patterns of the Pfizer-BioNTech COVID-19 vaccine.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the full protocol and statistical analysis plan (SAP).

3.7. Limitations of the Research Methods

This study will use data from the well-established OTIS Pregnancy Registry which collects detailed data on prenatal/birth exposures (including timing of exposures during pregnancy) and outcomes. However, potential selection bias is the primary limitation of a cohort study utilizing volunteer participants; women who agree to enroll in the cohort study may represent particularly high or low risk pregnancies (Johnson, 2001).

Another limitation of the study design relates to the evaluation of spontaneous abortion rates. Rates of early spontaneous abortion, i.e., at 7-9 weeks post-LMP or less, will not be measured in a study that enrolls women after recognition of pregnancy. Therefore, spontaneous abortion will be defined as late first-trimester and early second-trimester pregnancy loss. Analysis of spontaneous abortion will be restricted to those who enroll prior to 20.0 weeks' gestation. In addition, if a high proportion of women enroll later in pregnancy, other survival biases may be introduced. A sensitivity analysis by gestational age at enrollment will be performed in order to address these questions. Analyses will be stratified by gestational age at enrollment to help address the potential selection bias.

Because early prenatal testing is so prevalent in the U.S. and Canada, it may be difficult to achieve adequate numbers of participants if all pregnancies with prenatal testing prior to enrollment are excluded from the analysis. Therefore, the study will include pregnant women enrolled prior to outcome but after a prenatal test has been performed as long as the

test does not indicate the presence of a major congenital malformation. The FDA guidance document ([FDA Postapproval Pregnancy Safety Studies Draft Guidance for Industry, 2019](#)) acknowledges that such an approach may be necessary to accrue adequate numbers. However, this practice could potentially bias the results by lowering the overall estimate of the prevalence of major congenital malformations ([Honein, 1999](#)).

4. MILESTONES

The full protocol will be submitted for FDA review by 01 July 2021. Proposed milestones are listed below.

Milestone	Planned date
Registration in the EU PAS register	To be registered before the start of data collection
Start of data collection	01 November 2021 ¹
Interim Reports	31 January 2022 31 January 2023 31 January 2024 31 January 2025
End of data collection	31 December 2024 ²
Final study report	01 December 2025

1 To meet sample size goals, enrollment of participants into study cohort is planned to begin 01 May 2021. The start of data collection is defined as start date of data extraction for the first interim report.

2 The end of data collection is defined as the date that the analytic dataset is available for analysis.

5. REFERENCES

FDA. Postapproval Pregnancy Safety Studies Draft Guidance for Industry. Maryland, May 2019

Honein MA, Paulozzi LJ, Cragan JD, Correa A. Evaluation of selected characteristics of pregnancy drug registries. *Teratology* 1999; 60:356-64.

Johns Hopkins University. Coronavirus Resource Center. Available at: <https://coronavirus.jhu.edu/>. Accessed March 23, 2021.

Johnson KA, Weber PA, Jones KL, Chambers CD. Selection bias in Teratology Information Service pregnancy outcome studies. *Teratology* 2001; 64:79-82.

Leen-Mitchell M, Martinez L, Gallegos S, Robertson J, Carey JC. Mini-review: history of organized teratology information services in North America. *Teratology* 2000; 61:314-7.

MMWR Morb Mortal Wkly Rep. Birth and Infant Outcomes Following Laboratory-Confirmed SARS-CoV-2 Infection in Pregnancy — SET-NET, 16 Jurisdictions, March 29–October 14, 2020 Nov 6;69(44):1635-1640.