# PREGNANCY AND LACTATION CUMULATIVE REVIEW

## 1. INTRODUCTION

As part of the Biological Licensing Application (BLA) submission, the U.S. Food and Drug Administration (FDA) has requested a cumulative review and summary of relevant cases reported in Pfizer's pharmacovigilance (Safety) database from the time of drug product development to 28-FEB-2021.

## 2. METHODOLOGY

Pfizer's safety database contains cases of adverse events (AEs) reported spontaneously to Pfizer, cases reported by the health authorities (HAs), cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious adverse events (SAEs) reported from clinical studies regardless of causality. The safety database was searched for all BNT162b2 vaccine cases reporting any exposure to vaccine during pregnancy (mother and/or baby) or exposure to baby via lactation from all time through 28 February 2021. A search of the Pfizer safety database identified 673 case reports.

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an adverse event, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.

- Because many external factors influence whether or not an adverse event is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.

- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.

- An accumulation of adverse event reports does not necessarily indicate that a particular adverse event was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.

## 3. RESULTS

Of the 673 case reports identified in the search, 458 involved BNT162b2 exposure during pregnancy (mother/fetus) and 215 involved exposure during breast-feeding.

- In 210 out of the 458 cases, maternal exposure (PTs Maternal exposure timing unspecified, Maternal exposure during pregnancy, Maternal exposure before pregnancy,

Exposure during pregnancy) was reported either with no associated AEs or with AE off-label use/product use issue for either the mother or the baby.

- Among the remaining 248 cases, the most commonly reported AEs were product use issue (83), off-label use (81), pain (including but not limited to vaccination site pain/pain/pain in extremity)(101), headache (57), abortion spontaneous (51), fatigue (43), pyrexia (26), chills (24), myalgia (23), nausea (22), arthralgia (16), dizziness (15), malaise (12), lymphadenopathy (11) and asthenia (11).

- There were 6 cases reporting AE(s) related to premature deliveries.

    - AER 2021166927 Baby report of fetal tachycardia noted 1 week after the neonate's mother received the second dose of the vaccine. The baby was delivered at 35 weeks and 3 days of gestation due to non-reassuring status during monitoring post vaccination. The baby was hospitalized for 5 days. The clinical outcome of fetal tachycardia was unknown.

    - AER 2021015910 Maternal report of a 29-year old female who was pregnant when receiving BNT162B2. She had spontaneous rupture of membranes at 36 weeks of gestation, one day after her 2$^{nd}$ dose of vaccine. Unspecified therapeutic measures were taken as a result of premature rupture of membranes and the mother was recovering.

    - AER 2021191405 Baby case of a fetus of unspecified gender who received BNT162B2 transplacentally. The patient's mother received vaccination during the second trimester (13-28 weeks) and experienced premature labor. A live infant was delivered but passed away a day later. Cause of death was cited as extreme prematurity with severe respiratory distress and pneumothorax.

    - AER 2021182609 Maternal report (AER 2021193635 associated Baby report) of a 32-year-old female patient received BNT162B2 during the second-trimester (13-28 weeks) and experienced preterm premature rupture of membranes, premature baby/Premature delivery. Outcome of preterm premature rupture of membranes and premature delivery was recovered with sequelae. Concomitant medications included acetylsalicylic acid and dalteparin sodium.

    - AER 2021155967 Baby report: A neonate patient's mother (mother was reported as 37-year-old) received BNT162B2 during 13-28 weeks of gestation and experienced foetal exposure during pregnancy, premature baby less than 26 weeks, respiratory distress and pneumothorax. Cause of death for the neonate was premature baby less than 26 weeks and severe respiratory distress and pneumothorax.

    - AER 2021203938 Baby report: Patient's 33-year old mother had preterm delivery at 24 weeks and 2 days via emergency caesarean section. The fetus experienced maternal exposure during pregnancy via transplacental route on an unspecified date.

- There were 53 reports of spontaneous abortion (51)/ abortion (1)/ abortion missed (1) following BNT162b2 vaccination. Of these reports, 4 cases were COVID-19 positive (including suspected), and 13 cases had relevant medical history of endometriosis (1), abortion spontaneous (10), polycystic ovaries (1), menstruation irregular (1). These cases were therefore excluded from the review. One patient had a medical history of COVID-19 (unknown if ongoing) and was excluded from the review. The remaining 39 cases are summarized in Table 1.

**Table 1. Summary of Patients with Outcome of Pregnancy – Abortion spontaneous**

| Age | Medical History | Outcome of Pregnancy |
|---|---|---|
| 40 years | Not provided | The patient was unaware of her pregnancy at the time of vaccination. Suspected abortion occurred at 6 weeks of pregnancy. |
| 37 years | Not provided | Patient received vaccine during first trimester (1-12 weeks) on 19 Jan 2021 and suffered spontaneous abortion on 3 Feb 2021. |
| 33 years | Not provided | Patient received first dose of vaccine during first trimester (1-12 weeks). Abortion occurred at 3 weeks of pregnancy. |
| 32 years | Not provided | Patient was vaccinated during first trimester (1-12 weeks) on 23 Dec 2020 and suffered a spontaneous abortion on 06 Jan 2021. |
| 39 years | Asthma / Eosinophilic oesophagitis | Patient received vaccination at gestation of 6 weeks and spontaneous abortion occurred 11 days post vaccination. |
| 31 years | Not provided | Patient experienced spontaneous abortion 8 days after receiving 2nd vaccine at 6 weeks pregnant. |
| 35 years | Asthma / Gastrooesophageal reflux disease | Patient experienced missed abortion in the 7th week of pregnancy on an unspecified date with outcome of unknown. |
| 33 years | Pregnancy | The patient was unaware of her pregnancy at the time of vaccination, which occurred at gestational age of approximately 3 weeks. Spontaneous abortion occurred at gestational age of 6 weeks. |
| 34 years | Pregnancy | Patient was 3 weeks pregnant at the time of the first vaccination, without knowing she was pregnant. She found out she was pregnant one week after the vaccination. She then had a spontaneous abortion in week 6 of pregnancy. |
| Unknown | Not provided | Patient received vaccine at an unspecified time during pregnancy Spontaneous abortion, gestational age unknown. |
| 34 years | Continuous positive airway pressure / Overweight / Sleep apnoea syndrome | Patient reported that she was unknowingly pregnant upon receiving COVID-19 vaccine dose 1. Spontaneous abortion occurred at 4 weeks of pregnancy. |
| Unknown | Not provided | Patient received vaccine during first trimester of pregnancy. Spontaneous abortion occurred at 5 weeks of gestation. |
| 37 years | Not provided | Patient received vaccine during first trimester of pregnancy. Spontaneous abortion occurred at 6 weeks of pregnancy. |
| 31 years | Not provided | Patient received vaccine during first trimester of pregnancy. Spontaneous abortion occurred at 5 weeks of gestation. |
| 32 years | Not provided | Patient received her first vaccine dose at 3 weeks of pregnancy and experienced spontaneous abortion about 5-6 days before her second dose. |

**Table 1. Summary of Patients with Outcome of Pregnancy – Abortion spontaneous**

| Age | Medical History | Outcome of Pregnancy |
|---|---|---|
| 23 years | Not provided | Patient received vaccine during first trimester of pregnancy. Spontaneous abortion occurred at 1 month of pregnancy. |
| 29 years | Pregnancy | Patient received vaccine during first trimester of pregnancy. Spontaneous abortion occurred at 4-5 weeks of gestation. |
| 34 years | Not provided | The patient experienced spontaneous abortion at a routine OBGYN visit, gestational age unknown. |
| 38 years | Not provided | Patient had spontaneous abortion at 12 weeks after receiving the second dose of vaccine. |
| 29 years | Anxiety/Seasonal allergy | Patient received vaccine during first trimester of pregnancy. Spontaneous abortion occurred at 6 weeks of gestation. |
| 41 years | Pregnancy | Patient was vaccinated during first trimester (6 weeks, also reported 1-12 weeks). Spontaneous abortion was diagnosed on 09 Jan 2021 (17 days after vaccination administration). |
| 32 years | Pregnancy | The patient had spontaneous abortion at 5.5 weeks, which was conceived 3 days after receiving the vaccine. |
| 36 years | Allergy to animal/Food allergy/Seasonal allergy | The patient was unaware of her pregnancy at the time of vaccination. Spontaneous abortion occurred during 5$^{th}$ week of pregnancy. |
| 30 years | Clinical trial participant | Patient was vaccinated during first trimester (1-12 weeks). Spontaneous abortion occurred 1 week after first dose. |
| 26 years | Not provided | Patient was vaccinated during first trimester (1-12 weeks). Spontaneous abortion occurred 1 day after vaccination. |
| 28 years | Not provided | Patient received vaccine at an unspecified time during pregnancy. Spontaneous abortion, gestational age unknown. |
| Unknown | Not provided | Patient received vaccine at an unspecified time during pregnancy. Spontaneous abortion, gestational age unknown. |
| 25 years | Not provided | Patient received vaccine at an unspecified time during pregnancy. Spontaneous abortion, gestational age unknown. |
| Unknown | Not provided | Patient received vaccine at an unspecified time during pregnancy. Spontaneous abortion, gestational age unknown. |
| 34 years | Not provided | Patient received vaccine at 4 weeks 5 days of pregnancy. Spontaneous abortion occurred during Week 8 of gestation. |
| 29 years | Pregnancy | Patient experienced spontaneous abortion 10 days after first dose of vaccine during first trimester of pregnancy. |
| 21 years | Not provided | Patient was vaccinated during first-trimester (1-12 weeks) and experienced spontaneous abortion after 12 days. |
| 30 years | Not provided | Patient received vaccine during first trimester of pregnancy. Spontaneous abortion occurred at 11 weeks of pregnancy. |
| 36 years | Coronavirus test negative/Deep vein thrombosis | Patient received vaccine at an unspecified time during pregnancy. Spontaneous abortion occurred at 4 weeks of pregnancy. |
| 39 years | Drug hypersensitivity | Patient received vaccine during first trimester of pregnancy. Spontaneous abortion occurred during Week 8 of gestation |
| 26 years | Not provided | Patient received vaccine during first trimester of pregnancy. Spontaneous abortion occurred after 5 weeks of pregnancy. |
| Unknown | Not provided | Spontaneous abortion occurred 3 days post first dose of BNT162b2. |
| Unknown | Not provided | Miscarriage after receiving both doses of COVID-19 vaccine |

- The remaining 215 cases reported exposure via lactation. In 174 of the 215 reports, there was no AE reported other than 'Exposure via breast milk/maternal exposure during breast feeding'. In the remaining 41 cases, AEs were reported in the infants following BNT162b2 exposure via lactation (see Table 2).

**Table 2. Number of Adverse Events Reported in Infants with 'Exposure via Lactation'**

| Preferred Term | Number of Events |
|---|---|
| Pyrexia | 9 |
| Off label use | 8 |
| Product use issue | 7 |
| Infant irritability | 5 |
| Headache | 5 |
| Rash | 5 |
| Diarrhoea | 3 |
| Illness | 3 |
| Insomnia | 3 |
| Suppressed lactation | 3 |
| Breast milk discolouration | 2 |
| Infantile vomiting | 2 |
| Lethargy | 2 |
| Pain | 2 |
| Peripheral coldness | 2 |
| Urticaria | 2 |
| Vomiting | 2 |
| Abdominal discomfort | 1 |
| Agitation | 1 |
| Allergy to vaccine | 1 |
| Angioedema | 1 |
| Anxiety | 1 |
| Axillary pain | 1 |
| Breast pain | 1 |
| Breast swelling | 1 |
| Chills | 1 |
| Cough | 1 |
| Crying | 1 |
| Dysgeusia | 1 |
| Dysphonia | 1 |
| Eructation | 1 |
| Epistaxis | 1 |
| Eyelid ptosis | 1 |
| Facial paralysis | 1 |
| Fatigue | 1 |
| Increased appetite | 1 |
| Lymphadenopathy | 1 |
| Myalgia | 1 |
| Nausea | 1 |
| Paresis | 1 |
| Poor feeding infant | 1 |
| Poor quality sleep | 1 |
| Pruritis | 1 |
| Restlessness | 1 |

**Table 2. Number of Adverse Events Reported in Infants with 'Exposure via Lactation'**

| Preferred Term | Number of Events |
|---|---|
| Rhinorrhoea | 1 |
| Roseola | 1 |
| Skin exfoliation | 1 |
| Vision blurred | 1 |

There were 10 SAEs reporting with the PT Exposure via lactation. Six of these SAEs were reported in infants.

- A 15-month old infant with medical history of vomiting experienced skin exfoliation and infant irritability while being breastfed (latency <7 days). The outcome of the event 'skin exfoliation' was not recovered and outcome of event 'infant irritability' was unknown. No causality was reported by the physician.

- A 9-month old infant with a medical history of meningococcal vaccine and no history of allergies, asthma, eczema or anaphylaxis experienced rash and urticaria a day after exposure via lactation. The outcome of the events was 'resolved' and event did not happen after the second day. No causality assessment was provided.

- A day after the mother received vaccination, a baby developed a rash after breastfeeding. At the time of the report, the event was 'not recovered. A causality assessment was not provided.

- An 8-month old infant experienced angioedema one day after his mother received vaccination. The event was considered non-serious by health authority and the outcome at the time of the report was unknown. No causality was provided.

- There were 2 cases reporting 'illness' after exposure via breast milk'. In the first case, a 6-month old infant developed an unspecified sickness 2 days post mother's vaccination. The outcome of the event sickness was recovered, and no causality assessment was provided. The second case, a 3-month old infant developed an unspecified illness and required hospitalization for 6 days post exposure via breast milk (>7 days latency). The event outcome was reported as 'recovering' and no causality assessment was provided.

## 4. SUMMARY AND CONCLUSION

The cases reviewed above are indicative of what is in the Pfizer safety database as of 28 February 2021. The sponsor (Pfizer/BioNTech) will continue to monitor and report on all pregnancy exposure and lactation cases. It is important to note that the spontaneous safety database is intended for hypothesis generation and not hypothesis testing.

# Document Approval Record

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