

PROTOCOL

COVID-19 Vaccine Safety, Spontaneous abortion (SAB) and Stillbirth in the Vaccine Safety
Data Link

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MONTHLY SPONTANEOUS ABORTION AND STILLBIRTH SURVEILLANCE AND COVID-19 VACCINE EXPOSURES

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Protocol Change History

Version	Date	Change
1.0	1/19/2021	N/A – Original protocol
1.1	1/26/2021	Minor edits to background, description of approach in response to comments from CDC
1.2	3/1/21	Updated chart review form to add question on COVID-19 testing during pregnancy and added background on Ad26.COV2.S (Janssen COVID-19 vaccine)
1.3	3/18/21	Minor edits to inclusion and exclusion criteria (replaced LBORSB with LBANDSB); also minor edits to chart review form
1.4	4/13/21	Minor edits to inclusion / exclusion criteria (enrollment from 2 months prior to LMP through pregnancy outcome or enrollment after 12/15/2020 and allowing up to 60 day gap after the last enrollment stop date for stillbirth surveillance and allowing 30 day enrollment gap for SAB surveillance)
1.5	4/28/21	Minor edits/updates to background based on feedback from CDC, fixed typo in Figure 2

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LIST OF ABBREVIATIONS

ACIP = Advisory Committee on Immunization Practices

ACOG = American College of Obstetrics and Gynecology

DPA = dynamic pregnancy algorithm

EDD = estimated delivery date

EUA = emergency use authorization

GADx = gestational age specific ICD-10-CM codes

IUFD = intrauterine fetal demise

LBANDSB = live birth and stillbirth, *DPA outcome applied for stillbirths occurring in multiple gestation pregnancies, when at least one fetus survives to a live birth*

LBORSB = live birth or stillbirth, *DPA outcome for pregnancies when a delivery is identified (usually based on procedural codes) but outcome of delivery cannot be confirmed*

LMP = last menstrual period

SAB = spontaneous abortion

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

SB = stillbirth

VSD = Vaccine Safety Datalink

ABSTRACT

Pregnant women were excluded from COVID-19 vaccine clinical trials and thus data to date on the safety of COVID-19 vaccines in pregnancy is limited. Two COVID-19 mRNA vaccines are now available in the United States and the first adenovirus vector vaccine was just approved under emergency use authorization (EUA) and pregnancy is *not* a contraindication to vaccination. As such there is an urgent need for outcome data following use of COVID-19 vaccines in pregnant populations. This protocol is the first phase of our work on COVID-19 vaccine safety, spontaneous abortion (SAB) and stillbirth surveillance. In this phase we describe our approach for 1) establishing monthly surveillance of stillbirths occurring following COVID-19 vaccine exposures during pregnancy, and 2) conducting monthly case-control surveillance of SABs. Eligible SABs will be frequency matched by maternal age group, receipt of prenatal care and calendar month to ongoing pregnancies at a similar stage of gestation to estimate the odds of COVID-19 vaccine exposure in the 28 days prior to an SAB. The stillbirth and SAB surveillance will be conducted for the period December 2020 – April 2023.

INTRODUCTION

Human infection with SARS-CoV-2, the virus that causes COVID-19, was first described in Wuhan, China in December 2019.¹ The first reported U.S. COVID-19 case was described in January 2020 in Seattle, WA.² Given lack of pre-existing immunity to the virus, asymptomatic transmission, along with other challenges in containment, there has been subsequent exponential worldwide spread of infection. In March 2020, the World Health Organization designated COVID-19 as a global pandemic. Worldwide, as of January 14, 2021 over 93 million people have contracted COVID-19 and there have been nearly 2 million deaths due to COVID-19. To date, approximately one-fourth of cases and one-fifth COVID-19 deaths have occurred in the U.S.³ The COVID-19 pandemic has profoundly impacted our economy, education, and nearly all aspects of day-to-day life.

Even with the rapid spread of COVID-19 disease, most countries, states, and regions are still far from achieving herd immunity.^{4,5} As such, protection from COVID-19 disease through vaccination will be necessary to fully re-open society without continued widespread outbreaks. Since the SARS-CoV-2 genome sequence was first published in January 2020, the race to develop and test a vaccine has been underway. In published data from their Phase III trial, including a median of 2 months of follow-up, the Pfizer-BioNTech COVID-19 (BNT162b2) vaccine had 95% efficacy in preventing symptomatic COVID-19 disease and vaccine-related side effects were consistent with other vaccines.⁶ Similarly, the Moderna vaccine (mRNA-1273) has been shown to have 94% efficacy for preventing symptomatic COVID-19 disease.⁷ Given the ongoing pandemic, the benefits of vaccination were presumed to far outweigh the risks and on December 11, 2020, the FDA issued the Pfizer-BioNTech COVID-19 vaccine an Emergency Use Authorization (EUA) for use in the United States.⁸ On December 12, 2020, the Advisory Committee on Immunization Practices (ACIP) issued recommendations regarding use of this vaccine in individuals 16 years and older.⁹ Subsequently, the FDA also issued an EUA for the Moderna vaccine for use in adults 18 years and older in the United States. On February 27, 2021, the FDA approved a third COVID-19 vaccine, developed by Janssen and using an adenoviral vector, known as Ad26.COV2.S. Additional COVID-19 vaccines are currently in Phase III trials. To date, clinical trials of the COVID-19 vaccines have been limited to non-pregnant adults. Pregnancy testing was conducted prior to each vaccine dose and thus vaccine exposures during

pregnancy were limited to pre-pregnancy or very early in pregnancy, prior to a positive pregnancy test. At the time of EUA submission, Pfizer-BioNTech reported to FDA on 23 pregnancies in the Phase II/III pivotal trial. Of these 12 were in the vaccine group and 11 in the placebo group. Among the vaccine group, 4 were vaccinated prior to their LMP (peri-pregnancy), 4 within 30 days after their LMP, and none were vaccinated later in pregnancy. One spontaneous abortion (SAB) was reported in the placebo group. To date, outcomes have not been reported among the remaining 22 pregnancies. The EUA Prescribing Information states, “Available data on Pfizer-BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.” Nevertheless, pregnancy is *not* a contraindication for vaccination. Similarly, Moderna reported to the FDA that as of December 2, 2020, there were 13 pregnancies among women in their pivotal Phase 3 trial, 6 in the vaccine group and 7 in the placebo group. There was one SAB and one therapeutic abortion in the placebo group. An additional pregnancy in the placebo group was lost to follow-up. The remaining pregnancies in this trial were ongoing as of December 2020. At the time of EUA submission for Ad26.COV2.S, there were 8 pregnancies reported including 1 SAB in a woman who had received the vaccine.

There is increasing evidence regarding the potential for SARS-CoV-2 infections during pregnancy to increase risks for morbidity in pregnant women and to be associated with adverse birth outcomes.¹⁰⁻¹² Despite the lack of comprehensive data on vaccine safety in pregnancy, the known risks of COVID-19 infection might potentially outweigh the unknown risks associated with COVID-19 vaccination. The American College of Obstetrics and Gynecology (ACOG) broadly supports that COVID-19 vaccines be available for use in pregnant women and that pregnant women not be denied vaccination when they are eligible, based on occupational or other risks for COVID-19 and CDC prioritization.^{13,14}

Now that multiple COVID-19 vaccines are authorized for use in the U.S., pregnant women who are included in phase 1a and 1b allocation groups are allowed to receive COVID-19 vaccination if they choose. Pregnancy is a high-risk category included in phase 1c allocation, and both inadvertent and intentional vaccination during pregnancy is likely to occur.¹⁴ As of February 28, 2021, a total of 35,691 v-safe participants reporting COVID-19 vaccination identified as pregnant.¹⁵ Intrauterine fetal demise (IUFD), including SAB or fetal demise before 20 weeks gestation, and stillbirth, or fetal demise at ≥ 20 weeks’ gestation, have been identified as important outcomes to be evaluated when evaluating the safety of vaccines in pregnancy.^{16,17} The Vaccine Safety Datalink (VSD), established in 1990, is a collaboration between the U.S. Centers for Disease Control and Prevention (CDC) and eight large health care organizations.¹⁸ With data on 3% of the U.S. population, automated identification of pregnancies, the availability of detailed electronic health record (EHR) clinical data, and comprehensive vaccine data, the VSD provides a robust infrastructure for monitoring SAB and stillbirth following COVID-19 vaccination in pregnancy.^{19,20}

In this phase 1 protocol we propose approaches to provide interim descriptive data on COVID-19 vaccinations and stillbirth, along with estimates of potential risks for SAB following COVID-19 vaccination, using a frequency matched case-control approach. This approach will provide timely, but limited data; the stillbirth cases we report will all be exposed to a COVID-19 vaccine, and no comparisons to unexposed or live births will be made. The SABs will not be chart confirmed and thus there is potential for outcome misclassification and for misclassification of the timing of any vaccine exposures in relation to fetal demise.

Given these limitations, in a future, phase 2 protocol we are planning to evaluate COVID-19 vaccine exposures in pregnancy and SABs and stillbirths through a rigorous case-control approach, with all eligible pregnancies ending in stillbirth or SAB undergoing chart review and expert adjudication, and optimal approaches to individual matching of cases and controls. In the future evaluation of SABs, we will chart review and adjudicate all SAB outcomes. In the future evaluation of stillbirths, we will use eligible stillbirths chart reviewed as part of this proposal, along with additional eligible stillbirths in the VSD during the same time period without known COVID-19 vaccine exposures. Given the lag for these SAB and stillbirth cases to accrue and then for chart review and adjudication to be completed, findings from this comprehensive, individually matched case-control surveillance will not be available for at least 2 years.

OBJECTIVES

1. On a monthly basis and with case confirmation through chart review and adjudication, to identify and describe characteristics of stillbirths in the VSD following a COVID-19 vaccine exposure during pregnancy (from pregnancy start or last menstrual period (LMP) through delivery date)
2. On a monthly basis and using automated data alone, to conduct case-control surveillance of all eligible SABs frequency-matched by maternal age group, receipt of prenatal care and calendar month compared to ongoing pregnancies at a comparable gestational age, in order to estimate odds of COVID-19 vaccine exposure in the 28 days prior to SAB. Analyses will be stratified by vaccine type (e.g. mRNA, viral vector, or recombinant protein) and by vaccine dose (e.g. first, second, or second during the 28 day interval).

SURVEILLANCE DESIGN

STILLBIRTH CASE SURVEILLANCE

Stillbirth, or intrauterine fetal demise at 20 weeks' gestation or later, is an important yet rare outcome, occurring at a background rate of approximately 5 per 1,000 live births in the VSD.¹⁹ In a prior VSD case-control study evaluating stillbirth following maternal vaccination, in order to have sufficient power, the study included stillbirth cases occurring over nearly four years. Given the need to conduct more timely surveillance, we propose that while waiting for stillbirth cases to accrue following the EUA for the COVID-19 vaccines, we will focus surveillance on the identification, chart review, and adjudication of stillbirth cases occurring following COVID-19 vaccine exposures. These cases will inform our understanding of potential vaccine-related risks, and will help us estimate power for the future, phase 2, case-control study of stillbirths.

Objective 1: Observational case series of stillbirths with maternal COVID-19 vaccine exposures occurring from pregnancy start (or LMP) through date of fetal demise. Stillbirth cases will accrue from December 15, 2020, following availability of COVID-19 vaccines in the VSD population, through April 30, 2023, with case ascertainment updated on a monthly basis. Potential stillbirth cases for chart review will be identified through the VSD's dynamic pregnancy algorithm (DPA) and stored in the DDF PREGEPS file. Pregnancy outcomes and gestational age at stillbirth will be confirmed through chart review and adjudication. Dates for case accrual may be modified based on accrual rates and review of findings with CDC.

CASE-CONTROL SAB SURVEILLANCE

Spontaneous abortion, or fetal demise before 20 weeks' gestation in a confirmed intrauterine pregnancy occurs in up to 15% of pregnancies and is an important safety outcome following vaccine exposures early in pregnancy.¹⁷ Recent modifications to how pregnancies are identified in the VSD using automated approaches, including the development and validation of the DPA, with the incorporation of EDD and LMP data and weekly data updates, have made near-real time surveillance of SABs and comparisons to ongoing pregnancies a possibility. As SAB is a common pregnancy outcome, we believe that evaluating vaccine exposures among frequency matched SABs and ongoing pregnancies is feasible and will allow for timely estimation of any increased risks for SAB following COVID-19 vaccine exposures. Nevertheless, findings from this SAB surveillance will be exploratory and require follow-up with a definitive, case-control study.

Objective 2: Observational case-control surveillance of SABs, frequency-matched by maternal age group, receipt of prenatal care and calendar month, to ongoing pregnancies at a similar stage of gestation, will be conducted. Eligible SAB cases and ongoing pregnancies occurring from December 15, 2020 - April 30, 2023, will be identified from the automated DPA with monthly updates. The odds of exposure to a COVID-19 vaccine in the 28 days prior to SAB among SAB cases will be compared to the odds of exposure to a COVID-19 vaccine among ongoing pregnancies in the VSD population in the 28 days prior to an assigned index date, such that case and control exposure windows are at similar gestational ages and that we are comparing women of similar age. Details regarding the approach to assigning a gestational week for ongoing pregnancies, and frequency matching based on estimated gestation age are described in Figure 1, below. Vaccine exposures will be stratified by vaccine dose (first, second, or second in 28 day interval) and by vaccine type (mRNA, viral vector, or recombinant protein).

DATA SOURCES

Data for Objective 1 and Objective 2 surveillance will come from standardized VSD DDF files, created by all participating sites and consistent with the VSD data dictionary. Pregnancies will be selected from the PREGEPS file, COVID-19 vaccine exposures will be identified using the DDF VACCINE file, with vaccines identified primarily from CVX Codes. We will also include vaccines identified by sites through CPT® or GPI codes, if available in the DDF Vaccine files. CONSTANT, ENROLL, INPT, OUTPT, AND PROCDRE files from the DDFs will also be used. The MORT and ancillary death file will be used, if available, to identify any pregnancies lost to follow-up due to maternal mortality.

All eligible pregnancies (ongoing and those ending in live births, stillbirths or SABs) will be identified in near-real time using the DPA. The DPA applies a hierarchical approach based on available diagnostic and procedure codes to identify pregnancies, and then assigns pregnancy start and end dates, or classifies pregnancies as ongoing. Additional data, including EDD, LMP, and gestational age specific ICD-10-CM codes (GADx) are used to assign gestational age for completed or ongoing pregnancies. Outcome specific default gestational ages are used when this specific gestational age data is not available. The DPA is an adaptation of the pregnancy episodes algorithm (PEA)²¹ that has been validated for identifying pregnancies ending in live birth and non-live birth outcomes. Of note, the DPA allows for the accurate identification of ongoing pregnancies with subsequent live birth outcomes 6 or more months prior to birth. [manuscript under review]

SURVEILLANCE POPULATION

The source population for surveillance of SAB and stillbirth following COVID-19 vaccine will be pregnant women at 8 VSD sites: Kaiser Washington, Kaiser Permanente Northwest, Kaiser Permanente Northern California, Southern California Kaiser Permanente, HealthPartners, Marshfield Clinic, Denver Health, and Kaiser Permanente Colorado. Detailed inclusion and exclusion criteria by objective are described below.

Objective 1 – Descriptive case series of stillbirths with COVID-19 vaccine exposures: Women 16-49 years of age at pregnancy outcome date, identified as having a stillbirth outcome from December 15, 2020 to April 30, 2023, and a COVID-19 vaccine exposure

Criteria for inclusion in chart review:

- DPA pregnancy outcome stillbirth (SB), live birth and stillbirth (LBANDSB), or SAB at 18 weeks' gestation or later (based on automated EDD, LMP, or gestational age specific ICD-10-CM codes) with outcomes occurring between December 15, 2020 – April 30, 2023. SABs identified from the DPA to occur at 18 or 19 weeks' gestation are included in the chart review to increase sensitivity, as some may be reclassified as stillbirths or intrauterine fetal demise at 20 weeks' gestation or later following chart review and adjudication.
- COVID-19 vaccine exposure during pregnancy or within 28 days of estimated pregnancy start or LMP. Pregnancies within 28 days of LMP are included for chart review in order to increase sensitivity for identifying all during pregnancy exposures, accounting for possible errors in dating from automated DPA data.
- One or more prenatal visits in health system
- Continuous insurance enrollment from 2 months prior to LMP through pregnancy outcome date, *or* enrollment after 12/15/2020, and allowing for an administrative gap of up to 60 days

Objective 2 – Frequency matched case-control evaluation of SABs: Women 16-49 years with a pregnancy between December 15, 2020 and April 30, 2023.

Inclusion criteria:

- DPA identified ongoing pregnancies or with one of the following pregnancy outcomes: live birth, SB, LBANDSB, SAB, identified on a monthly basis
- Continuous insurance enrollment, allowing for a 30-day gap, from 3 months prior to LMP through end of pregnancy or date of DDF closest to date of monthly surveillance for ongoing pregnancies
- Monthly surveillance of ongoing pregnancies will include those at an estimated gestational age of less than 20 weeks at the month of surveillance

Exclusions:

- Pregnancies with other non-live birth outcomes, including ectopic pregnancy, gestational trophoblastic disease or therapeutic abortion
- Pregnancies in women ≤ 15 years (not currently eligible for COVID-19 vaccination)
- Pregnancies resulting from assisted reproduction, from diagnostic or procedure codes

OUTCOMES

CHART REVIEW OF STILLBIRTH CASES

Suspected stillbirth cases with potential COVID-19 vaccine exposures during pregnancy identified through automated approaches, will be selected for chart review and expert adjudication. The DPA assigns gestational age based on available data including EDD, LMP and GADx. If these data are not available, the DPA assigns a stillbirth to occur at a default gestational age of 28 weeks' gestation. Adjudicated gestational age may differ from that available from the automated data. In addition, SABs occurring at 18 or 19 weeks' gestation based on automated data may be reclassified as stillbirths on adjudication. In order to identify all stillbirths with COVID-19 vaccine exposures during pregnancy, we will cast a wider net for chart review and adjudication, including vaccine exposures up to 28 days prior to LMP and including late SABs, at 18 or 19 weeks' gestation.

Goals of the chart review and adjudication are:

1. To confirm the pregnancy outcome to be a stillbirth (IUID at ≥ 20 weeks' gestation consistent with ACOG definitions).²²
2. To distinguish antepartum versus intrapartum fetal demise, defined according to the Brighton Collaboration definition of stillbirth, similar to our prior work.¹⁶
3. To determine the date and gestational age at fetal demise, utilizing available medical records, ultrasound reports with a focus on first trimester ultrasound, fetal autopsy and pathology reports, and health care encounter notes. As in prior work, pregnancy dating will be confirmed based on a predetermined hierarchy, using the physician-determined gestational age at delivery, estimated delivery date as reported closest to the time of delivery, and last menstrual period date in cases where the first two were not available.¹⁹
4. To identify possible etiologies for the stillbirth, including but not limited to: infections, fetal malformations, chromosomal abnormalities, complications of labor and delivery, complications of the umbilical cord or placenta, and maternal comorbidity.

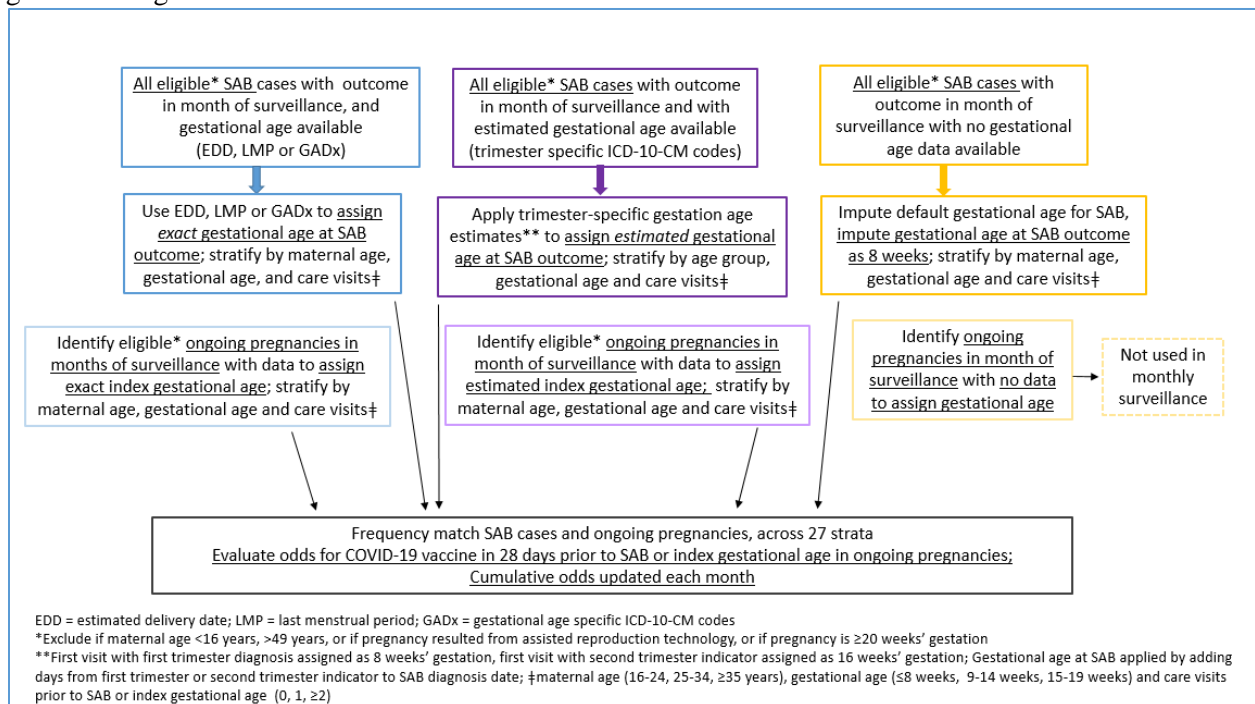
All chart reviews and adjudications will be recorded in REDCap, a web-based system for secure data capture, using standardized forms.²³ Data to be collected through chart abstraction will include: EDD, LMP, and maternal characteristics not available from automated data. Redacted results of ultrasounds, pathology testing, and selected prenatal and postpartum visit notes and laboratory tests will also be uploaded into REDCap. In order to facilitate timely completion of chart review, we are requesting limited data entry at sites. Please see chart abstraction form at end of protocol for more detail. Drs. Lipkind, Reddy, Greenberg, and Sheth, obstetricians with prior experience conducting stillbirth case adjudication, will adjudicate all stillbirth cases.

SAB CASES and CONTROLS

Objective 2: SAB cases will be identified from automated data. For pregnancies ending in SAB, the DPA assigns gestational age based on available data including EDD, LMP and GADx. If these data are not available, the DPA assigns the SAB to occur at 10 weeks' gestation. We will identify prenatal care visits, including supervision of care, pregnancy complications, and ultrasounds with an associated trimester of care to estimate gestational age for SABs occurring after prenatal care. If no prenatal care is received prior to the SAB outcome date, and no information on gestational age (LMP, GADx, and EDD) is available, we will impute the

gestational age at SAB to be 8 weeks. For SABs with one or more prenatal supervision visits but no information on gestational age, we will assign the first prenatal supervision visit as occurring at 8 weeks' gestation and we will re-assign the gestational age at SAB by adding the number of days after this first prenatal supervision visit. Using this approach in HealthPartners DDF data for November 2020, we were able to date 57% (12/21) of SABs with no information on gestational age. These methods will be adapted following exploration of similar data for all VSD sites. (Figure 1, below) Controls, will be ongoing pregnancies at similar gestational age during the same calendar month. Pregnancies that subsequently end in stillbirth or a late SAB would still be eligible controls for SABs occurring in early pregnancy if their pregnancy is ongoing during the index month. Pregnancy start date is assigned in the DPA based on a hierarchical algorithm using EDD, ICD-10-CM gestational week diagnostic codes (GADx), and LMP. However for ongoing pregnancies, dating may be missing in 30% of pregnancy episodes (internal DDF data from HealthPartners for November 2020). To increase the availability of dating for ongoing pregnancies, for a sample of pregnancies from all VSD sites, we will first pull pregnancy indicators with first, second, or third trimester identifiers from the look up tables used by the VSD's dynamic pregnancy algorithm (DPA) including supervision of normal or high-risk pregnancy, care for pregnancy complications with indication of trimester, GADx, or a CPT® code for first trimester obstetric ultrasound. We will select the first pregnancy indicator and date for this indicator for each identified pregnancy. For pregnancy indicators without a specified gestational age, we will assign an 8-week gestational age for the first diagnosis with a first trimester indicator, an 18-week gestational age for the first diagnosis with a second trimester indicator and a 29 week gestational age for the first diagnosis with a third trimester indicator. Gestational age assignments by trimester are informed by data exploration at HealthPartners and may be adjusted following review of data for all VSD sites.

Figure 1. SAB monthly surveillance and frequency matching with ongoing pregnancies at similar gestational age



For HealthPartners, applying this additional gestational age imputation, we were able to date 50% of ongoing pregnancies with no pregnancy start date in the DPA. In addition, by restricting the sample to pregnancies with at least two pregnancy indicators, 95% of ongoing HealthPartners pregnancies in the DPA for November 2020 would have a pregnancy start date. We will repeat this analysis for a sample of pregnancies from all sites (see data management section). We will then apply this additional gestational age dating to calculate an estimated pregnancy start. We may reevaluate pregnancy dating, inclusion criteria and frequency matching for the SAB case-control surveillance after exploring pregnancy data from all sites.

VACCINE EXPOSURES

VACCINE EXPOSURE IN STILLBIRTH CASES

Objective 1: All COVID-19 vaccines will be identified from standardized VSD DDF VACCINE files. Vaccines will be assigned as occurring during pregnancy and prior to fetal demise based on adjudicated date of fetal demise and adjudicated gestational age at fetal demise as occurring during pregnancy and stratified as first, second or third trimester. Exposure to vaccination will be further classified by dose (first, second, and second during the 28 day interval) and vaccine type (mRNA, viral vector, or recombinant protein).

VACCINE EXPOSURE IN SAB CASES AND PREGNANCY CONTROLS

Objective 2: All COVID-19 vaccines will be identified from standardized VSD DDF VACCINE files. For cases, exposures of interest will be COVID-19 vaccines administered within 28 days of the automated SAB outcome date. For controls, the exposure will be COVID-19 vaccines administered within 28 days of their index gestational week. The assignment of gestational week is described in Figure 2, below.

COVARIATES

Variables identified from automated data will include maternal age, and race-ethnicity.

For Objective 1, stillbirth descriptive case series, additional covariates will be collected through chart review including: prior pregnancy history, smoking status, pre-pregnancy obesity. We will also collect race/ethnicity if not available in the automated data. These variables will be used for descriptive purposes.

For the Objective 2 analyses, SAB case-control analyses, we will further classify cases and controls based on maternal age, number of antenatal pregnancy supervision visits prior to the SAB or index gestational age (0, 1, ≥ 2), gestational week at outcome or gestational age reached during the study month for controls (≤ 8 , 9-13, 14-19 weeks) and study month.

Prenatal care visits will include virtual or in-person pregnancy supervision visits or care visits for comorbidities in pregnancy, or a first trimester obstetric ultrasound. We will retain only the first encounter in each week.

ANALYSIS AND REPORTING

STILLBIRTH REPORTING

Objective 1. Reporting for Objective 1 is planned to be descriptive only. Potential stillbirth cases with COVID-19 vaccine exposures for chart reviews will be identified on a monthly basis, with a one month lag allowing for data maturation (e.g. stillbirths occurring between June 1 and June 30, 2021, will be identified through an automated data pull on August 1, 2021). On a monthly

basis, we will provide CDC and participating sites with updates regarding potential and confirmed stillbirth cases, as outlined in Table 1, below. Based on the time needed for data maturation, and for chart review and adjudication, our data on adjudicated stillbirths with during pregnancy or peri-pregnancy exposures will lag 2-3 months following the date of these outcomes. The unadjudicated, rough estimates of stillbirths and stillbirths following COVID-19 vaccine exposures will be subject to a lag of 1-2 months following the date of these outcomes.

Table 1. Mock-up of reporting for stillbirth case surveillance

Stillbirth outcomes by date	Stillbirths or SABs at 18 or 19 weeks' identified by DPA (N)	Stillbirths or SABs at 18 or 19 weeks' with COVID-19 vaccine* from DPA (N)	Stillbirths excluded (no EHR data, other adjudicated outcome or no COVID-19 vaccine during pregnancy, prior to fetal demise (N)	Adjudicated stillbirths with COVID-19 vaccine exposure <u>during pregnancy and prior fetal demise (N)</u>
Dec 2020				
Jan 2021				
...				

*Exposures estimated from dynamic pregnancy algorithm (DPA) to be from 28 days prior to last menstrual period (LMP) through stillbirth outcome date; EHR = electronic health record

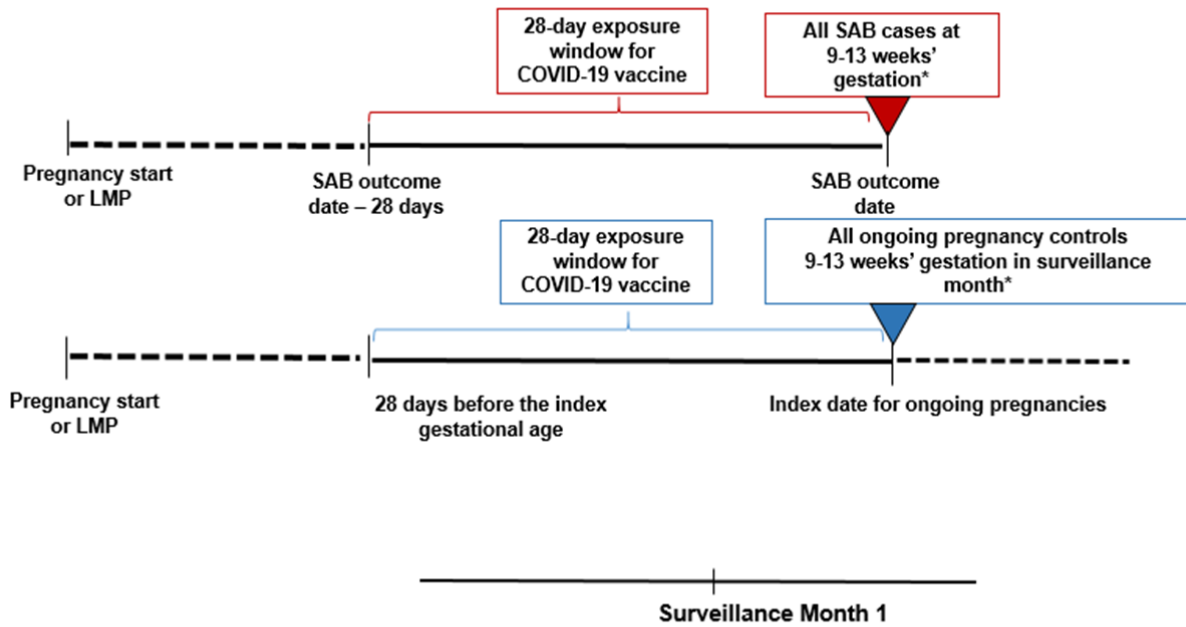
For pregnancies ending in a stillbirth and exposed to the vaccine, confirmed through chart review and adjudication, along with monthly counts, we will only report maternal and pregnancy characteristics once we have at least 5 cases in a cell, to avoid sharing of individually identifiable data. Descriptive characteristics include: maternal age at the time of the stillbirth (<25, 25-34, ≥35 years), race-ethnicity (Asian, Black, Hispanic, white, other), gestational age at stillbirth (20-24, 24-28, ≥28 weeks), gestational timing of vaccination (first trimester, second trimester, or third trimester), whether the stillbirth occurred antepartum or intrapartum, and whether the stillbirth had an identified or suspected etiology.

SAB CASES AND CONTROL FREQUENCY MATCHED ANALYSIS

Cases and controls will be frequency matched by maternal age group (<25, 25-34, ≥35 years), number of antenatal pregnancy supervision visits prior to the SAB or index gestational age (0, 1, ≥2) and gestational age strata (≤8, 9-13, 14-19 weeks' gestation) at time of the SAB or based on gestational week reached in the surveillance month for controls, study month, and site. At each data pull, we will classify cases and controls for all cumulative study months on the matching strata. Note that controls may be eligible to contribute data to more than one matching strata based on the gestational age reached during the surveillance month. See Figure 2 for matching diagram.

We will estimate the odds ratio of receiving the COVID-19 vaccine in the 28-day risk window. A binomial model with logit link and robust variance using a generalized estimating equation will be used to account for the correlation introduced by having the same controls in different strata. We will report as odds ratios with 95% confidence intervals. Analysis will be presented for the following subgroups by vaccine type (e.g. mRNA, viral vector, or recombinant protein) and by vaccine dose (e.g. first, second ever, and second during the 28-day interval).

Figure 2. Frequency matched case-control method for the first month, an example for SAB cases and ongoing pregnancies at 9-13 weeks' gestation during the month of surveillance.



*Use exact gestational age dating if available; if only estimated gestational age available, assign index gestational age of 8, 12, 16 weeks for gestational age groups ≤8, 9-13, 15-19 weeks, respectively

ALTERNATIVE METHODS

For objective 2, the frequency matched SAB-control surveillance, alternative methods may be considered for defining inclusion of cases and controls and matching procedures, once we have completed the exploratory analysis to better date pregnancies, and once we have completed the first month of surveillance.

LIMITATIONS

Limitations to the proposed surveillance should be noted. Prior VSD work on near real time surveillance of SAB and stillbirths has been challenging due to imprecision in real time gestational age dating and outcome confirmation. This prior work was conducted before the development of the DPA, which includes weekly updates and use of EDD, LMP and gestational week ICD-10 codes (GADx) to date pregnancies. In addition, we will take advantage of additional data to assign a gestational age based on trimester-specific ICD-10-CM diagnoses. For the proposed case-control SAB surveillance, cases will not be confirmed by chart review. Also, for both early SABs and ongoing pregnancies, gestational age will not be confirmed through chart review of ultrasound and other clinical data and so will be an estimate based on available data (EDD, LMP, GADx, or trimester-specific diagnostic or procedure codes), as described above. Risks for SAB also vary by gestational week and so there is potential for imprecise pregnancy dating to introduce bias if the vaccine exposure windows differ by gestational age. In addition, data on SABs and ongoing pregnancies may differ by month and by site, based on variation in pandemic related care patterns. Nevertheless, as described by McClure and

colleagues in their VSD study #288 final report, if the misclassification of SAB outcomes or gestational age dating is non-differential, it will widen confidence intervals or reduce power to detect a signal, but would be unlikely to bias findings. Second, stillbirths are uncommon, occurring in approximately 5 per 1,000 births. As such the accrual of cases with COVID-19 vaccine exposures is likely to be slow and limit inferences or comparisons that could be drawn from our descriptive surveillance. Finally, exclusions such as receipt of assisted reproductive technology (ART) may be missed based on diagnostic codes alone. Nevertheless, there is an urgent need for data to inform pregnant women and their providers deciding whether to receive a COVID-19 vaccine during pregnancy or following an inadvertent exposure. The methods we propose here will provide early estimates of potential risks. These studies will be followed by comprehensive, individually matched case-control studies with chart review and adjudication of all SAB and stillbirth outcomes. Furthermore, if cases are eligible, the stillbirth chart reviews we conduct will be accessed for the subsequent stillbirth case-control study.

DATA MANAGEMENT PLAN

The VSD team at HPI will be responsible for data management activities, including data extraction, surveillance evaluation documentation and archival. Once the initial cohort of eligible pregnancies has been identified, additional exclusions will be applied at HPI. Data will be exchanged using methods that will assure security, primarily through the VSD distributed data model (DDM). The DDM allows all individual level standardized data files to reside at the health plan, and ownership is retained by the VSD site. The DDM maintains confidentiality of the health plan's data by utilizing encrypted and secure methods. HPI will write all relevant SAS code and will share it with CDC and participating sites for approval prior to data extraction. For Objective 1, on a monthly basis we will pull individual level data on pregnancies ending in a stillbirth based on inclusion criteria; additional exclusion criteria for chart review will be applied at HealthPartners.

For the Objective 2 case-control surveillance, we will pull individual level data for all SAB, ONGOING, SB, LB, AND LBANDSB pregnancies identified in the PREGEPS file with the pregnancy outcome date or expected outcome date on or after 12/15/2020, or missing pregnancy outcome date for the first two data pulls to evaluate algorithms to date pregnancy beginning dates, and development of matching strata. Once the study programs are finalized, we will consider two strategies, analysis based on individual level data or data in tabular form. If possible, we will consider extracting data in a tabular form.

In order to explore the use of trimester-specific pregnancy indicators (ICD-10-CM or CPT® codes) across VSD sites, to inform our approach to optimize dating for ongoing pregnancies and pregnancies ending in a SAB, and review the inclusion criteria and matching procedures, we are planning a single data extraction for pregnancies ending after December 1, 2020 or ongoing at the time of data extraction, excluding ectopic pregnancy, therapeutic abortion, or gestational trophoblastic disease. For these women, we will pull data from the following DDF files, CONSTANT, ENROLL, INPT, OUTPT, PROCDRE, PREGEPSD, EDD and LMP. We will extract all pregnancy-related ICD-10-CM codes from the pregdiag201808 lookup table, and a subset of pregnancy-related CPT® codes from the PREGCPT201808 lookup table. Data will include records with dates after January 1, 2020.

Archiving will be overseen by the HPI Project Manager and Data Manager and will include the updated surveillance evaluation protocol, work plans, programs, IRB documents, SAS output, manuscripts, surveillance evaluation and analysis documentation, and analysis data sets. The archival process will clearly identify and permanently save those files that were used to produce the interim and final reports and manuscripts.

Data Sources: Eligible pregnancies for women 16-49 years will be continually identified from the DDF PREGEPDS files. COVID-19 vaccine exposures will be identified using the DDF VACCINE file. CONSTANT, ENROLL, OUTPT, INPT, PROCDRE MORT and ancillary death if available files from the DDFs will also be used.

Table 3. VSD Data Files

VSD File	Purpose
CONSTANT	Basic demographics of population, VSD site
ENROLL	MCO membership start and stop dates to identify pregnant women with constant enrollment from 3 month prior to pregnancy start
VACCINE	Determine during pregnancy and pre-pregnancy vaccinations
INPT	Inpatient hospitalizations and diagnoses codes
OUTPT	Outpatient and ED visits and diagnoses codes
PROCDRE	Procedure diagnoses codes
PREGEPDS	Pregnancy episode file to identify eligible pregnancies
MORT	Mortality data

SITE RESPONSABILITIES

It is our hope that all VSD sites with appropriate data will participate, contributing both electronic and chart review data. We request that sites complete any assigned chart reviews within 2 weeks and that case adjudication is completed within 2 weeks of the completion of the chart reviews.

HUMAN SUBJECTS AND CONFIDENTIALITY

This surveillance protocol will be reviewed for a non-research determination in accordance with CDC policy. The protocol will also undergo a determination and IRB review if needed and as required by each participating VSD site. Data use agreements (DUA) will be entered into with participating sites as needed. As the lead site, the HP project manager will help coordinate obtaining IRB approvals and DUAs (where applicable) from each site. The privacy and confidentiality of all subjects will be strictly protected, according to standard VSD procedures. The risks to patient privacy and confidentiality are minimal. Only specific members of the surveillance team will have access to the data. Only VSD Participant IDs will be used; HP and Yale based teams will not have access to names or medical record numbers at other sites.

The surveillance project does not involve intervention or interaction with human subjects. We request to waive the requirement to obtain informed consent, parental permission, and assent for this surveillance project under 45 CFR 46.116(d). As an analysis of existing data collected for non-research purposes, this activity presents minimal risk to subjects, and use of patient data for this purpose will not adversely affect subjects' rights or welfare.

TIMELINE

Table 4. Timeline

Date	Description
December 19, 2020	Draft proposal to CDC and participating sites
January 19, 2021	Final protocol to CDC and sites
February 1, 2021	Submit data abstraction code for exploratory data pull to sites*
February 19, 2021	IRB approvals and DUAs completed, as needed
March 1, 2021	SAS code development/testing
March 19, 2021	Submit final data abstraction code to CDC and sites
April 19, 2021	Start monthly surveillance, and ongoing dissemination activities
April 19, 2023	Final surveillance, start end of surveillance analyses
June 19, 2023	Submit draft manuscript to CDC
August 19, 2023	Submit final manuscript to CDC
September 19, 2023	Archive of final datasets

*Program to be run as soon as approved by sites, as results needed to inform final program due on 3/19/21; Will await IRB approval as needed, based on site-based requirements.

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Stillbirth Abstraction form**GENERAL INSTRUCTIONS**

- DATA TO BE ENTERED DIRECTLY INTO REDCAP DATABASE
- ALL WOMEN SELECTED HAVE A SUSPECTED OR POSSIBLE STILLBIRTH BASED ON AUTOMATED DATA (DIAGNOSTIC OR PROCEDURE CODES)

PART A: DEMOGRAPHICS AND CHART SCREENING

A1. Abtractor ID: _____

A2. Abstraction date: __ / __ / __ - - - -

Questions A3 through A6 will be pre-populated in REDCap, from VSD automated files

A3. VSD study ID: _____

A4. Site:

- 1 SCK (Kaiser Southern California)
 2 NCK (Kaiser Northern California)
 3 KWA (Kaiser Washington)
 4 NWK (Kaiser Permanente Northwest)
 5 HPM (HealthPartners)
 6 MFC (Marshfield Clinic)
 7 KPC (Kaiser Permanente Colorado)
 8 DH (Denver Health)

A5. Date of pregnancy outcome: __ / __ / __ - - - -

A6. Mother's age at delivery: __ - years

A7. Please enter the mother's month and year of birth __ / ____ (to confirm in correct chart)

A8. Are there encounters with documented pregnancy information between the [ref diagnosis date - 90 days] and the [ref diagnosis date + 30 days] in the electronic medical record?

- 1 Yes
 2 No (**STOP abstraction**)

A9. Is a fetal demise (stillbirth or spontaneous abortion) documented in the medical record between [ref diagnosis date-30 days] and [ref diagnosis date + 30 days]? *Note for multiple gestation pregnancies, please mark as yes if there has been a demise of at least one fetus*

- 1 Yes (Continue with question A10)
 2 No (Continue with question A9.1)

A9.1 Please indicate the outcome of this pregnancy. (**STOP abstraction after completing A9.1**)

- 1 Ectopic pregnancy
 2 Elective / therapeutic abortion
 3 Live birth
 4 Ongoing pregnancy
 5 Pregnancy outcome not known

6 Other _____

A10. Was this a multiple gestation pregnancy? (e.g. twin, triplet, ...)

1 Yes (Continue with question A10.1)2 No (Continue with A11)

A10.1 Please indicate the type of multiple gestation pregnancy

1 Twin2 Triplet3 Quadruplet4 Other _____A10.2 Please indicate which fetus was a fetal demise (*mark all the apply*)1 Fetus A2 Fetus B3 Fetus C4 Other _____

Note, if a single fetal demise, for the remaining questions, please respond with respect to this fetus; If demise of two or more fetuses, can answer for the fetus that was first to be diagnosed as a fetal demise

A11. Please indicate the earliest date that a fetal demise was diagnosed (no fetal heart beat) based on pregnancy dating at that visit

__ / __ / ____ or date unknown

A12. Please indicate the estimated gestational age at fetal demise (date from A11)

__ weeks __ days or gestational age unknown

A13. Please indicate EDD (estimated delivery date) for this pregnancy

__ / __ / ____ or date unknown

A13.1 Please indicate date of last menstrual period (LMP)

__ / __ / ____ or date unknown

PART B: CLINICAL FINDINGS

B1. Please indicate delivery or pregnancy end date __ / __ / ____

B1.2 Was there spontaneous or induced labor, or was a D&C (dilation and curettage) or D&E (dilation and evacuation) or other surgical procedure performed?

1 Spontaneous

- 2 Induced
- 3 D&E
- 4 D&C
- 5 Other surgical procedure

B1.3 Was a heartbeat noted in the fetus after delivery?

- 1 Yes
- 2 No / not documented

B1.4 Was a resuscitation attempted after delivery? (Includes positive pressure ventilation, administration of oxygen, chest compressions or administration of epinephrine)

- 1 Yes
- 2 No / not documented

B1.5 Was fetal demise confirmed at delivery (Apgars = 0, 0; No spontaneous respirations)

- 1 Yes
- 2 No / not documented

PART C: MATERNAL LABORATORY TESTING

PLEASE INDICATE IF ANY OF THE FOLLOWING TESTS WERE PERFORMED DURING PREGNANCY OR IMMEDIATELY POSTPARTUM

C1. COVID-19 PCR at time of delivery

- 1 **COVID-19 PCR positive, redacted results uploaded**
- 2 COVID-19 PCR negative
- 3 COVID-19 PCR performed, results not available
- 4 COVID-19 not performed

C2. COVID-19 PCR during pregnancy, before delivery

- 1 **COVID-19 PCR positive, redacted results uploaded**
- 2 COVID-19 PCR negative
- 3 COVID-19 PCR performed, results not available
- 4 COVID-19 not performed

C3. Antiphospholipid antibody

- 1 **Antiphospholipid antibody abnormal, redacted results uploaded**
- 2 Antiphospholipid antibody performed, results within normal limits
- 3 Antiphospholipid antibody performed but records not available
- 4 Antiphospholipid antibody not performed

C4. Group B Strep Culture (GBS)

- 1 **GBS culture positive, redacted results uploaded**
- 2 GBS culture negative
- 3 GBS culture performed but records not available
- 4 GBS culture not performed

C5. Toxoplasmosis (serum antibody, IgG and IgM)

- 1 **Toxoplasmosis serum antibody abnormal, redacted results uploaded**
- 2 Toxoplasmosis serum antibody performed, results normal / negative
- 3 Toxoplasmosis serum antibody performed but records not available
- 4 Toxoplasmosis serum antibody not performed

C6. Cytomegalovirus or CMV (serum antibody, IgG and IgM)

- 1 **CMV serum antibody abnormal, redacted results uploaded**
- 2 CMV serum antibody performed, results normal / negative
- 3 CMV serum antibody performed but records not available
- 4 CMV serum antibody not performed

C7. Herpes Simplex (serum antibody, blood, skin culture or PCR)

- 1 **Herpes Simplex (serum antibody, blood, skin culture or PCR) abnormal, redacted results uploaded**
- 2 Herpes Simplex testing performed, results normal / negative
- 3 Herpes Simplex testing performed but records not available
- 4 Herpes Simplex testing not performed

C8. Syphilis (RPR, treponemal antibody testing (FTA-ABS))

- 1 **Syphilis (RPR or FTA-ABS) abnormal, redacted results for both tests uploaded**
- 2 Syphilis (RPR or FTA-ABS) performed, results normal / negative
- 3 Syphilis (RPR or FTA-ABS) performed but records not available
- 4 Syphilis (RPR or FTA-ABS) not performed

C9. Drug screening (urine or blood)

- 1 **Drug screening (urine or blood) abnormal for drug other than THC, redacted results uploaded**
- 2 Drug screening (urine or blood) performed, results normal / negative
- 3 Drug screening (urine or blood) performed but records not available
- 4 Drug screening (urine or blood) not performed

C10. Please indicate if cell-free DNA testing (NIPT) was performed with records available during this pregnancy (upload any available results)

- 1 **Yes and records available for uploading**
- 2 Yes, but records not available for uploading
- 3 No, cell-free DNA testing was not performed for this pregnancy

C11. Please indicate if first trimester screening (nuchal translucency ultrasound and blood tests) performed with records available during this pregnancy (upload any available results)

- 1 **Yes and records available for uploading**
- 2 Yes, but records not available for uploading
- 3 No, first trimester screening not performed for this pregnancy

C12. Please indicate if second trimester screening (quad screening or maternal serum alpha-fetoprotein (MSAFP) alone) performed with records available during this pregnancy (upload any available results)

- 1 **Yes and records available for uploading**
- 2 Yes, but records not available for uploading
- 3 No, second trimester screening not performed for this pregnancy

C13. Please provide any additional notes regarding abnormal laboratory testing during pregnancy or immediately postpartum, particularly if redacted results not available

PART D: PATHOLOGY FETAL KARYOTYPE SCREENING

D1. Please indicate if placental pathology performed with records available during this pregnancy

- 1 **Yes and records available for uploading**
- 2 Yes, but records not available for uploading
- 3 No, placental pathology not performed for this pregnancy

D2. Please indicate if fetal autopsy performed with records available during this pregnancy

- 1 **Yes and records available for uploading**
- 2 Yes, but records not available for uploading
- 3 No, fetal autopsy not performed for this pregnancy

D3. Please indicate if fetal karyotype performed with records available during this pregnancy

- 1 **Yes and records available for uploading**
- 2 Yes, but records not available for uploading
- 3 No, fetal karyotype not performed for this pregnancy

Note fetal karyotype may follow amniocentesis, chorionic villus sampling

Please uploaded redacted copies of all pathology and karyotype screening reports for this pregnancy

D4. Please provide any additional notes regarding pathology results, particularly if redacted results not available

PART E: ULTRASOUND

E1. Please indicate total number of ultrasounds with records available during this pregnancy

--

E2. Please provide any additional notes regarding ultrasounds, particularly if redacted results not available

PART F: CLINICAL ENCOUNTERS

F1. Please indicate total number of health care encounters (include prenatal and postnatal obstetric care visits, emergency department (ED) visits) with records available for the period [ref diagnosis date – 30 days through ref diagnosis date + 60 days]

--

F2. Please provide any additional notes regarding prenatal, 6-week postpartum, ED and delivery records, particularly if redacted results not available

PART G: DEMOGRAPHICS AND PRIOR HISTORY

G1. Race

- 1 Asian
- 2 Black or African American
- 3 Native American or Alaskan Native
- 4 Native Hawaiian or other Pacific Islander
- 5 White
- 6 Multiple
- 7 Unknown
- 8 Other _____

G2. Ethnicity

- 1 Hispanic
- 2 Non-Hispanic
- 3 Unknown

G3. Is maternal weight pre-pregnancy (during pregnancy or a pre-pregnancy adult height, measured at age 18 or older, or within past year for those 17 or younger) available?

- 1 Yes → G3.1
- 2 No → G4

G3.1 Is pre-pregnancy weight in pounds (lb) or kilograms (kg)

- 1 lb
- 2 kg

G3.2 Please enter weight _____

G4. Is maternal weight during first trimester available? (*if more than one, choose earliest first trimester weight*)

- 1 Yes → G4.1
- 2 No → G6

G4.1 Is first trimester weight in pounds (lb) or kilograms (kg)

- 1 lb

2 kg

G4.2 Please enter weight _____

G5. Is maternal weight height (within 12 months prior to pregnancy or during pregnancy) available?

- 1 Yes → G5.1
- 2 No → G6

G5.1 Is height in feet and inches or centimeters (cm)

- 1 Feet and inches
- 2 Centimeters

G5.2 Please enter height _____

G6. Is there evidence of maternal tobacco use in the medical record?

- 1 Mother documented cigarette smoker during pregnancy
- 2 Mother documented as cigarette smoker but unknown if during pregnancy
- 3 Mother documented as non-smoker
- 4 No information on smoking status available

G7. Number of prior pregnancies

- 1 None
- 2 1
- 3 2
- 4 3
- 5 4
- 6 5 or more

G8. Number of prior stillbirths

- 1 None
- 2 1
- 3 2
- 4 3 or more

G9. Please provide any additional notes regarding demographics, height and weight or prior pregnancy history here

Data from medical record to be redacted and uploaded (based on data entered in chart review)

1. Any abnormal laboratory tests noted and any available nuchal, quad, AFP, or cell free DNA screening (from Part C)
2. All pathology results for this pregnancy: fetal autopsy, fetal karyotype, and placental pathology report (from Part D)
3. Ultrasound reports: All available for this pregnancy if possible; If all ultrasounds are not available, priority is to include at least one official ultrasound between 8-14 weeks to establish dating, at least one official ultrasound between 18-22 weeks to evaluate for fetal anomalies, and all ultrasounds within 30 days of delivery (from Part E)
4. Clinical encounters: include notes from all prenatal or ED encounters from 30 days prior to delivery and include postpartum obstetric encounter and physician / obstetric note from delivery (from Part F)