Coronavirus Disease 2019 (COVID-19) Vaccine

Summary of Literature Search on the Use of Coronavirus Disease 2019 (COVID-19) Vaccine During Pregnancy, Lactation, and on the Drug's Potential Effects on Fertility

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1. INTRODUCTION

The BNT162b2 vaccine contains modified messenger RNA (modRNA), which is formulated in lipid particles that enable the delivery of the RNA into host cells to allow expression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral spike antigen, which in turn elicits a host immune response to this viral antigen. BNT162b2 is authorized for use under an Emergency Use Authorization (EUA 27034; Pfizer-BioNTech COVID-19 Vaccine) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 16 years of age and older. BNT162b2 is a suspension for injection and contains a volume of 0.45 mL. Each dose of BNT162b2 contains 30 µg of a nucleoside-modified messenger RNA encoding the viral spike (S) glycoprotein of SARS-CoV-2. The vaccine is administered intramuscularly as a series of two doses (0.3 mL each) 3 weeks apart.[1]

In the draft prescribing information, available data for BNT162b2 administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. In addition, data are not available to assess the effects of BNT162b2 on the breastfed infant or on milk production or excretion.

On 04 December 2014, the US Food and Drug Administration (FDA) published a draft guidance document on the content and format of labeling for human prescription drug and biological products regarding pregnancy, lactation, and reproductive potential.[2] The Pregnancy and Lactation Labeling Rule (PLLR) became effective on 30 June 2015 and requires a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to reproductive potential.

This clinical literature summary has been created to support the Biologics License Application (BLA) for BNT162b2.

2. LITERATURE SEARCH STRATEGY

The constructed clinical searches included 3 major keyword groups: Pregnancy, Fertility, and Lactation. The search included the following key words for COVID-19 Vaccine for clinical studies. Databases searched included LactMed, OVID MEDLINE and OVID MEDLINE(R) In-Process & Epub Ahead of Print, BIOSIS Previews, and Embase. The search timeframe was from 01-DEC-2020 to 26-FEB-2021.

Key words used for the literature search criteria for Pregnancy, Lactation, and Potential Effects on Fertility for COVID-19 Vaccine are listed below.

Pregnancy:

- pregnancy, pregnancy outcome, pregnancy complications, pregnant, pregnancies
- abortion, induced abortion, spontaneous abortion, miscarriage, embryo implantation, fetal resorption, embryo loss, nidation
- missed abortion, fetal death, stillbirth, neonatal death
- birth, parturition, fetus, embryo, in utero, childbirth, fetal, preterm birth, premature birth
- labor and delivery
- developmental toxicity
- epidemiology or causality or incidence (and pregnancy), prevalence (and pregnancy)
- malformation, birth or congenital abnormalities, defects or deformities, dysmorphology, fetal anomalies, teratogenicity, prenatal exposure delayed effects, structural abnormalities, functional impairment, growth impairment, growth restriction, excessive growth
- functional toxicity, deafness, endocrinopathy, neurodevelopmental effects, impairment of reproduction, delayed maturation, early maturation
- neonate, neonatal, newborn, newly born
- prenatal/perinatal exposure, prenatal drug exposure, maternal exposure, paternal exposure, fetus mortality, embryo mortality
- pharmacokinetics during pregnancy
- fetal exposure to drug

Pregnancy & Pharmacokinetics:

- pharmacokinetics, drug distribution, drug absorption, drug metabolism, drug elimination, absorption (and pregnancy)
- drug excretion in milk
- lacteal elimination
- distribution, absorption, metabolism, elimination (and pregnancy, lacteal, breast milk, milk)

Lactation:

- breast-feeding, breast secretion, lactation, milk
- exposure through breastmilk
- drug excretion in milk
- alteration in lactation
- milk supply

Females & Males of Reproductive Potential:

- fertility, reproduction, reproduction process, fecundity, fecundability, placentation, sperm, testis, ovary, implantation, ovum

Utilizing the recommended literature search criteria and methodology, preliminary literature search generated 158 results. Assessment of these literature search results was done by identification of potentially relevant studies based on abstract content, followed by further evaluation of the identified literature by reviewing their full text articles and appraising for relevancy. In this clinical literature search and review, 8 articles were reviewed in full, of which none was assessed to provide pertinent clinical data for inclusion in this clinical PLLR literature summary. The information provided by the articles reviewed are detailed in the accompanying PLLR Literature Summary Table.

3. LITERATURE SUMMARY REGARDING PREGNANCY

3.1. Human Data

Review of the published medical literature for COVID-19 Vaccine has been organized below within the following four groups of developmental toxicities, as defined in FDA's guidance for industry, *Reproductive and Developmental Toxicities – Integrating Study Results to Assess Concerns:*

1. Structural abnormalities, which describes dysmorphology, and includes malformations, variations, deformations, and disruptions.

2. Embryo-fetal and/or infant mortality, which describes developmental mortality, and includes miscarriage, stillbirth, and infant death (including neonatal death).

3. Functional impairment, which describes functional toxicity, and includes such outcomes as deafness, endocrinopathy, neurodevelopmental effects, and impairment of reproduction.

4. Alterations to growth, which describes outcomes such as growth restriction, excessive growth, and delayed and early maturations.

Doses of COVID-19 Vaccine and duration of exposure are outlined below, where provided. Within each category, literature describing both negative and positive experiences of *in-utero* exposure to COVID-19 Vaccine are presented.

3.1.1. Structural Abnormalities

There is no relevant published information or data available on structural abnormalities resulting from maternal exposure to COVID-19 Vaccine, as of this revision date.

3.1.2. Embryo-fetal and/or Infant Mortality

There is no relevant published information or data available on embryo-fetal and/or infant mortality resulting from maternal exposure to COVID-19 Vaccine, as of this revision date.

3.1.3. Functional Impairment

There is no relevant published information or data available on functional impairment resulting from maternal exposure to COVID-19 Vaccine, as of this revision date.

3.1.4. Alterations to Growth

There is no relevant published information or data available on alterations to growth resulting from maternal exposure to COVID-19 Vaccine, as of this revision date.

3.1.5. Change of Drug Pharmacokinetics Associated with Pregnancy

There is no relevant published information or data available on the change of drug pharmacokinetics associated with pregnancy resulting from maternal exposure to COVID-19 Vaccine, as of this revision date.

3.2. Summaries on the Effects of COVID-19 Vaccine on Pregnancy

The current review of clinical literature did not identify relevant published data or information on the effects of COVID-19 Vaccine on pregnancy.

4. LITERATURE SUMMARY REGARDING LACTATION

4.1. Human Data

4.1.1. Pharmacokinetics of Drug in Breast Milk

There is no relevant published information or data available on the pharmacokinetics of COVID-19 Vaccine in breast milk, as of this revision date.

An additional publication identified after the search cutoff date by Baird et al (2021)[3] reported significantly elevated levels of SARS-CoV-2 specific IgG and IgA antibodies in breast milk beginning at Day 7 after the initial vaccine dose, with an IgG-dominant response in a prospective cohort study of 6 lactating women who received 2 doses of Pfizer/BioNTech or Moderna SARS-CoV-2 vaccine (3 in each group). This publication is not yet peer-reviewed and no safety data were reported.

4.1.2. Estimated Infant Dose Obtained from Breast Milk

There is no relevant published information or data available on the estimated infant dose of COVID-19 Vaccine obtained from breast milk, as of this revision date.

4.1.3. Pharmacokinetics of Drug in Women who are Lactating

There is no relevant published information or data available on the pharmacokinetics of COVID-19 Vaccine in lactating women, as of this revision date.

4.1.4. Pharmacodynamics

4.1.4.1. Impact of Medication on Lactation (Changes in Volume Produced)

There is no relevant published information or data available on the impact of COVID-19 Vaccine on lactation, as of this revision date.

4.1.4.2. Impact of Medication Consumed from Breast Milk on Infant

There is no relevant published information or data available on the impact of COVID-19 Vaccine consumed from breast milk on infant, as of this revision date.

4.2. Summaries on the Effects of COVID-19 Vaccine on Lactation

The current review of clinical literature did not identify relevant published data or information on the effects of COVID-19 Vaccine on lactation.

5. LITERATURE SUMMARY REGARDING REPRODUCTIVE POTENTIAL

5.1. Human Data

There is no relevant published information or data available on the effects of COVID-19 Vaccine on human reproductive potential, as of this revision date.

5.2. Summaries on the Effects of COVID-19 Vaccine on Reproductive Potential

The current review of clinical literature did not identify relevant published data or information on the effects of COVID-19 Vaccine on male or female reproductive potential.

6. REFERENCES CITED IN LITERATURE SUMMARY

[1] Full Emergency Use Authorization (EUA) Prescribing Information: Pfizer-BioNTech COVID-19 Vaccine. Revised 25 February 2021

[2] U.S. Department of Health and Human Services, Food and drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biological Evaluation and Research (CBER). Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format. Draft Guidance, July 2020, Accessed March 2021: (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf)

[3] Baird JK, Jensen SM, Urba WJ, et al. SARS-CoV-2 antibodies detected in human breast milk post-vaccination. Preprint: https://doi.org/10.1101/2021.02.23.21252328

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