



## Commentary

## Spontaneous abortion and ectopic pregnancy: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data



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### 1. Preamble

*1.1. Need for developing case definitions and guidelines for data collection, analysis, and presentation for spontaneous abortion and ectopic pregnancy as adverse events following immunization during pregnancy*

Vaccine-preventable infectious diseases are responsible for maternal, morbidity and mortality. Immunization of pregnant

women can protect against vaccine-preventable infections, and may have the added benefit of direct fetal protection. Outcomes of spontaneous abortion and ectopic pregnancy following maternal receipt of vaccination have been less studied. There have been few prospective clinical trials evaluating vaccination in pregnancy; most safety data available are derived from registries where outcomes are passively reported.

Spontaneous abortion and ectopic pregnancy are important pregnancy outcomes that should be included in vaccine registries or included as important outcomes in vaccine research. As many organizations define pregnancy loss uniquely we will compare and contrast the existing definitions and provide guidance for use of this adverse event term in studies of maternal immunization.

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Abbreviations used	
β-HCG	beta human chorionic gonadotropin
HPV	human papillomavirus
IIV	Inactivated influenza vaccines
MMR	Measles, mumps, rubella
MR	Measles, rubella
SA	Spontaneous abortion
TT	Tetanus toxoid
Td	Tetanus, diphtheria vaccine
Tdap	Tetanus, diphtheria, pertussis vaccine
TVUS	Transvaginal ultrasound
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

### Definition and diagnosis of spontaneous abortion and ectopic pregnancy

*First trimester spontaneous abortion (Less than 14 weeks 0 days gestation)*

Many terms have been used to describe the failure of an early pregnancy, including: early pregnancy loss, early pregnancy failure, miscarriage, and spontaneous abortion. Pregnancy failure can be further classified as inevitable, missed, anembryonic, or embryonic demise [1,2]. For the purposes of this document, we will use the term “spontaneous abortion” (“SA”) to describe early pregnancy loss. Various national and international organizations have released guidelines for the diagnosis and/or workup of suspected early or first trimester spontaneous abortion, which are presented in the Tables.

*Second trimester spontaneous abortion (Between 14 weeks 0 days and 21 weeks 6 days)*

The arbitrary division by gestational age between abortion and stillbirth complicates the definition and diagnostic criteria for second trimester abortion. Existing definitions are outlined in the Tables.

#### Ectopic pregnancy

Ectopic pregnancy is one in which the pregnancy implants in a location other than the uterine endometrium. While most ectopic pregnancies occur in the fallopian tube (up to 97%), pregnancies can also implant in the abdomen, cervix, ovary and cornua of the uterus [3]. Society guidelines agree that the evaluation of a woman with a pregnancy of uncertain location should include an ultrasound examination followed by serum measurement of beta human chorionic gonadotropin (β-HCG) level if no intrauterine pregnancy is identified by ultrasound. If the serum β-HCG is above the discriminatory zone (the serum β-HCG level at which an intrauterine pregnancy should be visible, generally around 1500–2000 mIU/ml) and no intrauterine pregnancy is identified, an ectopic pregnancy is likely [3–5]. It should be noted that these society guidelines are primarily applicable for high resource settings given reliance on ultrasound for diagnosis, whereas the definitions in this document can be applied to all settings.

#### Induced abortion

While a full case definition for induced abortion is not included in this document, we recommend reporting this as a pregnancy outcome of interest. Induced abortion is the termination of pregnancy through medical or surgical procedures. Guidelines for safe, comprehensive care of women with induced abortion have been published by many groups, including the World Health Organization (WHO), the American Congress of Obstetricians and Gynaecologists (ACOG), the Royal College of Obstetricians and Gynaecologists (RCOG), the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), and the

Society of Obstetricians and Gynaecologists of Canada (SOGC) [6–11].

#### Epidemiology of spontaneous abortion and ectopic pregnancy

Spontaneous abortion (SA) is a common outcome. Published frequency of SA reported by several authors varies depending on the definition used [12–27]. In one systematic review study, the cumulative risk of SA for weeks 5 through 20 of gestation ranged from 11 to 22 miscarriages per 100 women (11–22%) [28]. This number varies by age group and study population, with women over 35 years of age experiencing the highest rates of SA [29], depending on gestational age, with a higher risk of SA earlier in gestation [30].

Ectopic pregnancy is a serious adverse pregnancy outcome and is one of the most common causes of maternal mortality in early pregnancy [31]. Because, particularly in high resource areas, it can be treated in the outpatient setting (the visits for which are not easily tracked) confirming the incidence of ectopic pregnancy is challenging. Reported rates range generally from 0.6% to 2.4% [32–36]. These rates may be increasing secondary to an increase in the use of assisted reproductive technologies and in pelvic infection [36]. The case mortality rate varies between low and high resource settings. The mortality rate for ectopic pregnancy in the United Kingdom is 3.6/10,000 cases [37]; this rate is ten times higher in developing countries [38], which may be in part explained by the difficulty diagnosing and managing ectopics in regions with limited availability of ultrasound and/or quantitative HCG.

#### Causes and risk factors of spontaneous abortion

The most common and well-documented cause of spontaneous abortion is aneuploidy, or abnormal chromosome number (genetic factors) [39]. Studies have shown that approximately 50% of spontaneous abortions are associated with fetal chromosomal abnormalities [39]. Many studies have shown that maternal age is also a risk factor for SA. A Danish registry study that examined the outcomes of more than 1.2 million pregnancies [29] demonstrated that the risk of spontaneous loss is three times higher in women age 40 or older as compared to the under 25 age group, making age a stronger risk factor than any other known effect [39]. Other risk factors include paternal age, previous pregnancy loss, thyroid abnormalities, pre-gestational diabetes, congenital uterine anomalies, exposure to lead, mercury, organic solvents and ionizing radiation, smoking and alcohol use [39]. A recent UK population based case-control study, found the following factors to be independently associated with SA after adjustment for confounding: high maternal age, previous SA, previous pregnancy termination and infertility, assisted conception, low pre-pregnancy body mass index, regular or high alcohol consumption, feeling stressed (including trend with number of stressful or traumatic events), high paternal age and conception occurring after a change in partner [40]. Additionally, multiparity carries a risk of reproductive failure, so pregnancy order, desired family size, and maternal age should be used in consideration of the etiology of SA [41]. Paternal exposures should also be considered when studying SA because theoretically any exposure of either parent prior to conception (i.e. males during spermatogenesis and females around time of conception and during pregnancy) could increase the risk of spontaneous loss [41]. Importantly, the risk of spontaneous abortion is inversely related to week of gestation; in one study, for example, the risk of SA at 6 completed weeks of gestation was found to be 9.4% while the risk at 10 completed weeks was 0.7% [42].

Several studies have suggested that certain psychological factors can contribute to the risk for SA, such as affective disorders (depression, dysthymia and mania), and anxiety disorders, including: agoraphobia, generalized anxiety disorder, panic disorder,

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