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Commentary

Antenatal bleeding: Case definition and guidelines for data collection, analysis, and presentation of 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 antenatal bleeding as an adverse event

Bleeding in the second and third trimesters of pregnancy affects 6% of all pregnancies, and has distinct etiologies from first-trimester bleeding [1]. In the vast majority of cases, antenatal bleeding is vaginal and obvious; however, rarely, it may be contained within the uterine cavity, the intraperitoneal space, or the retroperitoneal space. The etiologies of antenatal bleeding, also referred to as antepartum hemorrhage, are heterogeneous. In cases of severe antepartum hemorrhage, complications include preterm delivery, cesarean delivery, blood transfusion, coagulopathy, hemodynamic instability, multi-organ failure, salpingectomy/oophorectomy, peripartum hysterectomy, and in some cases, either perinatal or maternal death.

The goal of this Working Group was two-fold:

(1) to define sources of pathologic antenatal bleeding in the second or third trimester of pregnancy that are directly attributable to pregnancy and are either common and/or catastrophic;

(2) to define each source of antenatal bleeding for the purposes of future case ascertainment.

The charge to the Brighton Collaboration Working Groups to define various adverse obstetric and pediatric events includes an aim to more easily identify immunization-related adverse events. In the case of antenatal bleeding, our Working Group felt strongly that there is no biologic plausibility or mechanistic explanation linking immunizations to antenatal bleeding. Moreover, as immunizations and antenatal bleeding are common occurrences in the course of any individual pregnancy, it is quite likely that these events will co-occur without suggesting causation. To date, there is one case report of antenatal bleeding occurring in a pregnancy where a tetanus, diphtheria, and acellular pertussis vaccination was also administered [2]. However, the definition used to identify the antenatal bleeding event is not clearly presented. Standardized definitions across trials, surveillance systems, or clinical settings will facilitate case ascertainment and analysis of potential risk factors for antenatal bleeding.

In this document, we focus on placenta previa, morbidly adherent placentation, vasa previa, placental abruption, cesarean scar pregnancy, intra-abdominal pregnancy, and uterine rupture as important sources of antenatal bleeding. Cesarean scar pregnancy and intra-abdominal pregnancy are rarely listed as causes of antenatal bleeding in the second and third trimester. Nonetheless, we included these causes as they are more likely to result in late presentation with a high risk of heavy maternal bleeding in settings in which ultrasound diagnosis of pregnancy is limited or unavailable.

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Another common source of bleeding is labor, whether at term or preterm. Although preterm labor is pathologic and addressed in another document [3], bleeding in the context of labor alone is not. This is not addressed in our document. Non-obstetric genital tract bleeding may also occur during pregnancy, including neoplastic, infectious, traumatic, or iatrogenic causes. Urinary tract infections or hemorrhoids may also be misidentified as antenatal bleeding until additional workup is performed. This document will focus solely on the pregnancy-attributable etiologies of antenatal bleeding.

1.2. Methods for the development of the case definition, and guidelines for data collection, analysis, and presentation for antenatal bleeding as an adverse event

Following the process described in the overview paper [4] as well as on the Brighton Collaboration Website http://www.brightoncollaboration.org/internet/en/index/process.html, the Brighton Collaboration *Antenatal Bleeding Working Group* was formed in 2016 and includes members with a diverse background in clinical experience, location of practice, and scientific expertise in sources of antenatal bleeding. The composition of the working and reference group as well as results of the web-based survey completed by the reference group with subsequent discussions in the working group can be viewed at: http://www.brightoncollaboration.org/internet/en/index/working_groups.html.

To guide decision-making for case definitions, a literature search was performed in PubMed, including the following terms: pregnancy, antenatal bleeding, antepartum bleeding, antepartum hemorrhage, placenta previa, vasa previa, abruptio placenta, placenta accreta, morbidly adherent placenta, abdominal pregnancy, cesarean scar pregnancy, uterine rupture, abdominal pregnancy, intra-abdominal pregnancy, and vaccination. Major obstetric textbooks and published guidelines from major obstetric societies throughout the world were also surveyed. This review resulted in a detailed summary of 33 articles used to establish case definitions for antenatal bleeding. The search also resulted in the identification of 1 reference containing information regarding vaccination administration and antenatal bleeding (as defined by the listed PubMed search terms above).

1.3. Description of sources of antenatal bleeding

We first begin with a brief description of each etiology, the underlying pathophysiology, incidence, and risk factors. For most conditions, incidence data are derived from settings in which the condition has been most systematically studied, often North America and Western Europe. Incidence data not derived from these areas is specified in the following paragraphs.

1.3.1. Placenta previa

Placenta previa occurs when the placenta partially or completely overlies the internal cervical os. This is in contrast with low-lying placenta, in which the placenta lies within 2 cm of the internal cervical os but does not extend across it. The etiology of placenta previa is unknown. Risk factors include smoking, advanced maternal age, multiparity, in vitro fertilization, multiple gestation, Asian race, prior endometrial damage, prior pregnancy termination or spontaneous abortion, prior cesarean delivery, and prior placenta previa [1,5,6]. These risk factors suggest that the pathogenesis may be driven by endometrial damage or suboptimal endometrial perfusion in other areas of the uterus. The incidence of placenta previa at term is approximately 1 in 200 pregnancies; the incidence is higher earlier in gestation, but many placenta previas resolve as the lower uterine segment develops and the placenta preferentially expands towards more vascularized areas of the uterus [1,5].

1.3.2. Morbidly adherent placentation

Morbidly adherent placentation occurs when the placenta implants abnormally into the uterine myometrium, rather than the normal implantation of the placenta into the uterine decidua basalis [1,5,7]. Invasive placentation occurs as a result of the absence of the decidua basalis and incomplete development of or injury to Nitabuch's layer [1,5,8]. The incidence of morbidly adherent placentation is 1 in 300 to 1 in 500 pregnancies [5]. The most significant risk factor is placenta previa in the context of one or more prior cesarean deliveries, or other uterine surgery. With one prior cesarean delivery and a placenta previa, the risk is 11%; with 3 or more cesarean deliveries and a placenta previa, the risk is greater than 60% [9]. Other common risk factors include advanced maternal age, advanced parity, cesarean scar pregnancy, and in vitro fertilization [5,7,10–12].

1.3.3. Placental abruption

Placental abruption occurs when the placenta detaches prematurely from its implantation site. Traditionally conceptualized as primarily an "acute" event often resulting from physical trauma to the abdomen, contemporary data suggest that placental abruption is often chronic [13–17]. Nevertheless, acute placental abruptions still occur. Abruptions may either be revealed, with vaginal bleeding as an early symptom, or concealed, with blood remaining trapped within the uterus. Pathophysiologic mechanisms involved in abruption include uteroplacental underperfusion, ischemia, placental infarctions, and chronic hypoxia [18–20]. In very rare circumstances abruption can follow second trimester diagnostic and therapeutic intrauterine procedures (amniocentesis, CVS, fetal surgery). Abruption affects about 1% of pregnancies, but is associated with a recurrence risk of about 10–15% for one prior abruption, 20–30% after two, and $\geq$30% after three or more abruptions [21,22]. Other risk factors include first trimester bleeding, hypertension, thrombophilia, illicit drug use (especially cocaine), smoking, trauma, in vitro fertilization, and premature rupture of membranes [23–26]. Pregnancies diagnosed with abruption end 3–4 weeks earlier than other pregnancies, with well over half delivering preterm. This is in contrast to a preterm birth rate of 12% among unaffected pregnancies [26–29].

1.3.4. Vasa previa

Vasa previa occurs when fetal blood vessels course within the amniotic membranes across the internal cervical os or within 2 cm of the os. Type I vasa previa occurs with a velamentous umbilical cord insertion into the membranes, consequently allowing for fetal vessels to run free within the membranes between the umbilical cord and placenta. Type II vasa previa occurs with the development of a succenturiate placental lobe and main placental lobe, connected by fetal vessels that freely course within the membranes. Vasa previa is rare, with an incidence of 1 in 2500 deliveries. Risk factors include resolved low-lying placenta, placenta previa, and multiple gestation [5,30].

1.3.5. Cesarean scar pregnancy

A cesarean scar pregnancy is an ectopic pregnancy implanted in a previous cesarean (hysterotomy) scar, surrounded by myometrium and connective tissue. This occurs due to a small defect in the cesarean scar, as a result of poor healing and poor vascularization of the lower uterine segment with resultant fibrosis [31]. The pathophysiology of cesarean scar pregnancies is similar to an