Title:

Obstetrics Risk Assessment: Evaluation of Selection Criteria for Vaccine Research Studies in Pregnant Women

Abbreviated Title: Obstetrics Risk Assessment in Vaccine Research

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Conflicts of Interest:

Linda O Eckert : Site investigator: Novavax Trial. Received no personal funding for these activities

Christine E Jones: Investigator for clinical trials done on behalf of her institutions, sponsored by vaccine manufacturers, but receives no personal funding for these activities.

Alisa Kachikis: Site investigator: Novavax Trial but receives no personal funding for these activities. Advisory Boards on Maternal Immunization for GSK and Pfizer

Azucena Bardaji: None

Fernanda Tavares Da Silva. Employee of the GSK group of companies. FTDS owns restricted shares from the GSK group of companies

Judith Absalon: Employee of Pfizer

Caroline E. Rouse: None

Asma Khalil: Chief Investigator and local principal Investigator for GSK and Novavax Vaccines studies

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Institutional support for maternal clinical vaccine trials from BMGF, Pfizer, Novavax. Institutional support for training from Sanofi Pasteur

Institutional Grants from BMGF, Pfizer for maternal immunization projects.

Sonali Kochhar: none

Flor M Munoz: Has received Research Funding from: Novavax, GSK, Jansen. Has served as a member DSMB: Pfizer, Moderna. Consultant: CEPI, GSK, Sanofi

Keywords: Maternal immunization, vaccine, vaccine safety, obstetric and neonatal risk factors, clinical trial, clinical research, inclusion criteria, exclusion criteria, pregnant women

Abstract:

Vaccines designed for use in pregnancy and vaccine trials specifically involving pregnant women are rapidly expanding. One of the key challenges in designing maternal immunization trials is that developing exclusion criteria requires understanding and quantifying the background risk for adverse pregnancy outcomes in the pregnancy being studied, which can occur independent of any intervention and be unrelated to vaccine administration.

The Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project has developed and published case definitions and guidelines for data collection, analysis, and evaluation of maternal immunization safety in trials involving pregnant women. Complementing this work, we sought to understand how to best assess obstetric risk of adverse outcomes and differentiate it from the assessment of vaccine safety. Quantification of obstetric risk is based on prior and current obstetric, and maternal medical history. We developed a step-wise approach to evaluate and quantify obstetric and maternal risk factors in pregnancy based on review of published literature and guidelines, and critically assessed these factors in the context of designing inclusion and exclusion criteria for maternal vaccine studies. We anticipate this risk assessment evaluation may assist clinical trialists with study design decisions, including selection of exclusion criteria for vaccine trials involving pregnant women, consideration of sub-group classification, such as high or low risk subjects, or schedule considerations, such as preferred trimester of gestation for an intervention during pregnancy. Additionally, this tool may be utilized in data stratification at time of study analyses.

Words: 240

**Introduction**

Immunization of pregnant women, or maternal immunization, is a practical, evidence-based strategy to prevent severe morbidity and reduce mortality in mothers, neonates and young infants.1 Vaccine research requires careful assessment of safety and efficacy in all study participants. When administering a vaccine to pregnant women, safety evidence must encompass the mother, the developing fetus, and subsequently the neonate, infant, and the child. Accumulating this safety data with the ability to reliably measure potential adverse events of interest is improved by standardization of definitions of potential adverse events and data collection in a manner that is applicable across all resource settings.

With the goal towards broadening future maternal immunization trials, in 2014 the World Health Organization (WHO) convened a stakeholder meeting where key obstetric and neonatal terms were identified and prioritized for standardization of definitions.2 The Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project was established, and since 2014, GAIA,3 utilizing Brighton Collaboration methodology, has developed and published case definitions and guidelines for data collection, analysis, and presentation of maternal immunization safety data in trials involving pregnant women for twenty-one obstetric and neonatal terms.4 These case definitions and tools have been adopted in recent maternal immunization studies to evaluate maternal and neonatal outcomes, including use in a recent Phase III maternal immunization trial.5,6

Clinical trials in pregnant women are complex because, even in healthy pregnant women, adverse obstetric outcomes (such as fetal abnormalities, preterm birth, miscarriage, growth restriction and preeclampsia) occur and thus can also be anticipated to occur in the setting of a clinical trial, independent of the intervention. Many of the women who develop these problems do not have risk factors, making complications which occur in pregnancy difficult to predict. The risk of pregnancy complications can be, in part, informed by the background rates of these events in any given population. However, data on background rates of adverse pregnancy outcomes may not always be available.7

Hence, it is challenging for clinical investigators to know which prior and current pregnancy risk factors are appropriate study exclusion criteria. The selection of criteria for inclusion or exclusion of subjects in the study is among the more critical study design decisions. In early phase clinical trials, it is common to enroll the healthiest populations to minimize risk. As the product profile is better defined in later stage studies, a broader group of individuals are generally enrolled. By Phase 3, study participants more closely mirror the target population for the vaccine and are enrolled in larger numbers, and it is typical to have fewer exclusion criteria.

Currently, standardized guidance is lacking that may inform the choice of inclusion and exclusion of pregnant participants for any of the vaccine trial development phases. Understanding the obstetric risk of common inclusion and exclusion criteria may facilitate not only a more informed choice of inclusion and exclusion criteria in these clinical studies of vaccines in pregnant women, but also a tailored use of these criteria based on the phase of development (I-IV) of the vaccine.

In an effort to assist clinical investigators in maternal immunization trials, a GAIA Working Group with broad geographic and specialty representation was formed to evaluate the selection criteria that have previously been used to select women for participation in clinical trials of vaccines in pregnancy and to develop a strategy to help assess obstetric risks for designing maternal immunization trials. The overriding aim is to develop a consolidated evaluation and quantification of risk factors in pregnancy that would be useful to investigators in designing vaccine trials involving pregnant women. While this assessment is designed specifically for vaccine trials, it may also offer applicability for other interventions being assessed in pregnant women.

**METHODS**

We used several methods to identify the criteria previously used for inclusion and exclusion of study participants in studies of vaccines in pregnancy. We searched the National Institutes of Health U.S. National Library of Medicine ClinicalTrials.gov database to to identify current, completed or withdrawn studies of vaccines in pregnant women. Studies were identified the search terms “pregnancy”, “pregnant women”, “maternal”, “mothers”, “immunization”, “vaccination”, “vaccine”, “vaccines”, and a combination of the term “pregnancy” or “maternal” with specific vaccines including “influenza”, “tetanus”, “Tdap”, “pertussis”, “respiratory syncytial virus” , “RSV”, “group B streptococcus”, “GBS”, “pneumococcal”, “pneumococcus”, “meningitis”, “meningococcal”, “hepatitis”, “pandemic”, “seasonal”. All relevant studies listed in the ClinTrials.gov through 07 October 2018 were included. We identified a total of 43 interventional and 21 observational studies of vaccines in pregnant women. We abstracted and reviewed the complete list of inclusion and exclusion criteria utilized in each of these studies. Appendix 1 delineates the list of included studies .

We used similar search terms to conduct a literature search (2005-2018) in Medline, Embase, and leading textbooks to identify and catalogue published US and international guidelines used to classify pregnancies based on obstetric risk, and to identify guidelines for referral from a mid level provider to a high risk provider, or from a low risk facility to a high risk or tertiary facility. We chose to include guidelines for referral in our approach because high risk prenatal referral guidelines represent what pregnancy care providers utilize to judge increased obstetric risk, and could inform trial design. Lastly, we conducted a literature review searching for articles listing obstetric risk factors as they pertained to clinical trials and vaccine trials.

Based on these findings, we derived a comprehensive matrix of exclusion criteria and obstetric conditions used to determine the risk of adverse outcomes during pregnancy. We classified these into broad categories, including past obstetric and gynaecological history, family history, medical and obstetric conditions during the current pregnancy and fetal conditions. Individual tables were then derived from this matrix for interventional studies classified by development phase (phase I to IV), observational studies, and practice guidelines, detailing the number of studies or guidelines where each potential risk factor was cited. Based on this matrix, we created a heat map to indicate frequency of occurrence.

After creating this matrix, we identified the most commonly listed exclusion criteria in clinical studies conducted in pregnant women, and considered the most common factors that could increase the risk for adverse outcomes during pregnancy. In order to provide more detail about the risk of adverse events in the current pregnancy associated with these exclusion criteria, we looked for studies documenting risk of various adverse pregnancy outcomes when the identified condition listed as an exclusion criteria occured during pregnancy.

**RESULTS**

**Exclusion Factors Matrix**: Sixty three maternal immunization studies (25 Phase I/II, 7 Phase III, 11 post licensure, 21 observational) were identified from ClinicalTrials.gov (Appendix 1)and six practice guidelines were identified by obstetric experts. Table 1 is an alphabetical and categorized line listing of the most common exclusion factors by study type with their respective frequency. Appendix 2 is a summation of all exclusion factors included in these studies and risk factors in practice guidelines. The exclusion and risk factors were grouped by MedDRA criteria/organ system classification. Because the exclusion factors listed and referral risk factors were consistent, they were included in one matrix for ease of analysis.

**Exclusion Factors Tabulation**: When evaluating the matrix, for all phases of studies and for the practice guidelines investigated, a few obstetric risk factors were most commonly chosen as exclusion criteria. These included general risk factors present during the current pregnancy such as advanced (over 35) or young (10-19 years) maternal age, and current alcohol or drug use; past obstetric history of congenital anomalies, hypertensive disease during pregnancy, perinatal death or stillbirth, prior preterm birth, and spontaneous abortion; current maternal medical conditions varying from HIV or other immunodeficiency, to psychiatric disorders (see BOX 1).

BOX 1

Current Pregnancy General Risk Factors

Advanced Maternal Age (over 35 years old)

Young maternal Age (10-19 years old)

Current alcohol or drug misuse/dependency/teratogenic drug

Past Obstetric History

Congenital anomalies/aneuploidy

Hyptertensive Disease

Perinatal Death/Stillbirth

Preterm Birth

Spontaneous Abortion

Current Maternal Medical Conditions

AutoImmune/Connective Tissue/SLE

Bleeding Disorders

Cardiac disorders

Diabetes Mellitus

HIV /Other immunodeficiency

Obesity

Psychiatric Disorders

**Exclusion Criteria and Study Development Phase:** More exclusion criteria were utilized in earlier phase clinical trials, as depicted in the overall heat map (Appendix 2) of potential factors. In Phase I/II trials (n=25), the number of exclusion criteria listed at least one time was 119. Thus far, the number of Phase 3 clinical trials in maternal immunization was limited (n=7). While the number of exclusion criteria (74 ) was less than in the Phase I/II trials, exclusion criteria were extensive. As expected, in observational studies (n=21), we observed the least exclusion criteria (48) (Table 1).

**Adverse outcomes for the most common exclusion criteria:** While Table 1 presents the frequencies that each of these factors were listed as exclusion criteria in different phases of clinical trials of vaccines in pregnancy and in relevant practice guidelines. Table 2 summarizes the risks of adverse outcomes for some of the factors.

In addition to the Table 2 summary of risk factors, we used our literature search to provide more detailed and highly referenced text discussions of these risk factors in Appendix 3. Due to the length of this discussion on these 15 most common exclusion criteria (listed in Box 1), this text discussion is presented in Appendix 3 as Supplemental Material.

**DISCUSSION**

The purpose of this project was to provide clinical researchers with data that may be helpful in selecting appropriate exclusion criteria for maternal vaccine clinical trials. We created a comprehensive matrix of exclusion and risk factors delineating the frequency of exclusion criteria and risk factors used across the spectrum of clinical studies of vaccines in pregnancy. The selection of subjects and the selection of the risk threshold that is acceptable will depend on the type of vaccine being used, the phase of the clinical study, and various other factors such as the perception of risk and potential real risks in a given population. We sought to catalogue and provide specific data on adverse pregnancy outcomes associated with the more commonly utilized exclusion criteria, to guide the use of obstetric risks for the selection of participants in clinical trials of maternal immunization. Adverse outcomes may occur in normal low risk pregnancies without interventions. These obstetric risks do not imply an increased risk of vaccination. Therefore, a better understanding of obstetric risks may facilitiate not only a more informed choice of inclusion and exclusion criteria in these clinical studies of vaccines in pregnant women, but also a tailored use of obstetric risk criteria based on the phase of development of the vaccine.

The field of maternal immunization has continued to evolve and rapidly expanded after the 2009 influenza pandemic. Because of obstetrics risks and the complexity of the maternal-fetal dyad, pregnant women have been considered a vulnerable population, excluded from participation in experimental trials of vaccines and drugs, particularly when these are not intended for the management of obstetric conditions. To facilitate inclusion of pregnant women in studies and research on immunizations targeting pregnant women, bodies such as the Food and Drug Administration and the National Institues of Health have addressed and published guidance on inclusion of pregnant women in clinical trials. Topics addressed have included ethical and consent consideration,49 and development of standards for laboratory and physiologic parameters in pregnant women to assist in evaluation of outcomes in pregnant women participating in clinical trials.50-54 General guidance on the conduct of research in pregnancy has been developed by the National Institutes of Health after conducting clinical trials of licensed and experimental vaccines since the 1980’s, and global experience has been growing as more studies funded by industry and other organizations like the Bill and Melinda Gates Foundation are being pursued in all resource settings in the last decade.1 Consensus statements, such as PREVENT, advocating for inclusion of pregnant women in vaccine trials are now published.55 The exclusion of pregnant women and their infants from the benefits of potentially life-saving drugs and vaccines through clinical trials is no longer considered acceptable.56,57 At present, vaccines specifically for use in pregnant women against at least two pathogens: Respiratory Syncytial Virus (RSV) and Group B Streptococcus (GBS), are in clinical development. Active evaluation of these and other vaccines for women during or prior to pregnancy is ongoing (eg. Pertussis, Cytomegalovirus (CMV) and Hepatitis E).

Complications in pregnancy can occur even in normal low risk pregnancies, and all medicinal products including vaccines can have side effects – although not everyone has them. In clinical studies where there is a placebo or comparator group, similar frequency of obstetric adverse events is expected to occur in both groups. For Phase III trials, ideally the study population should mirror the target population. Exclusion criteria based on selection of women with low risk for obstetric complications can be too restrictive and limit the ability to assess safety of the vaccine in the populations who need it the most. Additionally, exclusion criteria may act indirectly to alter study results by excluding participants who would otherwise be at increased risk for a condition. For example, Group B Streptococcus (GBS) is considered an important cause of stillbirth and preterm labor globally. Eliminating pregnant women with a prior stillbirth or prior preterm labor from participation in clinical research on GBS may also impact efficacy results of an intervention and may add bias to the study.58,59 In fact, inclusion of “higher risk” populations may better allow the ability to demonstrate differences between vaccine and control and potentially make a vaccine available to women sooner.

Researchers should determine what population they will evaluate (such as healthy and at risk), understand the potential risks (obstetric risks versus vaccine risks), and wherever possible, utilize the background rates of certain obstetric, maternal and neonatal events of interest in the general population for interpretation and assessment of these risks to determine if vaccination would potentially increase the occurrence of these events above such expected background rates. While the assessment of exclusion criteria presented in this article does not differentiate obstetric risks from vaccine risks, the quantitation of risk may facilitate trialists’ ability to consider appropriate inclusion/exclusion criteria that reaches a balance between minimizing risk to participants and enabling inclusion of relevant populations. Its use may facilitiate not only a more informed choice of inclusion and exclusion criteria in these clinical studies of vaccines in pregnant women, but also a tailored use of these criteria based on the phase of development of the vaccine. Having more granular information about the obstetric risks, as provided in Appendix 3, may help trialists to anticipate the potential obstetric risks in each trimester. For instance, with spontaneous abortion risks mostly in the first trimester, or pre-eclampsia in the third trimester, a trialist could have a more accurate estimation of magnitude of adverse events, and consider these combined these considering the expected (background) risk in the studied population, the known or anticipated product safety profile, and the timing of the intervention (trimester of exposure) in pregnancy. Its use may facilitiate not only a more informed choice of inclusion and exclusion criteria in these clinical studies of vaccines in pregnant women, but also a tailored use of these criteria based on the phase of development of the vaccine.

Using the information provided in this manuscript and its supplements may actually be most useful for the design of the studies that are currently being planned for some emerging infections. This is because there is a need to be more inclusive (with less restrictive criteria) which may be associated with the occurrence of adverse events linked to the population being evaluated. However, we cannot choose to leave pregnant women out of the opportunity to benefit from vaccines that are being given to or studied in the general population, such as Ebola or those to protect against coronavirus disease 2019 (COVID-19). In fact, the inclusion of pregnant and lactating women in studies of vaccines in epidemic or pandemic settings has been a topic of debate and publication even before the current COVID-19 pandemic.55,60-62

This approach has several strengths. To our knowledge, this delination and frequency mapping of exclusion criteria based on a comprehensive search of prior maternal immunization trials has not been done previously. Adding stratification by study phase offers additional information for trialists. Including referral guidelines for high risk pregnancies in the matrix adds an obstetric provider perception of risk factors for adverse events. Another unique aspect of our approach and perhaps of the most useful to trialists may be to offer more quantitative information about these factors for the most commonly listed exclusion criteria.

This obstetrics risk assessment method we present here is not exhaustive nor is it meant to be prescriptive. This tool will not replace the need for detailed literature reviews about potential risk factors and exclusion criteria for specific products in pregnant populations, nor will it replace the need for using background rates of adverse events to assess safety. It is not designed to replace the clinical acumen and knowledge base that is offered by involving experienced obstetric providers and vaccine evaluators in trial design of vaccines in pregnancy. However, given that a standardized approach to the selection of participants in studies of vaccines in pregnancy is necessary, this information may serve to help clinical researchers reassess how conservative they need to be as a product progresses in development. The balance between deciding exclusion criteria and choosing a study population that mirrors the general population is complex. As clinical trials for vaccines specifically designed for an indication in pregnant women are novel, initial early phase trials may have more strict exclusion criteria. However, ongoing reassessment of criteria for inclusion in these and other protocols where pregnant women are study subjects will be imperative as data on background rates of expected obstetric events and safety information from epidemiologic studies and maternal immunization trials become more widely available. Word count: 2948

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Table 1: Enumeration of most frequent exclusion factors in study types and risk factors in antenatal clinical care guidelines

\* Total number of exclusion or risks factors listed in each study type or clinical guideline

Table 2. Elevation of Adverse Pregnancy, Maternal or Neonatal Outcomes Associated with Exclusion Criteria

| **Factor** | **Outcome in current pregnancy, OR (95% CI)** |
| --- | --- |
|  | **SAB** | **Preterm****labour** | **Preterm** **birth** | **Stillbirth** | **Adverse neonatal outcome** | **Adverse obstetric outcome** |
| AMA8,9  |  | 1.2 (1.1-1.2) |  | 1.5 (1.4-1.7) | ND 1.4 (1.3-1.5) | MM 1.7 (1.2-2.6) |
| Young Age10-14  |  |  | 1.6 (1.2-1.9) | 1.3 (1.1-1.6) | 1.6 (1.2-1.7) | EclampsiaInfectionsC/D rate  |
| Drug and Alcohol use15,16  | ↑ IUFD 5.1 (3.3-7.2) | 2.1 (2.0-2.3) | 3.38 (2.7-4.2) | 3.0 (1.4-6.4)1.5 (1.3-1.8) | FGR 2.7 (2.4-2.9)Cong Anom 33-100%† | Plac ABR 2.4 (2.1-2.6)\*Plac ABR 5.5 (4.9-6.3) ‡Plac ABR 3.9 (2.8-5.5) š |
| Hypertension17-22  |  |  | 2.7 (1.9-3.6) |  | ND 4.2 (2.706.5)LBW 2.7 (1.9-3.8)NICU 3.2 (2.2-4.4) | Plac ABR 2-fold29% pregnancies SIPE |
| Prior Stillbirth23-29  |  |  | 4.9 (1.5-15) | 2-10 fold  |  |  |
| Prior Preterm Birth30 |  |  | 22% vs 9% | 5.6 (1.8-17) |  |  |
| Prior Pregnancy Loss31  |  |  | 1.4 (1.1-1.9) |  | LBW 1.4 (1.2-1.6) |  |
| Bleeding Disorders32-35  | FVL 1.7 (1.1-2.6)ACA 3.4 (1.3-8.7) |  |  |  | FGR, ACA 6.9 (2.7-17.7) | FVL, PIH 2.2 (1.5-3.3)Plac ABR, FVL 4.7 (1.1-19.6)PIH, ACA 2.7 (1.7-4.5) |
| Pre-gestational Diabetes Mellitus36-42 |  |  | 1.6 (1.2-2.2)iPTD 8.1 (6.0-10.9) | 6.1 (4.4-8.4) | Cong Anom 2.4 (1.9-3.1) | C/D 1.6 (1.3-2.0)PIH 1.3 (1.2-1.4) |
| HIV Positive43-46 | 4.0 (2.8-6.0) |  | 1.8 (1.6-2.1) | 3.9 (2.7-5.8) | FGR 1.7 (1.4-2.0)ND 1.8 (1.1-2.8) | MM 1.8 (1.0-3.3) |
| Obesity (BMI >30)47,48 |  |  |  | 1.4 (1.1-1.7) |  | GDM 3.6 (3.3-4.0)PIH 2.1 (1.9-2.5)IOL 1.8 (1.7-1.9)C/D 1.8 (1.7-1.9)PPH 1.4 (1.3-1.5)Wound infection 2.3 (1.9-2.6) |

**Abbreviations:** ACA, anti-cardiolipin antibodies; AMA, advanced maternal age; C/D, cesarean delivery; FGR, fetal growth restriction; FVL, Factor V Leiden; GDM, Gestational Diabetes Mellitus; IOL, Induction of labour; iPTD, iatrogenic or medically indicated preterm birth; LBW, low birth weight; MM, maternal mortality; ND, neonatal death; NICU, neonatal intensive care admission; PIH, Pre-eclampsia / Pregnancy induced hypertension; Plac ABR, placental abruption; PPH, postpartum haemorrhage; SAB, spontaneous abortion.

\*Opioid use

†Alcohol

‡Methamphetamine use

šCocaine use

Appendix 1

Studies on Maternal Immunization published in ClinicalTrials.gov (as of October 2018)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **No.** | **Name and Identifier** | **Type/Sponsor** | **Vaccine(s)** | **Site** | **Status** |
| **Phase 1-2 Studies** |
| 1 | Seroprevalence of Bordetella Pertussis Antibodies and Anti-pertussis Antibodies Response After Its Single Dose of Reduced-antigen, Combined Diphtheria, Tetanus, and Acellular Pertussis Vaccine (Tdap) in Thai Pregnant WomenNCT03498300 | Phase 1Clinical TrialRandomized Parallel AssignmentMahidol University | Pertussis acellular, tetanus and diphtheria toxoids (Tdap) vaccinevs. Td | Thailand | Start 2018Ongoing |
| 2 | An Observer-blind Study to Assess the Safety, Reactogenicity and Immunogenicity of GSK Biologicals' Investigational RSV Vaccine (GSK3003891A), in Healthy Pregnant Women and Infants Born to Vaccinated Mothers[NCT03191383](https://clinicaltrials.gov/show/NCT03191383) | Phase 2Clinical TrialRandomizedParallel assignmentGlaxoSmithKline | RSV vs. Placebo | Global | Withdrawn 2017 |
| 3 | Evaluation of Tdap in Pregnancy to Prevent Infant PertussisNCT02301702 | Phase 2RandomizedParallel AssignmentEmory University | Pertussis acellular, tetanus and diphtheria toxoids (Tdap) vaccinevs. Td | Guatemala | Start 2016Ongoing |
| 4 | Safety and Immunogenicity of Anti-Pneumococcal Vaccines in HIV-Infected Pregnant WomenNCT02717494 | Phase 2RandomizedParallel AssignmentWestat | Pneumococcal vaccine | NA | Start 2016Ongoing |
| 5 | A Phase II Randomized, Observer-Blind, Placebo-Controlled, Study to Evaluate the Safety and Immunogenicity of a Respiratory Syncytial Virus (RSV) F Nanoparticle Vaccine With Aluminum, in Healthy Third-trimester Pregnant Women and to Assess the Impact of Maternal Immunization on Infant Safety Through One Year of LifeNCT02247726 | Phase 2Clinical TrialRandomizedParallel assignmentNovavax | RSV F vaccine with adjuvantvs. Placebo | USA | Completed 2016 |
| 6 | A Phase II, Multicenter, Randomized, Observer-Blind, Controlled Study to Evaluate Safety and Immunogenicity of a Trivalent Group B Streptococcus Vaccine in Healthy Pregnant WomenNCT02046148 | Phase 2Clinical TrialRandomizedParallel assignmentGSK | GBS trivalent vaccine (Ia, Ib, III) conjugated with CRM197vs.Placebo | USA | Completed 2016 |
| 7 | Immunization of Women With Diphtheria and Tetanus Toxoids Combined With Acellular Pertussis (Tdap) During the Mid Third Trimester of Pregnancy: An Evaluation of the Potential for Immunological Protection for the NeonateNCT00553228 | Phase 2RandomizedParallel AssignmentDalhousie University | Pertussis acellular, tetanus and diphtheria toxoids (Tdap) vaccinevs. Td | Canada | Completed 2016 |
| 8 | Immunogenicity and Safety of an Acellular DPT Vaccine in Pregnant Women in Nuevo Leon, MexicoNCT01445743 | Phase 2RandomizedParallel AssignmentHospital Universitario Dr. Jose E. Gonzalez | Pertussis acellular, tetanus and diphtheria toxoids (Tdap) vaccinevs. Placebo | Mexico | Completed 2014 |
| 9 | A Double-Blind, Randomized, Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of Standard Dose Quadrivalent Inactivated Influenza Vaccine, and Double Dose Quadrivalent Inactivated Influenza Vaccine in HIV-Infected and HIV-Uninfected Pregnant Women in a Malaria-Endemic Area of Rural Western KenyaNCT01810731 | Phase 2RandomizedParallel AssignmentCenters for Disease Control and Prevention | Quadrivalent inactivated influenza vaccine  | Kenya | Completed 2014 |
| 10 | Administration of Polysaccharide or Conjugated Pneumococcal Vaccines to HIV-Infected Pregnant Women: Safety and Magnitude, Persistence, and Transplacental Transfer of Vaccine-Serotype Pneumococcal Anti-Capsular AntibodiesNCT01443117 | Phase 2RandomizedParallel AssignmentNational Institute of Allergy and Infectious Diseases  | Conjugated Pneumococcal vaccine | NA | Completed 2014 |
| 11 | A Phase II Randomized, Observer-Blind, Multi-Center, Controlled Study of a Trivalent Group B Streptococcus Vaccine in Healthy Pregnant WomenNCT01446289 | Phase 2Clinical TrialRandomizedParallel assignmentNovartis Vaccines | GBS trivalent vaccinevs.Placebo | Global | Completed 2013 |
| 12 | Clinical Trial to Evaluate the Immunogenicity and Safety of the 2011-2012 Vaccine Against Seasonal Influenza on Pregnant WomenNCT01577316 | Phase 2Non-RandomizedParallel AssignmentCenter of Research in Infectious Diseases, Instituto Nacional de Salud Publica | Trivalent inactivated Influenza vaccine | Mexico | Completed 2013 |
| 13 | A Phase Ib/II Randomized, Observer-Blind, Controlled, Single Centre Study of a Trivalent Group B Streptococcus Vaccine in Healthy Non-Pregnant Women Leading Into a Dose-Ranging Study in Pregnant Women in South AfricaNCT01193920 | Phase 1-2Clinical TrialRandomizedParallel assignmentNovartis Vaccines | GBS trivalent vaccinevs.Placebo | South Africa | Completed 2012 |
| 14 | A Phase II Open-Label, Multi-Center Study of a Group B Streptococcus Vaccine in HIV Positive and HIV Negative Pregnant WomenNCT01412801 | Phase 2Clinical TrialNon-randomizedParallel assignmentNovartis Vaccines | GBS trivalent vaccine | South Africa | Completed 2012 |
| 15 | Safety and Immunogenicity of Tdap Vaccine in Healthy Pregnant Women, Safety in Their Neonates, and Effect of Maternal Immunization on Infant Immune Responses to DTaP VaccineNCT00707148 | Phase 1-2Clinical TrialRandomizedCrossover AssignmentNational Institutes of Health, National Institute of Allergy and Infectious Diseases | Pertussis acellular, tetanus and diphtheria toxoids (Tdap) vaccinevs.Placebo | USA | Completed 2012 |
| 16 | Trivalent Influenza Vaccine in HIV-infected Pregnant Women and Kinetics of Transplacental Anti-influenza Antibody Transfer and Persistence in Young Infants: A Randomized Controlled Phase II Trial Evaluating Safety and ImmunogenicityNCT01306682 | Phase 2RandomizedParallel AssignmentUniversity of Witwatersrand | Trivalent influenza vaccinevs. Placebo | South Africa | Completed 2012 |
| 17 | A Randomized, Double-Blind Trial on the Safety and Immunogenicity of Seasonal 2010-2011 Inactivated Trivalent Influenza Vaccine in Pregnant WomenNCT01173211 | Phase 2RandomizedParallel AssignmentNational Institutes of Health, National Institute of Allergy and Infectious Diseases | Trivalent inactivated influenza vaccine | USA | Completed 2011 |
| 18 | A Phase II Study In Pregnant Women to Assess the Safety and Immunogenicity of an Unadjuvanted Novartis H1N1 Inactivated Influenza Vaccine Administered at Two Dose LevelsNCT00992719  | Phase 2RandomizedParallel AssignmentNational Institutes of Health, National Institute of Allergy and Infectious Diseases | Monovalent inactivated H1N1 influenza vaccine | USA | Completed 2011 |
| 19 | H1N1v Vaccination of Pregnant Women: A Longitudinal Cohort Study Characterizing Influenza AH1N1v Vaccination in Pregnant WomenNCT01012557 | Phase 2RandomizedParallel AssignmentCopenhagen Studies on Asthma and Childhood | Monovalent H1N1 influenza vaccine with and without MF59 | Denmark | Completed 2011 |
| 20 | A Randomized, Double-Blind Trial on the Safety and Immunogenicity of Inactivated Trivalent Influenza Vaccine in Pregnant WomenNCT00905125 | Phase 2RandomizedParallel AssignmentNational Institutes of Health, National Institute of Allergy and Infectious Diseases | Trivalent inactivated influenza vaccine | USA | Completed 2010 |
| 21 | A Phase II Study in Pregnant Women to Assess the Safety and Immunogenicity of an Unadjuvanted Sanofi Pasteur H1N1 Inactivated Influenza Vaccine Administered at Two Dose LevelsNCT00963430 | Phase 2RandomizedParallel AssignmentNational Institutes of Health, National Institute of Allergy and Infectious Diseases | Monovalent inactivated H1N1 influenza vaccine | USA | Completed 2010 |
| 22 | A Phase II Study to Assess the Safety and Immunogenicity of an Inactivated Monovalent Influenza A (H1N1) Vaccine in HIV-1 Infected Pregnant WomenNCT00992017 | Phase 2Non-RandomizedSingle Group AssignmentNational Institute of Allergy and Infectious Diseases | Monovalent H1N1 influenza vaccine | USA | Completed 2010 |
| 23 | Etude de Phase II évaluant l'immunogénicité et la tolérance d'un Vaccin inactivé Non adjuvanté Contre la Grippe A(H1N1)v Chez la Femme EnceinteNCT01024400 | Phase 2Single Group AssignmentInstitut National de la Sante et de la Recherche Medicale | Monovalent H1N1 influenza vaccine | France | Completed 2010 |
| 24 | Comparison of Maternal and Infant Immunization Strategies to Prevent Pneumococcal DiseaseNCT00142389 | Phase 1-2RandomizedParallel Assignment | Pneumococcal vaccine | Bangladesh | Completed 2006 |
| 25 | Maternal Immunization To Prevent Infant Otitis MediaNCT00617682 | Phase 1RandomizedParallel AssignmentNational Institutes of Health, National Institute of Allergy and Infectious Diseases | Pneumococcal polysaccharide vaccine | USA | Completed 2004 |
| **Phase 3-4 Studies** |
| 26 | Randomised, Double-blinded, Open Label Study in Pregnant Women, Exploring the Impact of Acellular Pertussis Vaccination in Pregnancy on the Immunogenicity in Infants Randomized to Receive Either an Acellular (aP) or Whole Cell Pertussis (wP) Vaccine SubsequentlyNCT03606096 | Phase 4Clinical TrialRandomizedParallel AssignmentLondon School of Hygiene and Tropical Medicine | Pertussis acellular vaccine, tetanus and diphtheria toxoids (Tdap) | The Gambia | Start 2018Ongoing |
| 27 | Immunogenicity of a Single Dose of GSK Biologicals' Diphtheria, Tetanus and Acellular Pertussis (dTpa) Booster Vaccine (Boostrix™ [263855]) in Infants Prior to Primary Pertussis Vaccination, When Administered to Pregnant Women as Per Routine Practice in Bogota, ColombiaNCT03188458 | Phase 4Single Group AssignmentGlaxoSmithKline | Pertussis acellular vaccine, tetanus and diphtheria toxoids (Tdap) | Colombia | Start 2018Ongoing |
| 28 | Field Trial of Maternal Influenza Immunization in AsiaNCT01034254 | Phase 3Clinical TrialRandomizedParallel assignmentChildren’s Hospital Medical CenterCincinnati | Influenza | Asia | Completed 2018 |
| 29 | Vaccine Responses in Infants After Acellular Pertussis Vaccination During Pregnancy in ThailandNCT02408926 | Phase 4RandomizedParallel AssignmentUniversiteit Antwerpen | Pertussis acellular vaccine, tetanus and diphtheria toxoids (Tdap) | Thailand | Completed 2018 |
| 30 | A Prospective, Randomized, Open-label Clinical Trial to Assess the Safety and Immunogenicity of Simultaneous vs Sequential Administration of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine and Inactivated Influenza Vaccine in Pregnant Women – PilotNCT02783170 | Phase 4RandomizedParallel Group AssignmentDuke University | Pertussis acellular vaccine, tetanus and diphtheria toxoids (Tdap)andQuadrivalent Inactivated influenza vaccine | USA | Completed 2018 |
| 31 | Immunogenicity and Safety Study of GSK Biologicals' dTpa Vaccine, Boostrix™ (263855) in Pregnant WomenNCT02377349 | Phase 4RandomizedCrossover AssignmentGSK | Pertussis acellular vaccine, tetanus and diphtheria toxoids (Tdap) | Europe | Completed 2017 |
| 32 | A Randomised Controlled Trial Comparing Two Pertussis-containing Vaccines in Pregnancy and Vaccine Responses in UK Mothers and Their InfantsNCT02145624 | Phase 4RandomizedParallel AssignmentPublic Health England | Pertussis acellular vaccine, tetanus and diphtheria toxoids (Tdap) | England | Completed 2017 |
| 33 | A Randomized, Controlled, Double-blind, Phase 3 Trial to Evaluate the Effects of Maternal or Neonatal Pneumococcal Conjugate Vaccination on Pneumococcal Carriage in Infants up to Nine Months of Age - The PROPEL TrialNCT02628886 | Phase 3Clinical TrialRandomizedParallel assignmentLondon School of Hygiene and Tropical Medicine | Pneumococcal Conjugate vaccine | The Gambia | Start 2016Ongoing |
| 34 | Impact of Pertussis Vaccination in Pregnancy on Maternal Protection Offered to Young InfantsNCT01698346 | Phase 4Non-RandomizedParallel AssignmentUniversiteit Antwerpen | Pertussis acellular vaccine, tetanus and diphtheria toxoids (Tdap) | Belgium | Completed 2016 |
| 35 | A Phase 3, Randomized, Observer-Blind, Placebo-Controlled, Group-Sequential Study to Determine the Immunogenicity and Safety of a Respiratory Syncytial Virus (RSV) F Nanoparticle Vaccine With Aluminum in Healthy Third-trimester Pregnant Women; and Safety and Efficacy of Maternally Transferred Antibodies in Preventing RSV Disease in Their InfantsNCT02624947 | Phase 3Clinical TrialRandomized Parallel assignment Novavax | RSV F vaccine with adjuvantvs. Placebo | Global | Start 2015Ongoing |
| 36 | Prospective, Randomized, Controlled, Observer-Blind Trial to Measure the Efficacy, Safety and Immunogenicity of Trivalent Inactivated Influenza Vaccine and the Safety and Immunogenicity of Quadrivalent Meningococcal Polysaccharide Diphtheria Conjugate Vaccine in Pregnant Malian Women and Their Infants up to 6 Months of AgeNCT01430689 | Phase 4RandomizedParallel AssignmentUniversity of Maryland | Trivalent inactivated influenza vaccine vs. Quadrivalent meningococcal polysaccharide diphtheria conjugate vaccine | Mali | Completed 2014 |
| 37 | Immunogenicity and Safety of Different Dosing Schedules of Trivalent Influenza Vaccine in HIV-infected Pregnant Women: a Randomized Controlled TrialNCT01527825 | Phase 3Clinical TrialRandomizedParallel AssignmentUniversity of Witwatersrand | Trivalent inactivated influenza vaccinevs. Placebo | South Africa | Completed 2014 |
| 38 | Immunogenicity and Safety of Trivalent Influenza Vaccine in Pregnant and Non-pregnant HIV-Uninfected Women: An Open Label TrialNCT01816464 | Phase 4Single Group AssignmentUniversity of Witwatersrand | Trivalent inactivated influenza vaccine | South Africa | Completed 2014 |
| 39 | Vaccination of HIV-uninfected Pregnant Women With Trivalent Influenza Vaccine in the Prevention of Influenza Illness During Early Infancy and in Mothers: Randomized Controlled Phase III Trial Evaluating Safety, Immunogenicity and EfficacyNCT01306669 | Phase 3Clinical TrialRandomizedParallel AssignmentUniversity of Witwatersrand | Trivalent inactivated influenza vaccinevs. Placebo | South Africa | Completed 2013 |
| 40 | The Safety and Immune Response to Influenza Vaccination in Pregnant WomenNCT01514708 | Phase 4Single Group AssignmentAdimmune Corporation | Influenza vaccine | NA | Completed 2012 |
| 41 | PneuMum: A Randomised Controlled Trial of Pneumococcal Polysaccharide Vaccination for Aboriginal and Torres Strait Islander Mothers to Protect Their Babies From Ear DiseaseNCT00714064 | Phase 3Clinical TrialRandomizedParallel AssignmentMenzies School of Health Research | Pneumococcal vaccine | Australia | Completed 2011 |
| 42 | A Stratified and Controlled Clinical Trial With Split-virion, Non-adjuvanted Influenza A/H1N1 Vaccines in Healthy Pregnant WomenNCT01842997 | Phase 4Single Group AssignmentJiangsu Province Centers for Disease Control and Prevention | Monovalent H1N1 influenza vaccine non-adjuvanted | China | Completed 2010 |
| 43 | PneuMum: A Randomised Controlled Trial of Pneumococcal Polysaccharide Vaccination for Aboriginal and Torres Strait Islander Mothers to Protect Their Babies From Ear DiseaseNCT00310349 | Phase 3Clinical TrialRandomizedParallel AssignmentMenzies School of Health Research | Pneumococcal vaccine | Australia | Completed 2009 |
| **Observational Studies** |
| 44 | Optimising Protection for Pregnant Women and Infants With Maternal VaccinationNCT03457194 | Cohort ProspectiveVaccinology and Immunology Research Trials Unit, Women's and Children's Hospital | Pertussis acellular vaccine, Tetanus and Diphtheria toxoids (Tdap) | Australia | Start 2018Ongoing |
| 45 | An Observational, Retrospective Cohort Database Study to Assess the Safety of Boostrix (U.S. Formulation), a Reduced Tetanus, Diphtheria, Acellular Pertussis Vaccine (Tdap), Following Routine Immunization of Pregnant Women in the United StatesNCT03463577 | Cohort RetrospectiveGlaxoSmithKline | Pertussis acellular vaccine, Tetanus and Diphtheria toxoids (Tdap) | USA | Start 2018Ongoing |
| 46 | A Prospective Epidemiological Study of Pregnancy Outcomes and of Events of Interest in Pregnant Women, Neonates and Infants (PEPNI)NCT03614676 | Non-RandomizedSingle Group AssignmentEpidemiological StudyGlaxoSmithKline | NA | Global | Start 2018Ongoing |
| 47 | Impact of Boostrix™ Maternal Vaccination on Morbidity and Mortality of Pertussis Disease in Infants ≤6 Weeks of Age, in Bogota, ColombiaNCT02569879 | Ecologic or CommunityRetrospectiveGlaxoSmithKline | Pertussis acellular vaccine, Tetanus and Diphtheria toxoids (Tdap) | Colombia | Completed 2018 |
| 48 | Pertussis Immunization During Pregnancy: Assessment of the Role of Maternal Antibodies on Immune Responses in Term and Preterm Infants: the MAMA StudyNCT02511327 | Case ControlProspectiveUniversteit Antwerpen | Pertussis acellular vaccine, Tetanus and Diphtheria toxoids (Tdap) | Belgium | Completed 2018 |
| 49 | Impact of HIV Infection and Pregnancy on Humoral Responses to Pertussis ImmunizationNCT03519373 | Case ControlProspectiveCentre Hospitalier Universitaire Saint Pierre | Pertussis acellular vaccine, Tetanus and Diphtheria toxoids (Tdap) | France | Start 2017Ongoing |
| 50 | Clinical Study of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) Safety in Pregnant WomenNCT02209623 | ProspectiveVanderbilt University | Pertussis acellular vaccine, Tetanus and Diphtheria toxoids (Tdap) | USA | Completed 2017 |
| 51 | A Post-marketing, Observational, Retrospective, Cohort Study to Assess the Safety of RefortrixTM (Tdap) When Administered During Pregnancy in a Maternal Immunization Program in Brazil.NCT02757950 | CohortProspective | Pertussis acellular vaccine, Tetanus and Diphtheria toxoids (Tdap) | Brazil | Completed 2017 |
| 52 | Respiratory Syncytial Virus (RSV) and Vaccination in PregnancyNCT03096574 | ProspectiveUniversity Hospital Southamptom NHS Foundation Trust | NA | United Kingdom | Completed 2017 |
| 53 | Effectiveness of Trivalent Inactivated Influenza Maternal Vaccination Among Pregnant Women and Their Newborns in South AfricaNCT02465190 | Case Control ProspectiveNational Institute of Communicable Diseases, South Africa | Trivalent Inactivated Influenza vaccine | South Africa | Completed 2017 |
| 54 | The Role of Immunizing Pregnant Women In Protecting Young Infants Against InfluenzaNCT01496079 | CohortProspectiveUniversity of Utah | Influenza | USA | Completed 2015 |
| 55 | PregText: Assessing the Feasibility of Monitoring Influenza Vaccine Safety in Pregnant Women Using Text MessagingNCT01974050 | Single Group AssignmentHealth Services ResearchColumbia University | Influenza | USA | Completed 2015 |
| 56 | Women - Influencing Factors and Coverage RateNCT03007797 | CohortProspectiveUniversity Hospital, Saarland | Influenza | Germany | Completed 2014 |
| 57 | Protecting Pregnant Women From Infectious Diseases: a Cluster Randomized Evaluation of the Comprehensive "P3" Intervention Package Within Obstetric Practices in GeorgiaNCT01761799 | Randomized Parallel Assignment (Education)Emory University | Pertussis acellular vaccine, Tetanus and Diphtheria toxoids (Tdap)and Influenza | USA | Completed 2014 |
| 58 | Attitudes to Immunisation Against Group B Streptococcus During Pregnancy in England and ScotlandNCT01982084 | ObservationalAttitudesUniversity of Oxford | Group B Streptococcus | United Kingdom | Completed 2014 |
| 59 | Flucelvax Pregnancy Registry: an Observational Study on the Safety of Flucelvax Exposure in Pregnant Women and Their OffspringNCT02258178 | CohortRegistrySeqirus | Influenza | USA | Start 2014Withdrawn |
| 60 | Knowledge Possessed by Pregnant Women Regarding Influenza Vaccination During PregnancyNCT00593970 | CohortCross SectionalSt. Michael’s Hospital Toronto | Influenza | Canada | Completed 2013 |
| 61 | Focetria adverse drug reactionsNCT01354730 | Cohort RetrospectiveAdimmune Corporation | Monovalent H1N1 influenza vaccine | Gobal | Completed 2011 |
| 62 | Opting In vs Opting Out: Impact on Influenza Vaccination in Pregnant WomenNCT01233804 | RandomizedParallel AssignmentUniversity of Texas Health Science Center, Houston | Influenza | USA | Completed 2011 |
| 63 | Cohort Study to Evaluate Clinical Expression and Maternofetal Consequences of A/H1N1 Influenza in Pregnant WomenNCT01192737 | CohortProspectiveInstitut National de la Sante et de la Recherche Medicale | Monovalent H1N1 influenza | France | Completed 2010 |
| 64 | A Post-Marketing, Observational, Comparative Safety Study of the Novartis Pandemic Influenza A (H1N1) Vaccine(s) in Pregnant Women Versus Non-Vaccinated Pregnant WomenNCT01037829 | CohortProspectiveNovartis Vaccines | Monovalent H1N1 Influenza | Global | Completed 2010 |

Appendix 2: Heat Map Matrix of Most Frequently Reported Exclusion Criteria Based on Study type

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Risk factors**  | Phase I/II studies (n=29) | Phase III studies (n=4) | Phase IV studies (n=12) | Observational studies (n=22) | Guidelines (n=6) | Total (n=73) |  |
| **A) Current General Risk Factors** | 0.34 | 0.25 | 0.08 | 0.27 | 0.00 | 0.25 |  |
| Advanced maternal age | 0.59 | 1.00 | 0.50 | 0.09 | 0.67 | 0.45 |  |
| Current alcohol or drug misuse/dependency/ teratogenic drug | 0.28 | 0.50 | 0.25 | 0.00 | 0.83 | 0.25 |   |
| Personal or social complications  | 0.00 | 0.00 | 0.08 | 0.05 | 0.33 | 0.05 |   |
| Young maternal age | 0.66 | 1.00 | 0.67 | 0.73 | 0.67 | 0.70 |   |
| **B) Past Maternal Medical History** | 0.14 | 0.25 | 0.17 | 0.00 | 0.00 | 0.10 |  |
| **1. Obstetric history** | 0.10 | 0.25 | 0.25 | 0.00 | 0.00 | 0.10 |  |
| Baby with encephalopathy  | 0.00 | 0.00 | 0.00 | 0.00 | 0.17 | 0.01 |  |
| Cesarean section | 0.00 | 0.25 | 0.00 | 0.00 | 1.00 | 0.10 |  |
| Cholestasis  | 0.07 | 0.00 | 0.00 | 0.00 | 0.33 | 0.05 |  |
| Congenital anomaly (genetic or structural) | 0.10 | 0.50 | 0.33 | 0.00 | 0.83 | 0.19 |  |
| Gestation diabetes | 0.07 | 0.25 | 0.08 | 0.00 | 0.33 | 0.08 |  |
| Hypertensive disease (pre-eclampsia/eclampsia) | 0.17 | 0.25 | 0.33 | 0.00 | 1.00 | 0.22 |  |
| Intrauterine Growth Retardation (IUGR) | 0.00 | 0.00 | 0.00 | 0.00 | 0.83 | 0.07 |  |
| Large or Small for Gestational Age (LGA or SGA) | 0.00 | 0.00 | 0.08 | 0.00 | 0.83 | 0.08 |  |
| Multi-parity | 0.03 | 0.00 | 0.08 | 0.00 | 0.50 | 0.07 |  |
| Previous neonatal death | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |  |
| Perinatal death/Stillbirth | 0.21 | 0.50 | 0.17 | 0.00 | 1.00 | 0.22 |  |
| Placental abruption  | 0.00 | 0.00 | 0.00 | 0.00 | 0.17 | 0.01 |  |
| Postpartum hemorrhage | 0.07 | 0.00 | 0.00 | 0.00 | 0.83 | 0.10 |  |
| Preterm birth | 0.24 | 0.50 | 0.33 | 0.00 | 0.83 | 0.25 |  |
| Retained placenta | 0.00 | 0.00 | 0.00 | 0.00 | 0.17 | 0.01 |  |
| Shoulder dystocia | 0.00 | 0.00 | 0.00 | 0.00 | 0.17 | 0.01 |  |
| Spontaneous abortion | 0.17 | 0.00 | 0.17 | 0.00 | 0.50 | 0.14 |  |
| Uterine rupture | 0.00 | 0.00 | 0.00 | 0.00 | 0.17 | 0.01 |  |
| **2. Gynaecological history** | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |  |
| Cervical surgery  | 0.00 | 0.00 | 0.00 | 0.00 | 0.50 | 0.04 |  |
| Female genital mutilation | 0.00 | 0.00 | 0.00 | 0.00 | 0.33 | 0.03 |  |
| Uterine surgery (myomectomy) | 0.00 | 0.25 | 0.00 | 0.00 | 0.83 | 0.08 |  |
| **3.Family history** | 0.00 | 0.00 | 0.08 | 0.00 | 0.00 | 0.01 |  |
| 1st degree family history of major congenital anomalies  | 0.03 | 0.00 | 0.08 | 0.00 | 0.17 | 0.04 |  |
| Hereditary immunodeficiency  | 0.03 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 |  |
| **C) Current Maternal Medical Conditions during Pregnancy** | 0.38 | 0.25 | 0.17 | 0.14 | 0.00 | 0.23 |  |
| **1.Blood and lymphatic system disorders**  | 0.07 | 0.25 | 0.08 | 0.00 | 0.33 | 0.08 |  |
| Anemia  | 0.07 | 0.25 | 0.08 | 0.05 | 0.83 | 0.14 |  |
| Congenital or acquired clotting or bleeding disorders  | 0.28 | 0.25 | 0.33 | 0.05 | 0.67 | 0.25 |  |
| Sickle cell disease | 0.03 | 0.25 | 0.08 | 0.00 | 0.83 | 0.11 |  |
| Thalassemia | 0.03 | 0.25 | 0.00 | 0.00 | 0.50 | 0.07 |  |
| Thrombocytopenia | 0.17 | 0.25 | 0.17 | 0.00 | 0.50 | 0.15 |  |
| Thrombophilia including APLS | 0.07 | 0.25 | 0.08 | 0.00 | 0.50 | 0.10 |  |
| Von Willebrands | 0.07 | 0.25 | 0.17 | 0.00 | 0.33 | 0.10 |  |
| **2.Cardiac disorders**  | 0.41 | 0.25 | 0.25 | 0.14 | 0.67 | 0.32 |  |
| Cardiac arrhythmias | 0.00 | 0.25 | 0.00 | 0.00 | 0.33 | 0.04 |  |
| Cardiac valve disease | 0.00 | 0.25 | 0.00 | 0.00 | 0.50 | 0.05 |  |
| Cardiomyopathy | 0.00 | 0.25 | 0.00 | 0.00 | 0.50 | 0.05 |  |
| Ischemic heart disease | 0.00 | 0.25 | 0.00 | 0.00 | 0.33 | 0.04 |  |
| **3.Congenital, familial and genetic disorders**  | 0.03 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 |  |
| Any genetic disorder significant in pregnancy | 0.03 | 0.25 | 0.00 | 0.00 | 0.33 | 0.05 |  |
|  Structural abnormalities of the uterus or vagina | 0.07 | 0.00 | 0.08 | 0.00 | 0.33 | 0.07 |  |
| **4. Ear and labyrinth disorders**  | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |  |
| **5.Endocrine disorders**  | 0.07 | 0.25 | 0.08 | 0.00 | 0.17 | 0.07 |  |
| Thyroid disease (any)  | 0.07 | 0.00 | 0.08 | 0.05 | 0.50 | 0.10 |  |
| hypothyroid | 0.03 | 0.00 | 0.00 | 0.00 | 0.33 | 0.04 |  |
| hyperthyroid | 0.03 | 0.00 | 0.00 | 0.00 | 0.33 | 0.04 |  |
| **6.Eye disorders** | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |  |
| **7.Gastrointestinal disorders** | 0.03 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 |  |
| Inflammatory bowel disease, general | 0.03 | 0.25 | 0.00 | 0.00 | 0.33 | 0.05 |  |
| Inflammatory bowel disease, active | 0.03 | 0.25 | 0.00 | 0.00 | 0.17 | 0.04 |  |
| Inflammatory bowel disease, inactive | 0.03 | 0.25 | 0.00 | 0.00 | 0.17 | 0.04 |  |
| **8.General disorders**  | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |  |
| General symptoms  | 0.03 | 0.25 | 0.08 | 0.00 | 0.00 | 0.04 |  |
| **9.Hepatobiliary disorders**  | 0.28 | 0.25 | 0.25 | 0.05 | 0.17 | 0.19 |  |
| Hepatitis | 0.10 | 0.50 | 0.00 | 0.00 | 0.17 | 0.08 |  |
| acute | 0.03 | 0.25 | 0.08 | 0.00 | 0.17 | 0.05 |  |
| chronic active | 0.03 | 0.25 | 0.00 | 0.00 | 0.17 | 0.04 |  |
| **10.Immune system disorders** | 0.41 | 0.50 | 0.50 | 0.23 | 0.17 | 0.36 |  |
| Systemic lupus erythematosus  | 0.10 | 0.25 | 0.00 | 0.05 | 0.67 | 0.12 |  |
| Other autoimmune/connective tissue disorder | 0.28 | 0.50 | 0.33 | 0.09 | 0.83 | 0.29 |  |
| Immunodeficiency or immunosuppression (includes IVIG &blood transfusion) | 0.66 | 0.75 | 0.92 | 0.32 | 0.00 | 0.55 |  |
| **11.Infections and infestations**  | 0.03 | 0.25 | 0.00 | 0.05 | 0.00 | 0.04 |  |
| Any current infection requiring antibiotics or anti-virals | 0.03 | 0.00 | 0.00 | 0.05 | 0.00 | 0.03 |  |
| CMV | 0.03 | 0.00 | 0.08 | 0.09 | 0.50 | 0.10 |  |
| Genital herpes : primary  | 0.07 | 0.25 | 0.08 | 0.05 | 0.50 | 0.11 |  |
| Genital herpes : secondary | 0.03 | 0.00 | 0.08 | 0.00 | 0.50 | 0.07 |  |
| Hepatitis B | 0.28 | 0.25 | 0.33 | 0.05 | 0.67 | 0.25 |  |
| Hepatitis C | 0.24 | 0.00 | 0.25 | 0.05 | 0.33 | 0.18 |  |
| HIV | 0.52 | 0.25 | 0.67 | 0.23 | 0.83 | 0.47 |  |
| Listeriosis | 0.00 | 0.00 | 0.00 | 0.00 | 0.33 | 0.03 |  |
| Malaria | 0.03 | 0.25 | 0.08 | 0.00 | 0.17 | 0.05 |  |
| Parvovirus | 0.03 | 0.00 | 0.00 | 0.05 | 0.17 | 0.04 |  |
| Rubella | 0.03 | 0.00 | 0.08 | 0.05 | 0.67 | 0.10 |  |
| Any STI in pregnancy | 0.00 | 0.00 | 0.00 | 0.00 | 0.50 | 0.04 |  |
| Syphilis | 0.03 | 0.25 | 0.17 | 0.05 | 0.33 | 0.10 |  |
| Toxoplasmosis, acute | 0.03 | 0.00 | 0.08 | 0.05 | 0.50 | 0.08 |  |
| Tuberculosis  | 0.07 | 0.00 | 0.00 | 0.09 | 0.67 | 0.11 |  |
| Urinary Tract Infection | 0.00 | 0.00 | 0.00 | 0.00 | 0.50 | 0.04 |  |
| Varicella | 0.00 | 0.00 | 0.00 | 0.05 | 0.50 | 0.05 |  |
| Zika exposure | 0.03 | 0.00 | 0.00 | 0.05 | 0.17 | 0.04 |  |
| **12.Injury, poisoning and procedural complications**  | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |  |
| Trauma in pregnancy | 0.00 | 0.00 | 0.00 | 0.00 | 0.17 | 0.01 |  |
| **13.Investigations**  | 0.03 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 |  |
| Blood group antibodies (e.g. Kell, RH) | 0.07 | 0.50 | 0.00 | 0.00 | 0.83 | 0.12 |  |
| Haematological or biochemical values outside of normal range  | 0.03 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 |  |
| **14.Metabolism and nutrition disorders** | 0.03 | 0.25 | 0.00 | 0.00 | 0.00 | 0.03 |  |
| Obesity | 0.07 | 0.25 | 0.00 | 0.00 | 1.00 | 0.12 |  |
| Underweight | 0.07 | 0.00 | 0.00 | 0.00 | 0.67 | 0.08 |  |
| Glucose intolerance | 0.03 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 |  |
| Type 1 diabetes mellitus  | 0.31 | 0.25 | 0.33 | 0.05 | 0.83 | 0.27 |  |
| Type 2 diabetes mellitus  | 0.17 | 0.25 | 0.33 | 0.00 | 0.83 | 0.21 |  |
| **15.Musculoskeletal and connective tissue disorders**  | 0.07 | 0.00 | 0.00 | 0.00 | 0.17 | 0.04 |  |
| Neuromuscular disease | 0.00 | 0.00 | 0.00 | 0.00 | 0.33 | 0.03 |  |
| **16.Neoplasms benign & malignant**  | 0.14 | 0.00 | 0.00 | 0.00 | 0.00 | 0.05 |  |
| Malignancy | 0.34 | 0.00 | 0.08 | 0.14 | 0.67 | 0.25 |  |
| Uterine fibroids | 0.03 | 0.00 | 0.00 | 0.00 | 0.33 | 0.04 |  |
| **17.Nervous system disorders**  | 0.21 | 0.25 | 0.17 | 0.09 | 0.17 | 0.16 |  |
| Cerebrovascular accident, TIA | 0.00 | 0.00 | 0.00 | 0.00 | 0.67 | 0.05 |  |
| Guillain-Barre Syndrome | 0.34 | 0.00 | 0.17 | 0.05 | 0.00 | 0.18 |  |
| Multiple sclerosis | 0.03 | 0.25 | 0.00 | 0.00 | 0.50 | 0.07 |  |
| Any seizure disorder | 0.31 | 0.50 | 0.17 | 0.00 | 0.33 | 0.21 |  |
| Controlled seizure disorder | 0.00 | 0.00 | 0.00 | 0.00 | 0.50 | 0.04 |  |
| Poor seizure control or multiple medications | 0.07 | 0.00 | 0.00 | 0.00 | 0.67 | 0.08 |  |
| **18.Psychiatric disorders**  | 0.48 | 0.50 | 0.42 | 0.09 | 0.67 | 0.37 |  |
| Depression or anxiety  | 0.03 | 0.00 | 0.08 | 0.00 | 0.33 | 0.05 |  |
| Other mental health conditions | 0.07 | 0.00 | 0.00 | 0.00 | 0.17 | 0.04 |  |
| Stable mental health disorder | 0.00 | 0.00 | 0.00 | 0.00 | 0.17 | 0.01 |  |
| Unstable mental health disorder | 0.07 | 0.25 | 0.00 | 0.00 | 0.17 | 0.05 |  |
| **18.Renal and urinary disorders**  | 0.24 | 0.25 | 0.25 | 0.14 | 0.67 | 0.25 |  |
| Glomerulonephritis | 0.00 | 0.25 | 0.00 | 0.00 | 0.33 | 0.04 |  |
| Proteinuria | 0.00 | 0.25 | 0.00 | 0.00 | 0.17 | 0.03 |  |
| Renal abnormality | 0.03 | 0.25 | 0.00 | 0.00 | 0.33 | 0.05 |  |
| **19.Reproductive system and breast disorders**  | 0.03 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 |  |
| Cervical incompetence/insufficiency | 0.07 | 0.00 | 0.08 | 0.00 | 0.50 | 0.08 |  |
| Prolapse | 0.00 | 0.00 | 0.00 | 0.00 | 0.17 | 0.01 |  |
| **20.Respiratory, thoracic and mediastinal disorders**  | 0.17 | 0.25 | 0.25 | 0.14 | 0.33 | 0.19 |  |
| Asthma, general | 0.17 | 0.25 | 0.08 | 0.00 | 0.17 | 0.11 |  |
| Mild-moderate asthma | 0.03 | 0.25 | 0.00 | 0.00 | 0.33 | 0.05 |  |
| Severe asthma | 0.07 | 0.25 | 0.17 | 0.00 | 0.50 | 0.11 |  |
| Cystic fibrosis | 0.00 | 0.00 | 0.00 | 0.00 | 0.17 | 0.01 |  |
| Pulmonary hypertension | 0.00 | 0.00 | 0.00 | 0.00 | 0.33 | 0.03 |  |
| **21.Surgical and medical procedures**  | 0.03 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 |  |
| Major surgery during pregnancy | 0.03 | 0.00 | 0.00 | 0.00 | 0.17 | 0.03 |  |
| **23.Vascular disorders**  | 0.03 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 |  |
| Aneurysm  | 0.00 | 0.00 | 0.00 | 0.00 | 0.17 | 0.01 |  |
| Collagen vascular disease | 0.03 | 0.00 | 0.08 | 0.00 | 0.33 | 0.05 |  |
| Hypertension general | 0.17 | 0.25 | 0.25 | 0.00 | 0.50 | 0.16 |  |
| Hypertension (controlled) | 0.00 | 0.00 | 0.00 | 0.00 | 0.17 | 0.01 |  |
| Hypertension (uncontrolled) | 0.03 | 0.00 | 0.00 | 0.00 | 0.17 | 0.03 |  |
| Thromboembolism | 0.03 | 0.00 | 0.00 | 0.00 | 0.50 | 0.05 |  |
| **D. Current pregnancy-related conditions and fetal conditions** | 0.10 | 0.25 | 0.17 | 0.00 | 0.00 | 0.08 |  |
| Abnormal genetic screen/serum screen | 0.07 | 0.00 | 0.08 | 0.00 | 0.17 | 0.05 |  |
| Abnormal nuchal translucency | 0.07 | 0.00 | 0.08 | 0.00 | 0.50 | 0.08 |  |
| Antepartum hemorrhage | 0.00 | 0.00 | 0.00 | 0.00 | 0.83 | 0.07 |  |
| ART/IVF pregnancy | 0.03 | 0.25 | 0.00 | 0.00 | 0.17 | 0.04 |  |
| Cholestasis  | 0.07 | 0.00 | 0.00 | 0.00 | 0.50 | 0.07 |  |
| Cord prolapse | 0.00 | 0.00 | 0.00 | 0.00 | 0.17 | 0.01 |  |
| Fetal congenital anomaly (genetic or structural) | 0.21 | 0.00 | 0.33 | 0.14 | 0.50 | 0.22 |  |
| GBS infection in pregnancy  | 0.03 | 0.00 | 0.00 | 0.00 | 0.17 | 0.03 |  |
| Gestational Diabetes | 0.14 | 0.25 | 0.33 | 0.00 | 0.50 | 0.16 |  |
|  Gestatational diabetes controlled by diet | 0.00 | 0.00 | 0.00 | 0.00 | 0.50 | 0.04 |  |
|  Gestational diabetes - insulin dependent | 0.03 | 0.00 | 0.00 | 0.05 | 0.83 | 0.10 |  |
|  Gestational diabetes controlled by medication | 0.03 | 0.00 | 0.00 | 0.05 | 0.17 | 0.04 |  |
| Gestational hypertension | 0.17 | 0.75 | 0.17 | 0.05 | 0.83 | 0.22 |  |
| Gestational proteinuria | 0.00 | 0.25 | 0.00 | 0.00 | 0.50 | 0.05 |  |
| Hyperemesis gravidarium | 0.03 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 |  |
| Invasive placenta | 0.00 | 0.00 | 0.00 | 0.05 | 0.17 | 0.03 |  |
| IUGR or SGA | 0.03 | 0.25 | 0.08 | 0.05 | 0.83 | 0.12 |  |
| LGA | 0.00 | 0.00 | 0.00 | 0.00 | 0.83 | 0.07 |  |
| Low lying placenta | 0.03 | 0.00 | 0.00 | 0.00 | 0.17 | 0.03 |  |
| Malpresentation | 0.00 | 0.00 | 0.00 | 0.00 | 0.83 | 0.07 |  |
| Multiple pregnancy | 0.17 | 0.00 | 0.42 | 0.23 | 0.67 | 0.26 |  |
| Oligohydramnios | 0.03 | 0.00 | 0.00 | 0.05 | 0.67 | 0.08 |  |
| Placenta previa | 0.00 | 0.00 | 0.00 | 0.05 | 0.67 | 0.07 |  |
| Polyhydramnios | 0.00 | 0.00 | 0.00 | 0.05 | 0.67 | 0.07 |  |
| PPROM | 0.03 | 0.00 | 0.00 | 0.00 | 0.67 | 0.07 |  |
| Pre-eclampsia | 0.31 | 1.00 | 0.25 | 0.05 | 0.67 | 0.29 |  |
| Premature labor | 0.24 | 0.75 | 0.25 | 0.14 | 0.83 | 0.29 |  |
| PROM | 0.00 | 0.00 | 0.08 | 0.00 | 0.67 | 0.07 |  |
| Receiving anti-coagulants | 0.10 | 0.00 | 0.08 | 0.00 | 0.17 | 0.07 |  |
| Suspected aminotic fluid embolism  | 0.00 | 0.00 | 0.00 | 0.00 | 0.17 | 0.01 |  |
|   | Phase I/II studies | Phase III studies | Post licensure studies | Observational studies | Guidelines | All studies and guidelines |  |
| **Total risk factors** | **119** | **74** | **73** | **48** | **140** | **164** |  |

|  |  |
| --- | --- |
|  Appendix Key:  | Not mentionned |
|   | 10-20% |  |
|   | 21-40% |  |
|   | 41-60% |  |
|   | 61-80% |  |
|   | 81-100% |  |

Appendix 3: Obstetric Risk Factors Associated with Most Commonly Listed Exclusion Criteria

**Current Pregnancy General Risk Factors**

1. Advanced Maternal Age

A study published in 2014 by the WHO analyzed data from over 300,000 women with singleton pregnancies from 29 countries in Africa, Asia, Latin America, and the Middle East, found increasing risk of adverse pregnancy outcomes with increasing age. Compared with women aged 20-34 years, after adjusting for multiple confounding factors with multivariate regression, women above age 35 years had increased odds ratios of several adverse events. Odds ratios (OR) of maternal near miss (women who nearly died but survived a complication that occurred during pregnancy, childbirth, or within 42 days of termination of pregnancy) of 1.5 (95% confidence interval (CI) 1.3-1.8), maternal death of 1.7 (95% CI 1.2-2.6) and severe maternal outcome of 1.6 (95% CI 1.4-1.8) were observed.1 Also, perinatal outcomes such as preterm labor, OR of 1.2 (95% CI 1.1,1.2), still births, OR of 1.5 (95% CI 1.4,1.7) and perinatal mortality, OR of 1.4 (95% CI 1.3, 1.5) were increased.2

2. Young maternal age

Both adverse pregnancy and neonatal outcomes have been reported to be more common among adolescents. Over the past ten years, retrospective analyses of the association of young age and maternal and neonatal outcomes have described associations of increased preterm delivery, low birth weight and neonatal complications, such as admission to neonatal intensive care units (ICUs) and infant death.3-7 Higher rates of anemia and postpartum complications in the mothers have also been described.

The largest of these studies was a WHO survey conducted in 359 health centers in 29 countries.4 Outcomes in young women, 10-19 years of age, were compared with women aged 20 -24 years of age. Young age was associated with eclampsia, puerperal endometritis, systemic infections, low birthweight (adjusted odds ratio [aOR] 1.17; 95% CI 1.0-1.3), preterm delivery (aOR 1.6, 95% CI 1.2-1.87) and severe neonatal conditions (such as live born baby with birthweight <1500g, <32 weeks gestational age at birth or a 5 minute Apgar of <7, aOR 1.56; 95% CI 1.2-1.7). A high risk of stillbirth was found among all adolescent age groups, but the risk was significant only among adolescent mothers aged 16-17 years (aOR 1.32; 95% CI 1.11-1.57). This study noted that rates of cesarean section was higher among the younger adolescent mothers (15 years or younger).

A more recent prospective, population-based, multi country, observational study was conducted in 6 low and middle income countries (Kenya, Zambia, India, Pakistan, Guatemala, Argentina) to assess the association of age with maternal and neonatal outcomes.8 Approximately 269,000 women, aged 24 years or younger, were enrolled between 2010-2013. Compared to women 19-24 years old, age less than 19 years was not associated with increased adverse maternal outcomes in this study, however significantly higher rates of preterm birth and low birth weight infants were observed. There were some variability noted by region, with no perinatal differences noted in Asia between adolescents and adults.

3. Current alcohol or drug use

To ascertain risk for the exclusion criteria of current alcohol or drug use, we investigated some of the most commonly used substances. It may be useful to note that some of these complications listed may not be related to the actual drug, but to the associated social risk factors (e.g. smoking, domestic violence, sexually transmitted infections) that can accompany substance use.

Alcohol use in pregnancy can occur before conception is known, and its use can continue once pregnancy is diagnosed,9 yet there is no known safe level of alcohol consumption in pregnancy. Compared to women drinking <1 drink/week, women drinking ≥5 drinks/week have an increased risk of spontaneous abortion (1.4% versus 8.9% respectively),10 and an increased risk for stillbirth (relative risk [RR] 2.96; 95% CI 1.37, 6.41).11 Fetal alcohol exposure is associated with an increased risk of congenital anomalies in multiple organ systems. In a review of case series of individuals with fetal alcohol spectrum disorder, the rate of congenital heart disease ranged from 33% to 100%.12 The rate of intrauterine growth restriction is increased in fetal alcohol spectrum disorder, and pre- or postnatal growth deficiency is a requirement for the diagnosis.13

Opioid use in pregnancy is rapidly increasing in the United States,14 and becoming more common in other parts of the world.15 Data on the risk of congenital anomalies resulting from opioid exposure are conflicting, and these outcomes are rare.16 Pregnant women who use opioids are at increased risk of complications compared to those not using opioids, including placental abruption (3.8 vs. 1.1%); aOR 2.4 [95% CI 2.1 - 2.6]), stillbirth (1.2 vs. 0.6%; aOR 1.5 [95% CI, 1.3 - 1.8]); fetal growth restriction (6.8 vs. 2.1%; aOR 2.7 [95% CI 2.4 to 2.9]); preterm labor (17.3 vs. 7.4% ; aOR 2.1 [95% CI, 2.0 to 2.3]), and maternal cardiac arrest (0.04 vs. 0.01%; aOR 3.6 [95% CI 1.4 to 9.1]).17 Injection drug use in particular is associated with an increased risk of infection and maternal to child transmission of HIV and viral hepatitis.18

Methamphetamine use in pregnancy is associated with a two-fold increase in fetal growth restriction,19 as well as increased odds of gestational hypertension (OR 1.8; 95% CI 1.6-2.0), preeclampsia (OR 2.7; 95% CI 2.4-3.0), intrauterine fetal death (OR 5.1; 95% CI 3.7-7.2), and placental abruption (OR 5.5; 95% CI 4.9-6.3).20

Cocaine use in pregnancy is less common than alcohol or opioid use, but is associated with significant pregnancy risks. Preterm birth (OR 3.38, 95% CI 2.72-4.21), low birth weight (OR 3.66, 95% CI 2.90-4.63), and small for gestational age infants (OR 3.23, 95% CI 2.43-4.30) are all more common in pregnancies complicated by cocaine use.21 Cocaine use in pregnancy is also associated with an increased risk of placental abruption (OR 3.92, 95% CI 2.77-5.46).22 Furthermore, the hypertensive effects of cocaine place the pregnant woman at increased risk of intracranial hemorrhage and cardiac toxicity.23

Benzodiazepine use in pregnancy is associated with an increased risk of spontaneous abortion (OR 2; 95% CI 1-3)24 and preterm birth (OR 1.5; 95% CI 1.3-1.8).25 Administration proximal to delivery is also associated with neonatal toxicity and withdrawal.24

**Past Obstetric History**

4. Congenital anomalies

Congenital anomalies are conditions of prenatal origin that are present at birth, potentially impacting an infant’s health, development and/or survival.26 Congenital anomalies encompass a wide array of structural and functional abnormalities that can occur in isolation (i.e., single defect) or as a group of defects (i.e., multiple defects), and can be of variable severity. The causes of congenital anomalies are wide-ranging, with many anomalies remaining of undetermined etiology. Structural anomalies are often due to errors in embryogenesis occurring at critical periods of fetal development. Critical exposure periods during pregnancy can vary by organ system or type of anomaly. However, first trimester (gestational age 1–13 weeks) is generally considered the highest risk period. Some structural and many functional defects are attributed to underlying genetic defects or chromosomal abnormalities. These defects may be due to one or both parents being genetic carriers, one or both parents sharing the disease state, or the occurrence of de novo mutations. The timing of clinical recognition of major anomalies varies both by type of defect and by access to health care.

The consequences of congenital anomalies on the infant and the risk to the mother in subsequent pregnancies therefore can be variable, depending on the type and origin of the specific defect. Anomalies which affect an infant’s life expectancy, health status, physical or social functioning are described as “major” anomalies, while “minor” anomalies are those with little or no impact on health or short-term or long-term function.27

In addition to the type of anomaly itself, maternal factors may be associated with increased risk for congenital anomalies. In one study in Africa, the maternal factors of maternal age > 35 years (OR 2.2, 95% CI 1.1-4.3, p 0.024), inadequate attendance to antenatal clinics (OR 2.1; 95% CI 1.4-3.3, p=<0.001) and lack of peri-conceptional use of folic acid (OR 3.1; 95% CI 1.4-6.7, p=0.005) were significantly associated with congenital anomalies.28 Advanced maternal age is a well known risk factor for major congenital anomalies.29 In another study conducted in the US, elevated maternal body mass index (> 30 Kg/m2) and early gestationl age less than 18 weeks were associated with incomplete fetal anatomic surveys by ultrasound, with poor visualization of cardiac and spine structures, and 5% of these patients had anomalies or aneupleudy markers on subsequent scans, most being cardiac defects.30

In one study conducted in Denmark, women who delivered infants with congenital heart defects had increased risk of preterm preeclampsia (OR 7.00; 95% CI 6.11-8.03) and later preterm pre-eclampsia (OR 2.82; 95% CI 2.38-3.34) in the same pregnancy, with a less prominent association with term preeclampsia (OR 1.16; 95% CI 1.06-1.27). Association strengths were reported to be consistent across heart defect types. Similarly, having an infant with congenital heart defects in a previous pregnancy were strongly associated with preterm preeclampsia in subsequent pregnancies (early preterm preeclampsia: OR, 2.37; 95% CI, 1.68–3.34; late preterm preeclampsia: OR, 2.04; 95% CI, 1.52–2.75); and preterm preeclampsia in a previous pregnancy, (but not term preeclampsia or gestational hypertension), was associated with congenital heart defects in later pregnancies (early preterm preeclampsia: OR, 7.91; 95% CI, 6.06–10.3; late preterm preeclampsia: OR 2.83; 95% CI, 2.11–3.79; term preeclampsia: OR, 0.98; 95% CI 0.88–1.10; gestational hypertension: OR, 1.13; 95% CI 0.92–1.38).31 The authors hypothesize that the strong associations across pregnancies support a maternal origin of these findings.

5. Hypertensive Disease. Chronic hypertension complicates 5-8% of pregnancies and is associated with adverse maternal and fetal outcomes. Women with chronic hypertension are more likely to have a cesarean delivery (OR 2.7; 95% CI 2.4-3.0)32 and develop gestational diabetes (OR 1.8; 95% CI 1.4-2).33 Chronic hypertension is associated with two-fold higher risk of placental abruption.34 Preterm birth (RR 2.7; 95% CI 1.9-3.6), low birth weight (RR 2.7; 95% CI 1.9-3.8), neonatal ICU admission (RR 3.2; 95% CI 2.2-4.4) and perinatal death (RR 4.2; 95% CI 2.7-6.5) are all more common in pregnancies complicated by chronic hypertension.35 Superimposed preeclampsia develops in 29% of these pregnancies (compared to baseline risk of preeclampsia 5-8%).

Recurrence risk for hypertensive disorders of pregnancy varies depending on timing in pregnancy and severity of the initial disease. The risk may be as high as 65% in women with early-onset, severe preeclampsia.36 If an incident pregnancy was complicated by gestational hypertension, the odds of recurrence was found to be 1.58 (95% CI 1.4-2.2).37

6. Stillbirth

Several meta-analyses reported 2 to 10-fold increase in the risk of stillbirth and other complications (placental abruption, preterm delivery, low birth-weight, and preeclampsia) in subsequent pregnancies in women with a previous stillbirth compared to the general population.38 In a retrospective analysis, the reported adjusted risk for unexplained stillbirth after any stillbirth was 4.18 (95% CI 1.36 to 12.89).39 Trends have also show that stillbirth rates are slightly higher among male compared to female fetuses.40 Worldwide, 67% of stillbirths occur in rural families, where access to skilled birth attendance and caesarean sections are much lower than in those births occurring in urban settings.41 Different systematic reviews have confirmed very young or advanced maternal age, and nulliparity, irrespective of age, to be associated with a higher risk of stillbirth.42

A multi-site, population-based, case-control study conducted in the US involving 614 cases and 1816 controls in 59 tertiary care and community hospitals evaluated the association between stillbirth and risk factors known at pregnancy confirmation.43 In this study, nulliparity and history of prior stillbirth remained strongly associated with increased risk of stillbirth. When compared with nulliparous women without previous pregnancy losses (aOR 1.98; 95% CI 1.51–2.60), there was a progressive increase in the risk for stillbirth for nulliparous with previous pregnancy losses (aOR 3.13; 95% CI 2.06–4.75), and multiparous with previous pregnancy losses (aOR 5.91; 95% CI 3.18–11.00). A large number of other risk factors associated with stillbirth, including diabetes; maternal age > 40 years; maternal AB blood type; history of drug addiction and substance abuse (including cocaine, cannabis and alcohol); smoking during the 3 months prior to pregnancy; obesity/overweight; not living with a partner; and multiple gestation with significantly higher rates of stillbirth observed in monochorionic twins than in dichorionic, were also cited in other review articles.44-49

7. Preterm Birth:

Having a prior preterm birth (delivery at less than 37 weeks of gestation) significantly increases the risk of preterm birth in a subsequent pregnancy; women with a history of preterm birth have a 22% risk of preterm birth in a following pregnancy compared to 9% in women without a history of prior preterm birth. The tendency to recur increases with the number of prior preterm deliveries, earlier gestational age at prior delivery, and the order, with higher risk of subsequent preterm delivery if the immediately preceding birth was preterm.50 If the prior preterm birth was iatrogenic due a maternal health factor such as elevated blood pressure, or fetal factor, such as an anomaly, that is also relevant in assessing the risk of preterm birth in the subsequent pregnancy.

8. Prior Abortion

Adverse pregnancy and neonatal outcomes have been associated with a history of prior abortion. Published studies have evaluated the impact of prior spontaneous abortions, elective/induced abortions, and the effect of multiple spontaneous abortions on pregnancy and neonatal outcomes. Preterm birth is the most commonly reported association with early pregnancy loss, however risk of perinatal death, small gestational age and low birth rate have also been reported.51-53 Conversely a few studies in specific populations (teenagers or among those with recurrent spontaneous abortions) have not identified increased risk of adverse obstetrical outcomes with prior abortions.54,55

In a large meta-analysis of 36 studies involving over 1 million women, the authors concluded that women with a history of induced or spontaneous abortion had a higher risk of preterm birth than those without this history (5.7% vs 5.0%; OR, 1.44, 95% CI, 1.09-1.90), as well as a higher risk of having a low birth weight infant (7.3% vs 5.9%; OR, 1.41, 95% CI, 1.22-1.62) or small for gestational age (10.2% vs 9.0%; OR, 1.19, 95% CI, 1.01-1.42).56

**Current Maternal Medical Conditions**

9. Autoimmune Disease

Autoimmune diseases, and in particular rheumatalogic diseases, affect women of childbearing age. Women with these diseases, especially systemic lupus erythematosus (SLE), are at increased risk of adverse pregnancy outcomes and complications as a result of poor placentation. These adverse outcomes are often cited as maternal–placental syndrome (i.e. pre-eclampsia (14–23%),57 eclampsia, preterm delivery (20–31%)58,59 and fetal growth restriction (5–23%). 60,61 Flares of SLE including lupus nephritis are associated with worse obstetric outcomes, including a particularly high risk of pre-eclampsia and preterm deliveries, especially if their disease is active within 6 months of conception.62-64 For the fetus/neonate there is an increased risk of miscarriage, preterm birth, low birth weight, admission to neonatal special care units and neonatal death.65-68

10.Bleeding Disorders

The heterogeneity of bleeding abnormalities underscore the challenge for discussing the impact on future pregnancies. However, the impact on pregnancy for a few of the thrombophilias have been well characterized and consistently demonstrate increased risk for adverse pregnancy outcomes. Factor V Leiden carriers have an increased risk of early pregnancy loss (OR 1.68; 95% CI 1.1-2.6), recurrent first trimester loss (OR 1.9; 95% CI 1.0-3.61), late pregnancy loss (OR 2.1; 95% CI 1.1-3.8), preeclampsia (OR 2.2; 95% CI 1.5-3.3), and placental abruption (OR 4.7; 95% CI 1.1-19.6). This data can include both the homozygous and heterozygous carriers, making it difficult to separate risk between these carrier states. The presence of anticardiolipin antibodies have been associated with increased early pregnancy loss (OR 3.4; 95% CI 1.3-8.7), and reccurent first trimester loss (OR 5.5; 95% CI 1.8-14.0), as well as late loss (OR 3.3; 95% CI 1.6-6.7) and preeclampsia (OR 2.7; 95% CI 1.7-4.5), and fetal growth restriction (OR 6.9; 95% CI 2.7-17.7). Lupus anticoagulants are associated with early pregnancy loss (OR 3.0; 95% CI 1.0-9.8), and second trimester loss (OR 14.3; 95% CI 4.7-43.2).69 Pregnancy outcomes in women with von Willebrand Disease are generally favorable, but post partum hemorrhage is increased, and may occur in up to 50% of women.70 Abnormal platelet levels are relatively common in pregnancy (in one study, 6% of 15,471 women had platelets less than 150,000/μL)71 and may precede pregnancy, develop during pregnancy, or be induced by pregnancy. Immune thrombocytopenic purpura (ITP), caused by antibodies directed against one or more platelet glycoproteins, can be a primary, chronic autoimmune disease and the impact of pregnancy on this condition is not consistent. Secondary forms of chronic thrombocytopenia appear in association with lupus, and several other systemic diseases.72

11. Cardiac disease

Maternal and fetal risks related to cardiac disease in pregnancy are dependent on the type and severity of cardiac condition in question. Multiple risk stratification tools are available to help determine risk status. The modified WHO classification assigns pregnant women a category of risk that is reflective of the cardiac condition in question.73 The classes range from Class I (conditions associated with no detectable increased risk of maternal mortality and no/mild increase in morbidity) through Class IV (associated with extremely high risk of maternal mortality or severe morbidity; pregnancy is contraindicated).

Fetal outcomes are inextricably linked to type and severity of maternal cardiac disease. Rates of fetal mortality range from baseline for women with normal functional class to 30% for women with severe symptoms.74 In women with cyanotic heart disease, the rate of fetal mortality is around 50%, and for those women with live births, 37% are premature.75 Infants of mothers with congenital heart disease are at increased risk of cardiac anomalies, though the rate is dependent on type of congenital lesion, and the rate differs among various studies but is roughly 4%.76

12. Diabetes Mellitus

Pre-gestational diabetes (diabetes known and diagnosed prior to pregnancy) complicates 1-2% of all pregnancies and confers significant risks to both the mother and the fetus.77 The risk of major congenital malformations in fetuses of diabetic mothers is more than twice that of the general population (RR 2.44; 95% CI 1.92-3.10).78 This risk is predominantly related to glycemic control; the absolute risk of congenital anomalies in a woman with a periconceptional glycosylated hemoglobin concentration of 5.5% is 2%, whereas the risk at a glycosylated hemoglobin concentration of ≥14% is 20%.79 Both medically indicated (OR 8.1; 95% CI 6.0-10.9) and spontaneous (OR 1.6; 95% CI 1.2-2.2) preterm births are more common in women with diabetes.80 Women with diabetes are also more likely to have fetuses with growth abnormalities, both macrosomia and growth restriction.81 The risk of stillbirth is significantly elevated in women with pre-gestational diabetes (RR 6.1; 95%CI 4.44-8.38).82

In women with pre-gestational diabetes, hypertensive disorders of pregnancy are more common. A prospective study found that 20% of pre-gestational diabetics developed preeclampsia, compared with 5-8% in those without. The odds of a cesarean delivery are elevated in women with pregestational diabetes (OR 1.65; CI 1.32-2.07).83 Additionally, diabetes is associated with an increased risk of maternal mortality.84

Gestational diabetes occurs in approximately 10-25% of pregnancies.85 While true gestational diabetes (diabetes that did not exist prior to pregnancy) is not associated with an increased risk of congenital malformations, macrosomia/large for gestational age (13.6% vs 7.7%)86 and preeclampsia (OR 1.29, CI 1.19-1.41)87 are more likely compared with pregnancies without gestational diabetes. In some studies, stillbirth is also more common in pregnancies complicated by gestational diabetes.88,89

13 Immunocompromise

13 a. HIV

Research studies on pregnancy in HIV seropositive women have largely focused on outcomes based on viral suppression, use of antiretroviral therapy (ART), and resource-setting. Two systematic reviews and meta-analyses from the UK in 1998 examined the effect of HIV in pregnancy on maternal survival and perinatal outcomes.90,91 These analyses found summary OR for maternal death of 1.8 (95% CI 0.99-3.3) while HIV disease progression was 1.41 (95% CI 0.85-2.33), and progression to an AIDS-defining illness was 1.63 (95% CI 1.0-2.67), indicating a possible small increase in adverse maternal outcome among HIV-positive women.90

In the analysis of perinatal outcomes related to maternal HIV infection there were findings of increased spontaneous abortion with OR 4.05 (95% CI 2.75-5.96); stillbirth OR 3.91 (95% CI 2.65-5.77); perinatal mortality OR 1.79 (95% CI 1.14-2.81); neonatal mortality OR 1.10 (95% CI 0.63-1.93); infant mortality OR 3.69 (95% CI 3.03-4.49); intrauterine growth restriction OR 1.7 (95% CI 1.43-2.02); low birth weight OR 2.09 (95% CI 1.86-2.35) and preterm delivery OR 1.83 (95% CI 1.63-2.06).91 A more recent systematic review and meta-analysis found that compared to HIV-negative women, pregnancy in HIV-positive *ART-naïve* women was associated with an increased RR for preterm birth 1.5 (95% CI 1.24-1.82), low birthweight 1.62 (95% CI 1.41-1.86), small for gestational age 1.31 (95% CI 1.14-1.51), and stillbirth 1.67 (95% CI 1.05-2.66). Retrospective cohort studies also analyzed in this project suggested an increased risk for term low birthweight infants with RR 2.62 (95% CI 1.15-5.93) and preterm low birth weight RR 3.25 (95% CI 2.12-4.99).92 While ART has been shown to decrease perinatal transmission of HIV, initiation of ART prior to or during pregnancy may not mitigate risk of perinatal adverse events in HIV-positive women. A systematic review and meta-analysis from the WHO in 2017, for example, found that compared to women who started ART after conception, women who began ART prior to conception had a higher risk of delivering preterm (pooled RR 1.20; 95% CI 1.01-1.44); delivering very preterm (pooled RR 1.53; 95% CI 1.22-1.92); and having a low-birth weight infant (pooled RR 1.30; 95% CI 1.04-1.62).93

13 b. Primary immunodeficiencies

There are no large studies on the effect of primary immunodeficiencies (non-HIV associated immunodeficiency) on pregnancy outcomes likely due to the heterogeneity of the conditions that comprise primary immunodeficiencies and the variable phenotypes of each individual condition. Results of an online survey on fertility and pregnancy outcomes of 490 women with common variable immune deficiency (CVID) and 100 women with hypogammaglobinemia found lower fertility rates, but similar spontaneous abortion and live birth rates compared to the general population.94 Furthermore, a Japanese case series of four cases of CVID in pregnancy demonstrated good overall pregnancy outcomes, however, all women experienced increased risk of antepartum infection including upper respiratory tract infection, sinusitis, cystitis and human papilloma virus-related genital warts and cervical dysplasia.95 A case series from Iran in 2018 reported on 9 pregnancies affected by primary immune deficiency which had overall good outcomes, however required complex prenatal care.96 A case of purine nucleoside phosphorylase deficiency in pregnancy resulted in a good neonatal outcome.97 Finally, a case report of chronic granulomatous disease carrier reported findings of chorioamnionitis in each pregnancy with the final pregnancy resulting in delivery at 25 weeks gestational age due to infection.98

14. Obesity

Adipose tissue is metabolically active, and pre-pregnancy obesity (body mass index [BMI] ≥ 30 kg/m2) and excessive weight gain during pregnancy have a serious impact on maternal, fetal and neonatal outcomes**.** According to a British cohort study of 28,713 pregnancies,99 a comparison of pregnancy outcomes was made on the basis of maternal BMI. Compared to women with normal BMI prior to pregnancy, the following outcomes were significantly more common in obese pregnant women (OR [95% confidence interval] for BMI 25-30 and BMI≥30 respectively): gestational diabetes mellitus (1.68 [1.53-1.84], 3.6 [3.25-3.98]); pre-eclampsia (1.44 [1.28-1.62], 2.14 [1.85-2.47]); induction of labor (2.14 [1.85-2.47], 1.70 [1.64-1.76]); delivery by emergency caesarian section (1.30 [1.25-1.34], 1.83 [1.74-1.93]), and postpartum hemorrhage (1.16 [1.12-1.21], 1.39 [1.32-1.46]). Infectious complications are increased in women with BMI 25-30 and BMI≥30: genital tract infection (1.24 [1.09-1.41], 1.30 [1.07-1.56]); urinary tract infection (1.17 [1.04-1.33], 1.39 [1.18-1.63]); wound infection (1.27 [1.09-1.48], 2.24 [1.91-2.64]). Additionally, birthweight above the 90th centile (1.57 [1.50-1.64], 2.36 [2.23-2.50]), and intrauterine death (1.10 [0.94-1.28], 1.40 [1.14-1.71]) are also increased. In all cases, increasing maternal BMI was associated with a higher degree of risk. 99 In a study evaluating 37,709 birth records from 1950 up to 1 January 2012,100 all-cause mortality was increased in offspring of obese mothers compared with mothers with normal BMI even after adjustment for maternal age at delivery, socioeconomic status, sex of offspring, current age, birth weight, gestation at delivery, and gestation at measurement of BMI (OR 1.35, 95 % CI 1.17–1.55). Offspring of obese mothers were also found to have an increased risk of hospital admission for a cardiovascular event (1.29, 1.06 to 1.57) compared with those of mothers with normal BMI.100

15. Psychiatric Disease

Women with psychiatric disease are commonly excluded from studies, including vaccine trials. This may be related to concerns for several factors not related to medical complications including the ability to comply and adhere to the study protocol, questions about the ability to offer informed consent, and also that persons with mental illness can be considered a vulnerable population and, as such, may not be routinely considered eligible for trials. A few reports of psychiatrics disorders and pregnancy outcomes link maternal psychiatric illness with adverse pregnancy outcomes. In a population-based cohort of more than 500,000 births, women with a psychiatric diagnosis (as recorded by Internatinal Classification of Diseases 9th Edition Clinical Modification (ICD-9-CM) codes) found women had up to a three-fold increased incidence of very low or low birthweight neonate or preterm delivery. Another study of 1100 women found women with depression were 1.5 times more likely to delivered early compared with non depressed women.101-104

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