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ABSTRACT

Background: Low birthweight (LBW) is when an infant is born too soon or too small, and it affects one in seven infants in low- and middle-income countries. LBW has a significant impact on short-term morbidity and mortality, and it impairs long-term health and human capital. Antenatal microbial and inflammatory exposure may contribute to LBW.

Methods: Ovid-Medline, Embase and Cochrane databases were searched for English-language articles evaluating inflammatory, microbial or infective causes of LBW, small-for-gestational age, intra-uterine growth restriction or prematurity. Inclusion criteria were human studies including published data; conference abstracts and grey literature were excluded. A narrative synthesis of the literature was conducted.

Results: Local infections may drive the underlying causes of LBW: for example, vaginitis and placental infection are associated with a greater risk of prematurity. Distal infection and inflammatory pathways are also associated with LBW, with an association between period-ontitis and preterm delivery and environmental enteric dysfunction and reduced intra-uterine growth. Systemic maternal infections such as malaria and HIV are associated with LBW, even when infants are exposed to HIV but not infected. This latter association may be driven by chronic inflammation, co-infections and socio-economic confounders. Antimicrobial prophylaxis against other bacteria in pregnancy has shown minimal impact in most trials, though positive effects on birthweight have been found in some settings with a high infectious disease burden.

Conclusion: Maternal inflammatory and infective processes underlie LBW, and provide treatable pathways for interventions. However, an improved understanding of the mechanisms and pathways underlying LBW is needed, given the impact of LBW on life-course.

Introduction

Low birthweight (LBW) is defined as a birthweight of <2500 g, regardless of gestational age. LBW is an easily obtained measure of risk, particularly where access to ultrasound gestational dating is limited [1,2]. Each year, more than 20 million live births are of LBW, equating to 14.6% of all live births worldwide, with 91% being in low- and middle-income countries (LMIC) [3]. Over 80% of neonatal deaths occur in LBW neonates [4]. The rates of reduction in LBW remain less than half of those required to meet global nutrition targets to reduce LBW by 30% by 2025 [5]. There is therefore a pressing need to understand the pathophysiology and determinants of LBW in order to identify preventive interventions and programmes of action to reduce its burden worldwide.

There are several different LBW phenotypes that collectively give rise to small, vulnerable newborns, with overlapping categories [6]. Being small for gestational age (SGA) is defined as a birthweight under the 10th percentile for sex and gestational age. Data for 2010 estimated that 27% of all births in LMIC were SGA [7,8]. SGA infants can be normal and healthy, but in areas of high prevalence, SGA is often used as a *de facto* proxy for intra-uterine growth restriction (IUGR), which is more typically associated with deficits in health and development. In settings where ultrasound monitoring of fetal development is readily available, IUGR is defined as a reduced fetal growth rate during pregnancy, rather than by birthweight. In contrast, growth that is appropriate for gestational age (AGA) is healthy growth regardless of gestation. Prematurity is defined as birth before 37 completed gestational weeks. Global trends in 2000–2014 showed an increase in preterm birth in a majority of countries with available data [8].

LBW can result from IUGR, SGA, preterm birth or a combination of these. These birth phenotypes have

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varying rates of mortality, morbidity and longer-term clinical outcomes, and so interventions for LBW infants are often targeted according to each adverse birth outcome. However, reliable methods of assessing gestational age such as early antenatal ultrasound scans are often unavailable in LMIC, making it challenging to determine whether a small newborn is SGA or premature. LBW is therefore often used pragmatically to capture all phenotypes, but prevents the use of targeted interventions. However, it is worth noting that whilst a significant proportion of SGA infants are born entirely healthy, preterm infants are considered to be at an increasingly high risk of morbidity and mortality with lower gestational ages, and infants who are SGA and preterm are considered to be at greatest risk owing to the combined effects of both phenotypes [8,9].

Child and life course of LBW

LBW is associated with increased infant mortality, poor child growth and impaired health throughout life [3,9,10]. In children, this includes reduced cognitive and motor development as well as physical strength and cardiovascular fitness [11,12]. LBW programmes the body to have less lean and muscle mass, leading to reduced capacity for homeostasis in the context of energy metabolism and cardiovascular health [13,14]. As LMIC experience the 'double burden of malnutrition' with increasing metabolic load caused by obesogenic lifestyle factors, being LBW in LMIC increases the risk of long-term non-communicable disease (NCD) in adulthood [15,16]. Observational evidence consistently associates LBW with several life-course outcomes, including type 2 diabetes, hypertension and cardiovascular disease [10,17,17–21]. Epidemiological studies outside LMIC also associate LBW with many other diseases including osteoporosis, impaired mental health, breast cancer and fertility problems [22,23].

LBW is also associated with broader psychosocial factors such as maternal education and maternal stress, together with community factors including the quality of the social environment, rural dwelling, levels of poverty and access to safe water [24–29]. Therefore, the lifetime effects of LBW reflect combined adversities experienced antenatally, leading to reduced postnatal metabolic capacity and lean mass, compounded by overlapping physiological and psychological risk factors for poor growth and child development [30]. LBW is a precursor of sustained linear and ponderal growth deficits, including stunting (length-for-age Z-score <-2) and wasting (weight-for-height Z-score <-2), indicative of undernutrition. LBW therefore feeds into an intergenerational cycle whereby poor maternal nutritional status during pregnancy increases the risk of subsequent LBW and stunting [30].

Rationale for review

New approaches are required to reduce LBW and the associated risk factors in order to meet global nutrition targets. To enable rational design of interventions, it is necessary to understand the pathogenic processes underlying LBW. The recent Lancet Series on Small Vulnerable Newborns provides a broad overview of the mechanisms underlying preterm birth and SGA [31], including maternal infectious and nutritional causes, as well as broader household and societal issues such as access to hygiene, maternal education, antenatal care, and other social factors [31–33]. Whilst a wide range of interventions to reduce LBW have been appraised, addressing infective pathways such as HIV and the range of inflammatory pathways associated with a poor long-term outcome are mechanisms that may be addressed [31–33]. The Series also provides a contemporary evidence base for current interventions to reduce LBW, including interventions applicable to all women, women at greater risk of delivering small vulnerable newborns, or women with imminent preterm birth [31,31]. These include smoking cessation, having good access to midwife-led continuity antenatal care, zinc supplementation, periconception food fortification with folic acid, insecticide nets, and medical interventions for high-risk women such as cervical cerclage and anticoagulant therapy, amongst others [31,34]. This review focuses in depth on microbial causes owing to the high infectious exposure of pregnant women delivering in LMIC, and inflammation owing to its role in common pathways underpinning fetal growth restriction and prematurity. It also reviews the scope for antimicrobial and anti-inflammatory interventions for LBW, which remain relatively underexplored. Knowledge gaps for future research are identified, and the potential for novel interventions to prevent LBW in LMIC is discussed.

Methodology and aims for review

A narrative review of relevant studies which explore the relationship between maternal inflammation and/or infection and LBW was undertaken. Although this is not a systematic review, full details of the search strategy and approach to screening and selecting studies in the supporting material in the supplementary appendix and search strategy in an online repository are included [35]. Ovid-Medline, Embase and Cochrane databases were searched for English language articles between 1 January 1992 and 1 January 2022 which evaluated inflammatory, microbial and/or infective causes of LBW, SGA, IUGR or preterm/prematurity, and studies for inclusion were prioritised based on

the most recent and highest quality data as per the search strategy in the appendix and in LMIC. The review aims to include relevant studies and data to understand microbial and inflammatory drivers of LBW, SGA and prematurity.

Microbial and inflammatory pathways of LBW

Studies reporting data on LBW pathogenesis mainly addressed the following pathways: (i) localised infective and inflammatory pathways at the feto-maternal interface, (ii) distal inflammatory pathways in other maternal tissue, and (iii) systemic infection. The pathways in which infection may contribute to inflammation and subsequent reduced uterine growth and gestational age at birth are outlined in Figure 1, with supporting literature discussed in the local pathways section.

Local pathways

Placental, cord blood and fetal membrane inflammatory pathways

Healthy fetal growth relies on a series of tightly regulated processes mediated via the placenta which are disrupted by infection and inflammation. Maternal immune cells recognise and respond to fetal tissue but inflammatory activation is minimised in healthy pregnancies by placental structure, limited T-cell proportions in the uterus and placenta, and restricted HLA-class I expression on fetal trophoblasts [36]. Inflammation in the placenta, fetal membranes and cord blood can be triggered by maternal infections in local or distal tissue (discussed above), impaired development and/or damage to feto-maternal tissues and chronic inflammatory conditions (e.g. irritable bowel syndrome and auto-immune disease) [37,38]. Inflammation at these sites is consistently associated with adverse birth outcomes. For example:

- *Rupture of fetal membranes* leads to release of the extracellular matrix component fibronectin into cervicovaginal secretions, which is associated with preterm birth and lower mean birthweight in both high-income and LMIC settings [39,40]. Premature membrane rupture before the onset of labour triggers the release of the pro-inflammatory cytokine IL-6 into cervicovaginal secretions and cord blood and is a risk factor for
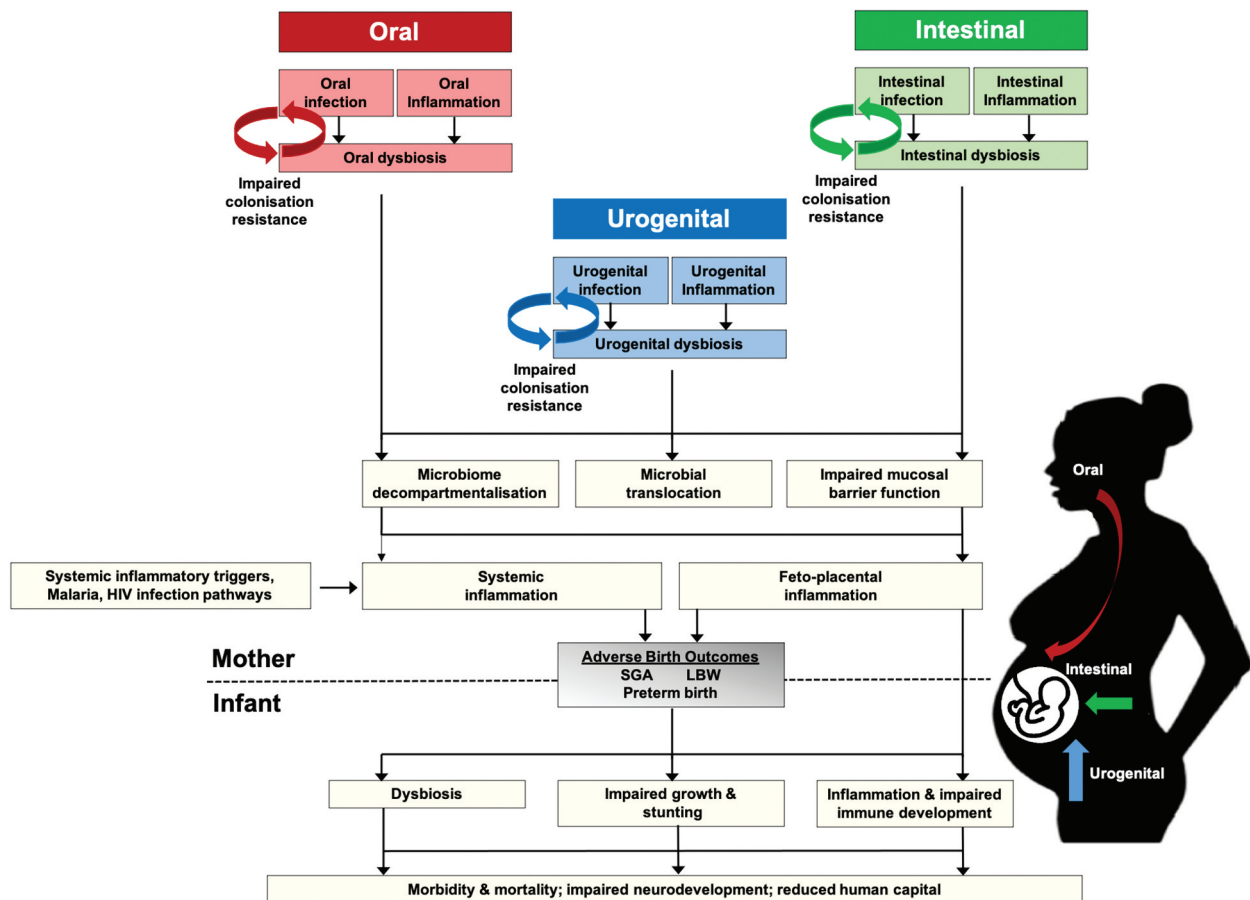

Figure 1. Local, distal and systemic contributors to maternal infection and inflammation pathways and their impact on low-birthweight infants. This simplified model depicts how different pathways contribute to the risk of premature birth and being small for gestational age, contributing to LBW and associated long-term poor outcomes. Maternal inflammatory pathways are above the dotted line; infant birth outcomes and long-term pathways are below the dotted line.

fetal sepsis and mother-to-child transmission of HIV [39,41,42].

- *Pre-eclampsia* is one clinical manifestation of defects in placental development; it is thought to arise from abnormal placental spiral artery formation driving increased maternal blood pressure and local and systemic inflammation during pregnancy. Plasma C-reactive protein (CRP) was elevated in 100 Bangladeshi women with pre-eclampsia in the 3rd trimester relative to age-matched normotensive pregnant women; both CRP and pre-eclampsia were associated with LBW in this cohort [43]. Small sample size limits the ability to draw significant conclusions and prospective trials are needed.

In addition, some data suggest that microbial communities are present in the placenta and fetal membranes, which in studies in both high-income countries (HIC) and LMIC are associated with birthweight and other anthropometric measures immediately following birth [44,45]. However, data supporting the existence of placental microbiomes are highly conflicting [46] and prone to confounders, and this is a contentious area.

Inflammation itself, whether infectious or non-infectious in origin, can also affect the placental tissue itself [47] and has been investigated in murine models of intra-uterine inflammation, which identified alterations in placental transcriptome and metabolomes [48]. Such pathways may lead to placental vascular and endothelial problems, including placental malperfusion and fetal vessel resistance, with subsequent IUGR and preterm birth [49].

There is therefore cumulative evidence that inflammation at the feto-maternal interface and in the systemic circulation contributes to an adverse birth outcome. Improving birthweight will rely on considering the independent and dependent impact of inflammation during pregnancy and identifying the most relevant mediators from the inflammatory repertoire.

It is plausible that inflammation in tissue distal to the feto-maternal interface could also contribute to LBW, including oral, respiratory, intestinal and cutaneous barrier tissue.

Genito-urinary microbiome and infection

The urogenital tract may be a simultaneous source of pathogens and a site of commensal microbiome dysbiosis which contribute to local inflammation and an adverse birth outcome. Few studies have explored interactions between the vaginal microbiome, local inflammation and birth outcome in LMIC.

There are well-established associations between sexually transmitted infections (STIs), chorioamnionitis (inflammation of the chorion and membranes of the placenta) and an adverse birth outcome [50–53], mediated by placental and fetal inflammation. Disturbances of the maternal commensal microbiome may also mediate infection and subsequent inflammation at various body sites. The composition and function of the vaginal microbiome influences susceptibility to local infection [54] and inflammation [55] via colonisation resistance. In high-income settings, the vaginal microbiome is dominated by one of four Lactobacillus species, providing a low pH environment to deter pathogen colonisation [56]. Shifts to a high-diversity, Lactobacillus-deficient vaginal microbiome are associated with preterm birth, plausibly through inflammation [57,58]. These disruptions to the commensal vaginal microbiome are collectively termed bacterial vaginosis (BV).

BV is defined by a lack of vaginal Lactobacillus species, which results in elevated vaginal pH and a relative over-abundance of other commensal vaginal species such as *Gardnerella vaginalis*. In the absence of speciation, this may be defined by yellow-green discharge, altered pH and the presence of clue cells on microscopy [59]. BV has consistently been associated with preterm birth and LBW in both HIC and LMIC [60]. This dysbiotic state results in a greater risk of STI and other urogenital infections and heightens vaginal inflammation which may interfere with fetal growth [61]. Healthy non-pregnant women in Saharan Africa were found to have low Lactobacillus/high diversity vaginal microbiomes; the latter was correlated with cervicovaginal lavage cytokine levels and activated T-cells (albeit not linked to LBW) [61]. A Lactobacillus-deficient vaginal microbiome is common in certain settings [62], suggesting that classical definitions of BV may not accurately reflect the more subtle vaginal microbiome signatures which have been associated with an adverse birth outcome in both HIC and LMIC [61,63]. Additionally, a Lactobacillus-deficient and overly abundant Gardnerella species in the vaginal microbiome predicts spontaneous preterm birth in women living with HIV [64]. Other studies have demonstrated potential associations between preterm birth and *Atopobium vaginae* species, among others [65–68].

Pelvic and sexually transmitted infections are an important cause of an adverse birth outcome [69,70]. Ascending genital tract infections trigger an inflammatory cascade leading to the onset of

labour. Chlamydia can cause partial activation of the systemic cytokine network via IFN-γ and IL10, IL 12, IL 23 and TNF-alpha, leading to preterm labour [71–74]. Histological chorio-amnionitis increases the risk of preterm birth and LBW [75].

Schistosomiasis is a parasitic helminth infection which entails cutaneous invasion and systemic migration by larvae and long-term residence of adult worms in capillaries surrounding the urogenital (*Schistosoma haematobium*) and intestinal (*S. mansoni*, *S. japonicum* and others) tracts. Adult worms release eggs which must cross from the bloodstream into urogenital/intestinal tracts and which elicit mucosal granuloma formation and characteristic type 2 and regulated type 2 immune responses in affected tissue. Because schistosomiasis causes both anaemia and undernutrition, maternal infection with schistosomes could have deleterious consequences during pregnancy [76], although not all studies have shown associations with an adverse birth outcome [76–79]. A study of *Schistosoma haematobium* in Zimbabwe (471/4437, 10.6% *S. haematobium* egg-positive) found no association with LBW, term SGA, preterm or preterm SGA outcome, while a study in Gabon (103/1115, 9% *S. haematobium* egg-positive) found an increased risk of LBW but not preterm birth [77,80]. Trials of praziquantel in pregnancy have not shown an effect on birth outcome [76,81], and praziquantel is often avoided in pregnancy owing to concerns about fetal toxicity.

Distal pathways

Peridontal and oral infection

Oral disease is highly prevalent in LMIC, with a frequent lack of preventive dental care. It has been estimated that approximately 7.4% of the adult population worldwide is affected by severe periodontitis [82], while its milder form may be as high as 50% [83]. Periodontitis is a chronic inflammatory disease of the tooth-supporting tissues; initiation and progression are driven by shifts in the supragingival and subgingival microbiome [84–87]. These dysbiotic changes in microbial communities can redirect the immune and inflammatory responses of the host towards destruction of periodontal tissue.

Periodontitis has been associated with a range of systemic diseases, including diabetes mellitus [88] and cardiovascular disease [88,89] as well as preterm birth and LBW [90]. The translocation of oral pathogens, their pathogenic products and/or inflammatory markers to the fetal-placental unit may lead to placental inflammation, suppression of growth factors and preterm labour [91–94], providing a plausible biological mechanism for the association between periodontal disease and LBW. A case–control study of 390 women in Vietnam found that those with periodontitis were significantly more likely to deliver an SGA infant than those without periodontitis [95]. Similarly, a rural Malawian study demonstrated an association between peri-apical infections, reduced gestation and birthweight [96]. In contrast, a hospital-based case–control study reported that maternal periodontal status and generalised periodontitis were not associated with an adverse outcome of pregnancy [97].

The impact of periodontal treatment on pregnancy duration and infant birthweight has also been investigated, showing that women with untreated periodontitis had a higher proportion of preterm LBW infants (79%) than treated groups [98,98]. Likewise, in a trial in Australia, women delivering SGA infants had poorer clinical dental parameters and more severe periodontal disease than mothers of appropriate-for-gestational age infants [99]. Although the treatment of periodontal disease during mid-pregnancy significantly reduced the levels of several inflammatory markers in gingival crevicular fluid, it did not benefit pregnancy-related outcome [99].

Although data on the composition and function of the oral microbiome in pregnant women in LMIC are scarce, studies in high-income settings report associations between the abundance of specific commensal members of the oral microbiome and birth outcomes. *Actinomyces naeslundii, Eikenella corrodens* and *Capnocytophaga* spp. were negatively associated and *Lactobacillus casei* was positively associated with birthweight and duration of pregnancy [100,101].

The current literature is still controversial and heterogeneous [99], meaning that a definitive causal relationship between periodontal disease and LBW has not been established. The small sample size limits many of the studies and the studies included are open to significant bias. Confounders with socio-economic status could contribute to significant proportions of the associations observed. Further, well designed longitudinal and prospective studies which follow women throughout the full duration of pregnancy should be considered to understand the mechanisms and impact of periodontitis as a risk factor for LBW, alongside obstetric outcome and assessment of local and systemic microbial and inflammatory biomarkers. This would help inform discussions with pregnant women on the potential risks related to untreated periodontitis and guide the implementation of oral health interventions to prevent preterm and/or LBW, especially in LMIC.

Gastro-intestinal infection

The gut is the densest and most diverse microbial ecosystem in the body and a major site for interaction

between immune cells and environmental antigens, but it is an under-explored site of dysbiosis, pathogen carriage and inflammation during pregnancy.

Environmental enteric dysfunction (EED), a subclinical disorder of the small intestine characterised by inflammation, altered gut morphology and loss of barrier function, is almost universal in LMIC, and is associated with dysbiosis and increased carriage of enteropathogens [102]. The authors of this review have previously hypothesised that maternal EED drives adverse birth outcome [103] since microbial translocation increases during pregnancy and triggers systemic inflammation [104]. Markers of intestinal damage (intestinal fatty acid-binding protein, I-FABP) and innate immune cell activation (sCD14 and sCD163) in early pregnancy are associated with preterm birth in HIC [105,106]. In LMIC, markers of microbial translocation and intestinal inflammation are associated with shorter gestation and reduced length at birth [107]; diarrhoea during pregnancy is associated with SGA [108], and poor sanitation with preterm birth [109]. Clinical and subclinical infection, intestinal inflammation and microbial translocation are potentially modifiable drivers of preterm birth and SGA. The gut microbiome helps to modulate gut barrier function and therefore disturbances to the normal gut microbiome structure may mediate some of the intestinal inflammatory pathways hypothesised to contribute to adverse birth outcomes. Evidence from high-income settings has shown a lower diversity of microbial species and relative abundance of Bifidobacteria, Streptococci and Clostridia in the gut of women delivering preterm versus those delivering at term [110]. In rural Zimbabwe, patterns of gut microbiome composition and function, including starch metabolism genes, were highly predictive of birthweight and subsequent neonatal growth [111]. Metagenomic pathways involved in biofilm formation in response to nutrient starvation are strongly associated with reduced birthweight [111].

EED and HIV enteropathy are virtually indistinguishable pathogenic processes in terms of circulating biomarkers; both are associated with systemic translocation of microbial antigens (including endotoxin), intestinal mucosal damage (e.g. circulating intestinal fatty acid binding-protein, IF-ABP), elevated circulating anti-bacterial antibody titres, and biomarkers of monocyte/macrophage activation (e.g. sCD163 and sCD14). In a prospective cohort study of women living with HIV in Uganda, anti-endotoxin and anti-flagellin titres were inversely associated with duration of gestation [107]. In a small cohort of women living with predominantly untreated HIV in India, the odds of preterm birth were associated with soluble CD14, CD163 and I-FABP but not CRP relative to term births in HIV-positive mothers [112].

Intestinal schistosomiasis (discussed above) and soil-transmitted helminth infection/s may influence cytokine concentrations at the distal maternal/fetal interface, and altered fetal cytokine production contributes to SGA [113]. In a study of the relationship between soil-transmitted helminth infection and the progress and outcome of pregnancy, hookworm infection was associated with LBW (adjusted OR 1.81, 95% CI 1.02–3.23) [114]. However, a randomised controlled trial in Uganda showed no effect of antihelminthic treatment on birthweight or proportion of LBW [76]. In a Cochrane systematic review in 2015, administration of antihelminthics for soil-transmitted helminths during pregnancy had no impact on LBW (RR 1.00, 95% CI 0.79–1.27, 3255 participants) [115].

Respiratory

The COVID-19 pandemic provided an opportunity to explore the effect of respiratory infections on birth outcomes. COVID-19 is a highly pro-inflammatory disease, and infection during pregnancy is associated with heightened systemic and placental inflammatory cascades in affected mothers [116,117]. Whilst the clinical effect of SARS-CoV-2 in LMIC is still to be fully established, it is clear that there has been an enormous global impact on adverse pregnancy outcome, including higher risk of abortion and stillbirth and, emerging data suggest, a greater risk of preterm birth [118,119]. A retrospective study in China demonstrated an increased prevalence of IUGR in mothers infected with SARS-CoV-2 during pregnancy but no increased risk of prematurity [120,121]. Data from high-income settings suggest that the risk of prematurity is increased with more severe maternal COVID-19 disease and with later gestation in pregnancy [122]. A global systematic review found higher risks of preterm birth (OR 4.29, 95% CI 2.41–7.63) and LBW (OR 1.89, 95% CI 1.14–3.12) in 14,264 pregnant women in Africa, Asia, Europe and the Americas, consistent with similar studies [122,123]. These studies largely included trials from HIC, and the effects of maternal COVID-19 on birth outcomes in LMIC still need to be established, as well as the evidence base for other respiratory infections. These data highlight the importance of studying the effects of a range of acute respiratory viral infections and their potential impact on LBW pathways.

Systemic infection

Emerging evidence suggests that systemic infection plays a role in driving LBW, including maternal brucellosis [124] and syphilis [125]. Here, the focus is specifically on two common systemic infections that affect pregnant women in LMIC: HIV and malaria.

HIV

A 2015 meta-analysis of cohort studies including 15,538 participants demonstrated a clear association between maternal HIV infection and LBW (OR 1.73, 95% CI 1.64–1.82), with a greater effect when analyses were limited to studies from LMIC (OR 2.12, 95% CI 1.81–2.48) [126]. The HIV landscape has changed considerably since most studies were conducted (with many from the 1990s), since women living with HIV are now more likely to start pre-conception or antenatal antiretroviral therapy (ART), and HIV-exposed children are consequently less likely to be HIV-infected. However, recent studies have found that the association between maternal HIV and LBW remains, even in the current ART era [127–130]. Furthermore, the effect is not limited only to children who acquire HIV; studies of infants who are HIV-exposed but uninfected have also demonstrated associations between maternal HIV and infant LBW, both before [131] and after [130] the availability of ART.

The drivers of LBW in HIV infection are probably multifactorial, including both biological and sociodemographic pathways [132]. Maternal chronic inflammation and immune activation, a hallmark of HIV infection, may be one explanation [133]. Elevated levels of the pro-inflammatory cytokines CRP and IP-10 have been reported in infants of women living with HIV, both at birth and up to 6 months of age [134]. The pathway leading from maternal HIV infection to LBW may include HIV-associated co-infections such as tuberculosis, cytomegalovirus and hepatitis B [135,136].

Although clearly required for maternal health and for the prevention of vertical HIV transmission, whether ART exposure is negatively associated with LBW is uncertain. A 2017 meta-analysis demonstrated a greater risk of LBW in infants born to women living with HIV who used ART at conception than in infants of women who commenced ART during pregnancy [relative risk (RR) 1.30, 95 CI 1.04–1.62]. However, advanced HIV infection may also be associated with increased ART, contributing to this association [137]. Encouragingly, in a study of women without HIV, use of ART for pre-exposure prophylaxis was not associated with LBW (adjusted OR 0.58, 95% CI 0.20–1.73) [138].

Malaria and other systemic infective-inflammatory pathways

Pregnancy is known to increase the risk and severity of malaria infection, and malaria increases the risk of maternal anaemia and LBW [139,140]. Much of the impact of malaria on birthweight has been studied in the context of clinical trials examining the effect of chemoprophylaxis, such as those included in a systematic review in 2013 with data from 6281 pregnancies [141]. The study found that an increase to three doses of intermittent preventive therapy using sulfadoxine-pyrimethamine for pregnant women was associated with a lower risk of LBW, alongside other benefits. In malaria-endemic areas, the absence of anti-malarial treatment, even in asymptomatic pregnant women, is associated with an increased relative risk of LBW. The impact of placental malaria is important. In one study in Uganda, placental infection on blood smear was associated with a higher risk of LBW (18.9%) compared with systemic malaria without placental infection (7.2%, $p = 0.01$), as well as a higher risk of preterm delivery (OR 4.7, 95% CI 1.28–17.5) [142]. Data suggest that the risk of malaria contributing to LBW differs between trimesters of pregnancy. In a study of 1628 women in a high-prevalence area in Malawi, malaria in the first trimester led to a higher risk of preterm birth than in subsequent trimesters [143]. The impact of malaria and its prevention may also be associated with gravidae. There is evidence that women in their first and second pregnancy may be at greater risk [144], although other studies have shown a greater impact of sulfadoxine-pyrimethamine on birthweight in multigravida than in primigravid women [145]. Moreover, malaria epidemiology may have an impact on birthweight: in areas with endemic, stable transmission, women might have partial immunity and chronic subclinical placental infection, leading to slightly reduced birthweight, whereas women in areas with unstable transmission might have less anti-malarial immunity, more clinical placental infection and a higher risk of LBW [145].

Malaria during early pregnancy alters the kinetics of systemic inflammatory, angiogenic and metabolic mediators [143,146], which might contribute to the relationship between malaria and adverse birth outcome (discussed above). However, in other studies of malaria infection during pregnancy, CRP was not predictive of LBW [147], and, although placental TNFα was associated with parasitaemia, monocyte infiltration and LBW, circulating TNFα was only weakly associated with infection [148]. The effects of malaria on birth outcome might be worsened further in the context of co-infection with HIV [149], schistosomiasis [77] and others.

Systemic inflammation provides an indicator of a mother's inflammatory status that is more readily accessible than tissue sampling and, in some cases, reflects tissue inflammatory pathways. In 1179 pregnant women in Malawi, plasma levels of the liver acute-phase protein alpha-1-acid glycoprotein (AGP) was a significant predictor of newborn weight-for-age Z-score [150]; pathway analysis of this cohort indicated that AGP had a mediating rather than independent effect on the relationship between maternal infection, anthropometry and nutritional status and infant birthweight [150,151]. In 653 mother-infant dyads in Nepal, serum AGP (but not CRP) was also inversely associated with birthweight, length and head and chest

circumference [152]. In two studies which simultaneously assessed a wider range of plasma biomarkers in 432 Tanzanian and 1506 Malawian women, a combination of pro-angiogenic and pro-inflammatory mediators was predictive of SGA [153] and preterm birth [154], respectively. However, it should be noted that large cohort studies have shown that first-trimester exposure to non-steroidal anti-inflammatory drugs such as ibuprofen is associated with small reductions in birthweight [155,156], although these studies took place in HIC where antenatal exposure and subsequent pathways leading to SGA and preterm may differ.

Antimicrobial interventions

Whilst it is beyond the scope of this review to appraise all potential antimicrobial interventions, a brief review of selected studies highlights the potential value of targeted antimicrobial interventions as a promising pathway to reduce SGA, prematurity and/or LBW.

Targeted interventions

There are positive impacts on LBW of several targeted interventions. Early antibiotic treatment of BV in pregnancy in the context of previous premature birth led to reduced odds of premature birth [157–160]. Antibiotic treatment of asymptomatic bacteriuria on microscopy led to reduced preterm birth (RR 0.34, 95% CI 0.13–0.88) and reduced LBW (RR 0.64, 95% CI 0.45–0.93) [161]. A systematic review in 2014 found that malaria chemoprevention led to a reduction in LBW of 27% (RR 0.73, 95% CI 0.61–0.87) in endemic settings compared with placebo or no intervention. Comparing antimalarial prophylaxis using cotrimoxazole or sulphadoxine-pyrimethamine in women with HIV, infant birthweight was similar between strategies in both randomised and observational analyses [160,160,162,163]. The screening and treatment of STI during pregnancy in a systematic review demonstrated a lower risk of premature birth (RR 0.55, 95% CI 0.41–0.75) and a reduced risk of LBW (RR 0.48, 95% CI 0.34–0.66) [164]. However, the potential benefits have not been universal. In a Cochrane systematic review, treatment of *Trichomonas vaginalis* with metronidazole in pregnancy was associated with an increased incidence of LBW and preterm delivery [165]. Moreover, there might be risks associated with certain anti-microbials in pregnancy, as highlighted by a study which demonstrated more functional impairments at age 7 years in children of mothers treated with erythromycin for spontaneous preterm labour with intact membranes and a higher risk of cerebral palsy in children whose mothers received either erythromycin or co-amoxiclav in labour [166]. However, many large-scale studies have demonstrated the safety of many antimicrobial agents [141].

Untargeted interventions

Several studies have explored untargeted antimicrobial prophylaxis during pregnancy. A systematic review of 4300 pregnant women in eight trials in mixed-income settings assessed the impact on birth outcome of prophylactic antibiotics in the second and third trimesters versus placebo [158]. Prophylactic antibiotics had no impact on LBW or prematurity in general populations. Moreover, other antimicrobial interventions such as mass anti-helminth administration have had no positive impact on LBW; this could be owing to marginal effects of helminths on birthweight, associations that are confounded by multiple coincident risk factors for helminth infection and LBW, and/or anti-helminthic treatments that are insufficiently effective (e.g. praziquantel and albendazole do not prevent re-infection). However, the potential impact of antimicrobial administration might be more pronounced in settings with a high burden of infectious disease. A review of eight studies [167] found that antibiotics during pregnancy had a positive impact on IUGR or preterm birth. Five positive trials were in sub-Saharan Africa, where broadspectrum antibiotics were generally used, ranging from single-dose cephalosporins to a 6-week course of erythromycin. The mean reduction in gestation was 0.5 weeks, or a 20% reduction in preterm birth in those receiving antibiotics rather than in those receiving a placebo. Studies in India, the US and the UK had heterogeneous results [167].

Taken together, data from these studies suggest that targeted antimicrobial interventions hold promise in reducing LBW and premature birth. Untargeted antimicrobial prophylaxis might have a role to play, particularly in specific settings with a high prevalence of infectious diseases such as reproductive tract infections, HIV or parasitic infections.

Future research priorities

This is a narrative review and should be considered for hypothesis generation and to inform new ideas for research. A systematic review is required in this field to comprehensively further appraise these data, and prospective trials are needed to assess causality.

Given the morbidity associated with LBW in LMIC, further research is needed to guide potential new strategies. Compared with the wealth of studies in HIC, there is a need for further studies in LMIC populations with a high infectious disease burden and high rates of LBW.

Specifically, research is needed to identify which groups of women with evidence of perturbed inflammatory and infective pathways are most at risk of a poor pregnancy outcome, including those with particular microbial colonisation patterns and genetic susceptibility to certain pathways. In addition, this review

highlights the importance of research into tissue-specific inflammation pathways, which may be harder to capture by existing clinical sampling. Mechanistic studies in LMIC should include longitudinal evaluation of microbial taxonomy and function, specific inflammatory pathways underlying adverse birth outcome and periods of highest risk during pregnancy to characterise typical fluctuations in microbial/inflammatory exposure during healthy pregnancies in LMIC, and also identify the mechanistic pathways leading to LBW. Dissecting the pathways in different LBW phenotypes (SGA versus preterm, versus SGA-preterm) needs further evaluation.

Additional research is needed to differentiate the value of different anti-infection strategies, including the efficacy and cost-effectiveness of chemoprophylaxis versus intermittent screen-and-treat approaches for specific infections (e.g. for malaria), and systemic versus local (e.g. vaginal) approaches. Efficacy studies in endemic settings should consider combinations of vaccines, antimicrobials and other preventive approaches such as prebiotics or probiotics to target intestinal dysbiosis and enteropathy during pregnancy. In addition to evaluating the effects on LBW phenotypes, studies could evaluate the impact of these strategies on other related adverse pregnancy outcomes, such as late spontaneous miscarriage. There is a concurrent need to explore both the positive and adverse effects of treatments in pregnancy which target inflammatory and microbial pathways, with an emphasis on population-level effects in LMIC, particularly in the context of increasing concerns regarding antimicrobial resistance in these settings.

Conclusion

An improved understanding of the mechanisms and pathways underlying LBW is needed, given the impact of LBW throughout life. LBW, comprising SGA and prematurity, persists despite global intervention, causing significant risks of death and illness over a lifetime in LMIC. There is a variety of proven interventions, including smoking cessation, access to antenatal care and micronutrient supplementation [31], although this paper emphasises the potential role of antenatal microbial and inflammatory exposure as a treatable pathway for intervention. The studies included here suggest that local infection and inflammation pathways such as vaginitis and placental infections contribute to prematurity. Distal pathways such as periodontitis and EED, and systemic infections such as malaria and HIV are also linked to LBW. Malaria chemoprophylaxis, the screening and treatment of asymptomatic bacteriuria and certain STIs have shown positive associations with reducing LBW through the effects on prematurity and SGA, although prophylaxis against other pathogens

requires further investigation. Scale-up of proven interventions and further research into how maternal infection and inflammation can be prevented are needed to reduce LBW and improve long-term health, growth and human capital.

Abbreviations

AGA	appropriate for gestational age
ART	antiretroviral
BV	bacterial vaginosis
CRP	C-reactive protein
EED	environmental enteric dysfunction
HIC	high-income countries
IFABP	intestinal fatty acid binding protein, an EED biomarker
IL	interleukin
LBW	low birthweight
LMIC	low- and middle-income countries
HIV	human immunodeficiency virus
IFN	interferon
IUGR	intra-uterine growth restriction
NCD	non-communicable disease
SGA	small for gestational age
STI	sexually transmitted infection.

Key takeaways

- Maternal inflammatory and infective pathways probably represent a small proportion of the overall burden of LBW but provide different treatable pathways for interventions.
- An intervention that prevents infection and inflammation in pregnancy at tissue sites local to and distal from the developing fetus may benefit both the mother and infant in LMIC, by reducing LBW through an effect on prematurity and SGA.
- Additional research is needed on how infection and inflammation can be prevented, specifically maternal vaccination, antimicrobial treatment and the value of different approaches and timing in pregnancy.

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