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Commentary

# Fetal growth restriction: Case definition & 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 fetal growth restriction as an adverse event following immunization

Fetuses that fail to meet their growth potential in utero are at risk for adverse antenatal and postnatal events such as stillbirth, preterm birth, and adverse neonatal and long-term health outcomes [1–5]. Therefore, antenatal recognition and monitoring of fetal growth restriction (FGR) is an important component of prenatal care [6–8]. Despite the clinical and public health importance of this problem there is no universally accepted definition of FGR [9–10]. Furthermore, terminology such as intrauterine growth restriction (IUGR) or small for gestational age (SGA) are used interchangeably and without specificity to describe this clinical entity. In its simplest form, FGR is defined as a sonographic estimation of fetal weight below the tenth percentile for a given gestational age [11–14]. Though this definition is simple to understand and translating into practice, it is an inadequate definition for FGR.

FGR can be a consequence of maternal, fetal, or placental factors. Diagnosing all fetuses with an estimated fetal weight (EFW) below the tenth percentile with FGR fails to account for the individual growth potential of each fetus. Constitutionally small fetuses who might be expected to have a lower birthweight based on parental characteristics may be misdiagnosed as pathologically small [15]. Conversely, fetuses destined for a higher birthweight may fail to reach their growth potential due to a pathologic process yet never fall below a threshold based on fetal or birth weight below a specific centile (e.g. 10th) [16]. An ideal definition of FGR would detect those fetuses with a pathologic failure to meet their growth potential subsequently at risk of adverse outcomes.

Numerous studies have attempted to improve the sensitivity and specificity of the definition through adjunct testing and optimization of growth curves used to define the tenth percentile diagnostic cutoff. The sentinel investigations into FGR used measurements of the fetal head, abdomen, and femur to develop growth curves within small homogenous patient populations [17]. Though these measurements yielded reliable estimations of fetal weight, the growth curves lacked generalizability, particularly in an international context [18]. Contemporary studies on FGR have advocated individualized growth curves accounting for maternal and fetal characteristics such as ethnicity and gender to solve this dilemma [19–21]. However, large-scale international prospective studies of healthy pregnancies show little difference in growth curves between populations [22]. Additional studies

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investigating the utility of adjunct studies such as amniotic fluid assessment and use of Doppler attempt to further clarify the definition of FGR [23,24].

Despite these controversies in defining FGR, its detection is an important component of antenatal care. The majority of the prior vaccine studies in pregnant women, including specifically those focused on obstetric outcomes, do not address FGR as an adverse outcome [25–28]. Some authors have reported neonatal outcomes including identification of low birth weight (LBW) and SGA infants without an attempt to detect these events in pregnancy [29–31]. Though neonatal disorders of growth potential could be considered a postnatal diagnosis of FGR, they are different diagnoses with distinct implications within the context of studies on immunizations.

The likely cause of pathologic FGR can vary in according to clinical setting. Some etiologies of FGR, such as preeclampsia or congenital anomalies, may be similar across clinical settings. FGR associated with maternal comorbidity such as advanced maternal age or gastric bypass surgery can be considered unique to countries with higher healthcare related expenditures [32,33]. In contrast FGR in lower income countries is more likely to be associated with malnutrition or parasitic diseases, with malaria being the classic example [34–38].

This relationship between maternal infection and FGR is well described for many diseases—even in the absence of congenital infection [39–44]. Specifically, FGR has been described as a consequence of vaccine-preventable illnesses, such as influenza [45,46]. As maternal vaccination becomes an increasingly prioritized component of routine prenatal care, monitoring for adverse vaccine-related outcomes gains similar importance. The complex interplay between FGR, infection, and medical comorbidity makes early detection and diagnosis of this pregnancy complication of paramount importance. Timely diagnosis of a pathologic disorder of growth potential in utero, as opposed to relying solely on a postnatal diagnosis of a pathologically small infant, is necessary to identify a temporal relationship between the diagnosis of FGR and a vaccine of interest.

There is a paucity of data on FGR in existing vaccine trials, perhaps in part due to the controversy surrounding the diagnosis within the medical community. Given the clinical variation in the definition, the absence of a uniformly accepted definition of FGR following immunizations is not surprising. This is, however, a missed opportunity, as data comparability across trials or surveillance systems would facilitate data interpretation and promote the scientific understanding of the event.

### *1.2. Methods for the development of the case definition and guidelines for data collection, analysis, and presentation for fetal growth restriction as an adverse events following immunization*

Following the process described in the overview paper as well as on the Brighton Collaboration Website http://www.brightoncollaboration.org/internet/en/index/process.html, the Brighton Collaboration *Fetal Growth Restriction Working Group* was formed in 2015 and included members from clinical, academic, public health, and industry backgrounds [47]. 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 the decision-making for the case definition and guidelines, a literature search was performed using Medline, Embase and the Cochrane Libraries, including the terms [fetal (Fetal) growth restriction or retardation], [intrauterine growth restriction or retardation] and [small for gestational age]. The search resulted in the identification of 23,441 English-language references, 5480 of which were published within the past five years. All abstracts were screened for relevance to a contemporary definition of FGR in a singleton pregnancy with particular attention to those related to infection, immunization, and under-represented countries. 102 articles with potentially relevant material were reviewed in more detail, in order to identify studies using case definitions or, in their absence, providing clinical descriptions of the case material. The literature search revealed extensive literature on the definition of FGR and development of associated growth curves and adjunct testing. No immuzation-related studies contained definitions of FGR and this outcome was seldom discussed. The most commonly encountered definitions were in medical society statements and contained substantial variation in both terminology and definitions. Similar heterogeneity was found in the definition of FGR throughout scientific studies addressing outcomes and management of this pregnancy complication. An inventory comprising the 102 relevant articles along with society definitions of FGR was made available to working group members via the Collections feature of MyNCBI.

### *1.3. Rationale for selected decisions about the case definition of fetal growth restriction as an adverse event following immunization*

#### *1.3.1. The term fetal growth restriction*

Terms such as intrauterine growth restriction (IUGR) and small for gestational age (SGA) are often used in clinical practice interchangeably with FGR. The term SGA has been proposed by some groups, including the Brighton Collaborative, as a diagnosis limited to neonates [11,48]. Other society guidelines suggest using IUGR to identify those fetuses at risk of pathologic growth restriction and limiting the use of SGA to reference a constitutionally small fetus without evidence of pathology [12–14,49]. In order to distinguish between a neonatal and fetal diagnosis of disorders of growth, use of the term SGA to reference a fetal disorder of growth will be avoided. IUGR and FGR are used interchangeably with less confusion as both clearly reference a diagnosis of growth restriction established prior to delivery. To limit confusion between these variably defined terms the Brighton definitions will utilize the term fetal growth restriction to define this adverse advent with levels of diagnostic certainty to further describe concern for pathologic FGR.

#### *1.3.2. Formulating a case definition that reflects diagnostic certainty: weighing specificity versus sensitivity*

The number of sonographic findings that will be documented for each case may vary considerably depending on availability of technology in a given setting and availability of additional clinical information, such as pregnancy dating, critical to establishing a diagnosis. The case definition has been formulated such that the Level 1 definition is highly specific for the condition. As maximum specificity normally implies a loss of sensitivity, an additional diagnostic level has been included in the definition, offering a stepwise increase of sensitivity from Level 1 to Level 2, while retaining an acceptable level of specificity at all levels. Each Level has been further subdivided into subcategories of A and B in an attempt to better define pathologic FGR. Within both Levels, a subgroup of A provides better specificity and certainty for a pathologic process. Level B may be more sensitive for FGR but includes less specific findings with less certainty for its pathology. In this way it is hoped that all possible cases of FGR can be captured with clarity as to the concern for a disorder of fetal growth potential.

It needs to be emphasized that the grading of definition levels is entirely about diagnostic certainty, not clinical severity of an event. Thus, a clinically very severe event may appropriately be classified as Level Two rather than Level One if it could reasonably be of non-FGR etiology (e.g. in cases of limited evidence of pregnancy dating). Detailed information about the severity of the event should additionally always be recorded, as specified by the data collection guidelines.