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Commentary

Small for gestational age: Case definition & guidelines for data collection, analysis, and presentation of maternal immunisation safety data

Elizabeth P. Schlaudecker [a,*], Flor M. Munoz [b], Azucena Bardají [c], Nansi S. Boghossian [d], Asma Khalil [e], Hatem Mousa [f], Mirjana Nesin [g], Muhammad Imran Nisar [h], Vitali Pool [i], Hans M.L. Spiegel [j], Milagritos D. Tapia [k], Sonali Kochhar [l,m,2], Steven Black [a], For The Brighton Collaboration Small for Gestational Age Working Group [1]

[a] Cincinnati Children's Hospital Medical Center, Division of Infectious Diseases and Global Health Center, Cincinnati, OH, USA
[b] Baylor College of Medicine, Department of Pediatrics and Molecular Virology and Microbiology, Houston, TX, USA
[c] ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic – University of Barcelona, Barcelona, Spain
[d] Department of Epidemiology & Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA
[e] Fetal Medicine Unit, St George's Hospital, University of London, UK
[f] Fetal Medicine Unit, University Hospital of Leicester, UK
[g] Office of Clinical Research Resources, NIAID/NIH, Rockville, MD, USA
[h] Aga Khan University, Department of Pediatrics and Child Health, Karachi, Pakistan
[i] Sanofi Pasteur, Swiftwater, PA, USA
[j] Kelly Government Solutions, Contractor to DAIDS/NIAID/NIH, Rockville, MD, USA
[k] Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD, USA
[l] Global Healthcare Consulting, Delhi, India
[m] Erasmus University Medical Center, Rotterdam, The Netherlands

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1. Preamble

1.1. Need for developing case definitions and guidelines for data collection, analysis, and presentation for small for gestational age (SGA) as an adverse event following maternal immunisation

Small for gestational age (SGA) fetuses or newborns are those smaller in size than normal for their gestational age, most commonly defined as a weight below the 10th percentile for the gestational age. This classification was originally developed by a 1995 World Health Organization (WHO) expert committee, and the definition is based on a birthweight-for-gestational-age measure compared to a gender-specific reference population [1,2].

Successful pregnancy, including optimal growth of the fetus, relies on a careful balance between immune tolerance and suppression. Several mechanisms work together to protect the fetus from rejection [3]. During normal placentation, several changes occur, including differentiation of the endometrium to decidua, development of the fetal placental trophoplast to invade the decidua, migration and differentiation of trophoblast, and remodeling of the uterine arteries [4]. Current evidence suggests that the placenta creates a micro-environment that controls immune cell differentiation at the implantation site and trophoblastic cell-induced differentiation of the immune cells into a phenotype beneficial for the trophoblast [5]. Mor and Cardenas categorized pregnancy into three different immunological stages [6]. The first pro-inflammatory phase, occurring during the first trimester, includes implantation and placentation. It is associated with increased levels of interleukin (IL)-8, macrophage chemo-attractor protein 1 (MCP-1), and activated T cells. The second anti-inflammatory phase, occurring during mid-pregnancy, is a unique period of fetal growth and

* Corresponding author.
E-mail address: contact@brightoncollaboration.org (E.P. Schlaudecker).
[1] Brighton Collaboration homepage: http://www.brightoncollaboration.org.
[2] Present address: University of Washington, Seattle, USA.

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development. It is characterized by predominant anti-inflammatory cytokines (IL-4, IL10 and IL-13). The third pro-inflammatory phase is similar to the first phase, and it is a preparatory stage for delivery [3]. Furthermore, different Pattern Recognition Receptors (PRRs), including Toll-like receptors and Nod-like receptors, and the innate immune system play a vital role in this process.

Dysfunction of the maternal innate immune response may predispose to placentally mediated diseases such as pre-eclampsia (PET), fetal growth restriction (FGR), placental abruption, and intrauterine fetal death. The complement system can affect angiogenesis-related endothelial cell function. It can indirectly, through macrophages, upregulate the anti-angiogenic soluble vascular endothelial growth factor receptor-1 (SFlt-1). In addition, SFlt-1 can combine with soluble endoglin (sEnd) to induce PET, FGR, and coagulation defects [7–10].

Traditionally, the causes for "pathological" growth restriction are subdivided into fetal, placental and maternal. Genetic and chromosomal disorders, fetal malformation, infection (e.g. rubella or cytomegalovirus), and toxic substances (e.g. alcohol, cocaine, or smoking) can contribute to FGR. Maternal diseases such as anemia and malnutrition may also affect fetal growth. However, classical utero-placental dysfunction accounts for the vast majority of cases of "placental" FGR, as well as to a variety of conditions such as pre-eclampsia and placental abruption [11]. The Brighton Collaboration fetal growth restriction manuscript addresses the impact of obstetric conditions on fetal growth restriction more fully [12].

Congenital infections by *Toxoplasma gondii*, rubella, cytomegalovirus, herpes simplex virus (HSV), varicella-zoster virus, *Treponema*, and HIV contribute to 5–10% of fetal growth restriction [13,14]. Several investigators believe that congenital infection could be associated with a spectrum of disease, and it could be quite variable, ranging from severe clinical manifestations to mild disease only presenting with a small for gestational age fetus. Many clinicians think that TORCH screens should be performed on every SGA newborn infant [15–17].

Placental malaria is a major cause of fetal growth restriction. In a case-control study of 492 pregnant Malawian women, a significant increase of placental complement C5a levels was associated with an increased risk of delivering a small-for-gestational-age infant [18]. C5a was significantly increased in placental malaria and was negatively correlated with the angiogenic factor angiopoietin-1 and positively correlated with angiopoietin-2, soluble endoglin, and vascular endothelial growth factor [18].

Maternal vaccination during pregnancy has emerged as a recommended public health approach to prevent maternal and childhood infections. All current maternal vaccines were initially designed for and tested in non-pregnant populations, but the diverse immune modulations during pregnancy may cause pregnant women to respond sub-optimally or differently compared with non-pregnant populations [19]. In addition, vaccine efficacy could be affected by other factors including the dose, route, and timing of the vaccination. Limited data exist on the effect of vaccinations in high-risk pregnancies. In spite of the success of several maternal vaccines, many gaps exist in our knowledge of this promising public health strategy and impact on fetal growth during pregnancy.

Tetanus and influenza vaccines were the first vaccines recommended for use during pregnancy. Trotta and colleagues evaluated the safety of A/H1N1 pandemic vaccination of 6246 pregnant women [20]. There was no difference in pregnancy outcome measures, including small for date. In an observational cohort study from UK, Donegan and colleagues examined maternal and neonatal outcomes among 6185 pertussis vaccinated pregnant women and 18,523 healthy unvaccinated historic controls [21]. There were no significant differences between the two groups regarding low birth weight or other maternal and neonatal outcomes [21], and these findings were confirmed by others [22]. Currently, the World Health Organization (WHO) provides guidance for vaccination during pregnancy (Table 1). The key question that remains is related to the safety and optimum timing of vaccination and if maternal vaccination has any negative effects on the immune system [23].

Placentally mediated severe FGR, indicated by abnormal uterine and umbilical artery Doppler velocimetry, is associated with impaired transplacental gas transfer and fetal hypoxaemia. This triggers compensatory re-distribution of blood towards essential organs (brain, heart, and adrenals) and decreases blood flow to other organs (kidneys and bowel). This "compensatory phase" can be recognised by observing Doppler changes (reduced resistance) in the middle cerebral artery (MCA), decreased amniotic fluid, and/or bright echogenic bowel. The duration of this compensatory phase is variable. This phase is followed by a phase of myocardial dysfunction and haemodynamic decompensation. This "decompensation phase" can be recognised by abnormal venous Doppler waveforms (absent or negative 'a' wave) and it is associated with fetal acidaemia. Both hypoxaemia and acidaemia can also be detected clinically by changes in fetal heart rate as well as the biophysical profile. The Brighton Collaboration growth restriction and fetal distress guidelines further explore these issues [12,24].

Despite the presence of many pathophysiological events that may lead to intrauterine growth restriction, SGA is not universally associated with growth restriction. Small for gestational age (SGA), is commonly used as a proxy for intrauterine growth restriction (IUGR), particularly in settings where serial ultrasonography is not readily available [2,25]. However, fetuses that are SGA are not necessarily growth restricted; they in fact may be constitutionally small. If SGA babies have been the subject of intrauterine growth retardation (IUGR), the term "SGA associated with IUGR" is used. IUGR refers to a fetus that is unable to achieve its genetically determined potential size. This functional definition aims to identify a population of fetuses at risk for poor pregnancy outcomes, and excludes fetuses that are SGA but are not pathologically small. Neonates born with severe SGA (or with severe short stature) are defined as having a length less than 2.5 standard deviation below the mean [26].

A related term is low birth weight (LBW), defined as a birth weight of less than 2500 g, regardless of gestational age at the time of birth. Additional related terms include very low birth weight (VLBW) which refers to less than 1500 g, and extremely low birth weight (ELBW) which is less than 1000 g. Normal weight at term delivery is 2500–4200 g. LBW is discussed further in a separate document for this definition. It is important to be clear that SGA is not a synonym of LBW, VLBW or ELBW. Approximately one third of LBW babies weighing less than 2500 g are also SGA [12,27].

In this case definition and associated guideline, we propose a systemic tool for evaluating the adverse event of SGA after maternal immunisation. It is important to emphasize that these tools have been developed in the absence of any data supporting such an association but rather to facilitate studies of the safety of vaccines used in pregnancy. The outcome of SGA has been examined in several published studies of the safety of influenza and pertussis vaccination during pregnancy. In one randomised clinical trial of influenza immunisation in pregnant women in Bangladesh, SGA was defined as less than 10th percentile weight for gestational age [28,29]. In this trial, two reference standards were used - the reference values for distributions of birth weights from the United States [30] and the global reference standard from the World Health Organization [31].

The remaining published studies were observational in design and used different SGA definitions and reference standards (Table 2) [32,33]. In most of these studies, SGA was defined as the lowest 10th percentile of the gestational age-specific birth