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Review

Antimicrobial stewardship and targeted therapies in the changing landscape of maternal sepsis

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ABSTRACT

Pregnant and postnatal women are a high-risk population particularly prone to rapid progression to sepsis with significant morbidity and mortality worldwide. Moreover, severe maternal infections can have a serious detrimental impact on neonates with almost 1 million neonatal deaths annually attributed to maternal infection or sepsis. In this review we discuss the susceptibility of pregnant women and their specific physiological and immunological adaptations that contribute to their vulnerability to sepsis, the implications for the neonate, as well as the issues with antimicrobial stewardship and the challenges this poses when attempting to reach a balance between clinical care and urgent treatment. Finally, we review advancements in the development of pregnancy-specific diagnostic and therapeutic approaches and how these can be used to optimize the care of pregnant women and neonates.

Introduction

Sepsis has a significant contribution to both global morbidity and mortality with approximately 30 million patients affected worldwide each year and a resulting 6 million deaths.[1,2] Poor outcomes from sepsis are a particular problem in certain vulnerable populations which includes pregnant and postnatal women. One in 10 deaths in pregnant and postnatal women worldwide is attributed to sepsis[2,3] and one million neonatal deaths are secondary to infection in pregnant women, including sepsis.[2,4] Physiological adaptations during pregnancy are thought to contribute to their vulnerability. In particular, changes in their cardiorespiratory and immune systems, alongside physical, hormonal, and immunological changes during labor and postpartum have been shown to have a significant impact.

Are Pregnant Women at Greater Risk of Sepsis?

Morbidity and mortality from sepsis in pregnancy worldwide have gradually been falling over the decades due to improvements in care. Age standardized infection rates have fallen from 800 per 100,000 pregnancies in 1990 to 550 per 100,000 pregnancies in 2019.[5] Despite this, in 2019 there were over 20 million cases of maternal sepsis and other maternal infections worldwide. The World Health Organization (WHO) reported global prevalence of maternal sepsis is 4.4%[5,6]. In the UK, significant risk factors include ethnicity and deprivation. Black and other ethnic minority groups are at an almost 2-fold increased risk.[7,8] Furthermore, when compared to age-matched non-pregnant controls, sepsis-related case fatality is higher during pregnancy, childbirth, and postpartum.[9] The reasons for the higher rates of sepsis-related maternal morbidity and mortality are not fully understood.

Evidence for poor outcomes from sepsis in pregnancy

Data from current and previous coronavirus pandemics as well as influenza and Ebola demonstrate the increased risk of severe infection during pregnancy and poorer outcomes. [10–14] For example, in pregnancy the risk of viral pneumonia and

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subsequent respiratory complications is far greater when compared to the general population.[15] During the coronavirus 2 (SARS-CoV-2) pandemic, pregnant patients with severe acute respiratory syndrome were more likely to require intensive care and mechanical ventilation, and their mortality rate was higher when compared to non-pregnant women.[12] Other pathology such as renal failure and disseminated intravascular coagulopathy (DIC) have also been shown to be more frequent in pregnancy. These vascular changes appear to extend to the placenta where findings consistent with abnormal blood flow and extensive thrombotic vasculopathy have been observed in women delivered during acute infection.[14] During antenatal bacterial sepsis, obstetric complications associated with abnormal uteroplacental blood flow such as fetal growth restriction, placental abruption, and preterm birth are more common.[16] This has also been shown in lipopolysaccharide (LPS) treated rats, simulating sepsis during pregnancy, where coagulopathy, structural abnormalities in the uteroplacental vasculature, and decreased placental blood flow lead to fetal hypoxia and pregnancy loss.[17]

Period of greatest risk and associative factors in pregnancy

The stage of pregnancy and postpartum is also important. Almost 34% of all maternal infections occur in the antenatal period. Moreover, of those infections that are complicated or severe, 17% and 28% respectively occur in the antenatal period. In comparison, 60% of all maternal infections occur during the intrapartum and postnatal periods, and they account for 60% of both complicated and severe infections.[18] Prospective studies conducted in the UK suggest that labor and the puerperium carry a much higher risk, approaching a 2–3-fold increase in risk when compared to the antenatal period.[19] It is possible that peripartum and postnatal invasive interventions such as Caesarean section and instrumental delivery, as well as intrauterine or vaginal tamponade for massive obstetric haemorrhage, increase the risk of developing infection.[7,20,21] These interventions have been the target of efforts to reduceis infection rates by changes in obstetric care and optimized use of antibiotic prophylaxis.[22,23] The promotion of aseptic techniques and antibiotics are of particular need in Low and Low Middle Income Countries (LMIC), where rates of maternal infections and severe maternal infections are 40% and 20% greater respectively than upper-middle income countries, and fatality following puerperal infection is as high as 50%.[6,18]

As discussed above, severe respiratory complications are more common in pregnancy during severe infection, and so are other downstream effects such as DIC, renal failure, and hypotension, which contribute to the rapid progression to septic shock. In a mouse model of LPS induced sepsis response, pregnancy was found to be associated with a profound hypotensive response and increased mortality when compared to non-pregnant mice.[24] In a second series of experiments, using a polymicrobial sepsis model caused by caecal ligation and puncture the same research group found that pregnancy was again associated with a marked hypotensive response and much greater mortality.[25] Interestingly, the use of broad-spectrum antibiotics and a vascular smooth muscle specific inhibitor of nitric oxide synthesis was associated with better outcomes.[26] This suggests that identification and treatment are important tools to improve poor outcomes. In humans, certain pathogens predominate. In maternal sepsis, *Escherichia coli* (*E. coli*) and group B Streptococcus (GBS) are the most common bacterial pathogens, although other causative organisms include other Gram-negative organisms such as *Klebsiellas, Mycoplasma,* and other coliforms, but also Gram-positive organisms such as *Clostridium sordellii.*[27] However, the most severe outcomes are associated with *E. coli* and group A Streptococcus (GAS).[19] Progression to septic shock is particularly a problem with GAS infection.[28] Furthermore, in pregnancy, the risk of group A and group B streptococcal bacteremia when compared to non-pregnant women is 20–100-fold higher.[29,30]

Why are Pregnant Women at Greater Risk of Sepsis?

Physiological changes in pregnancy such as immunological, cardiovascular and respiratory adaptations (Figure 1) may contribute to an increased risk of developing severe complications during sepsis.

Immunological

Peripheral blood adaptations

The earliest hypothesis proposed in the 1950′s described the immune adaptations of pregnancy as a series of changes designed to prevent rejection of the semi-allogenic fetus resulting in maternal immune tolerance.[31–33] Subsequently, the classic model of immune tolerance included a shift in T-helper subsets (Th1 to Th2) that favored an anti-inflammatory profile but also increased susceptibility to infections in pregnancy. Our current understanding is that the immune environment transitions with advancing gestation from a pro- to anti- and back to a pro-inflammatory state.[34–36] The innate and adaptive arms of the immune response are thus differentially activated to modulate these changes as well as compensate for each other. Immune modulation is thought to be influenced and maintained by endogenous factors that include feto-placental derived antigens and pregnancy hormones such as oestrogen and progesterone.[37–39] Fetal antigens elicit tolerogenic humoral and cellular responses in pregnant women through the generation of antigen specific CD4 and CD8 T cells, MHC-specific B cells (in murine models), and fetal-specific CD4 T-regulatory cells (Tregs). [40–42] The placenta is the likely source of fetal antigen exposure that is shed through microvesicles and exosomes, cellular debris and due to microchimerism.[43–47] Progesterone is a key hormonal modulator of immune responses in pregnancy that acts to suppress inflammatory and cytotoxic functions.[36,48–50]

Altogether, these changes described above result in a dynamic immune system in pregnancy that varies throughout gestation. In early pregnancy, we see T cells resembling a Th1 phenotype and Tregs that favor an effector subset.[51,52] As pregnancy progresses into the second trimester the immune environment becomes more immune tolerant. Thus, effector memory T cells predominate with upregulation of inhibitory markers, increased progesterone sensitivity of natural killer (NK) cells, altered dendritic cell (DC) subsets and indoleamine 2,3-dioxygenase activity, and a shift in Treg phenotype from effector to naive.[35,36,52] Finally, in the third trimester there is a move to favor immune activation with pro-inflammatory

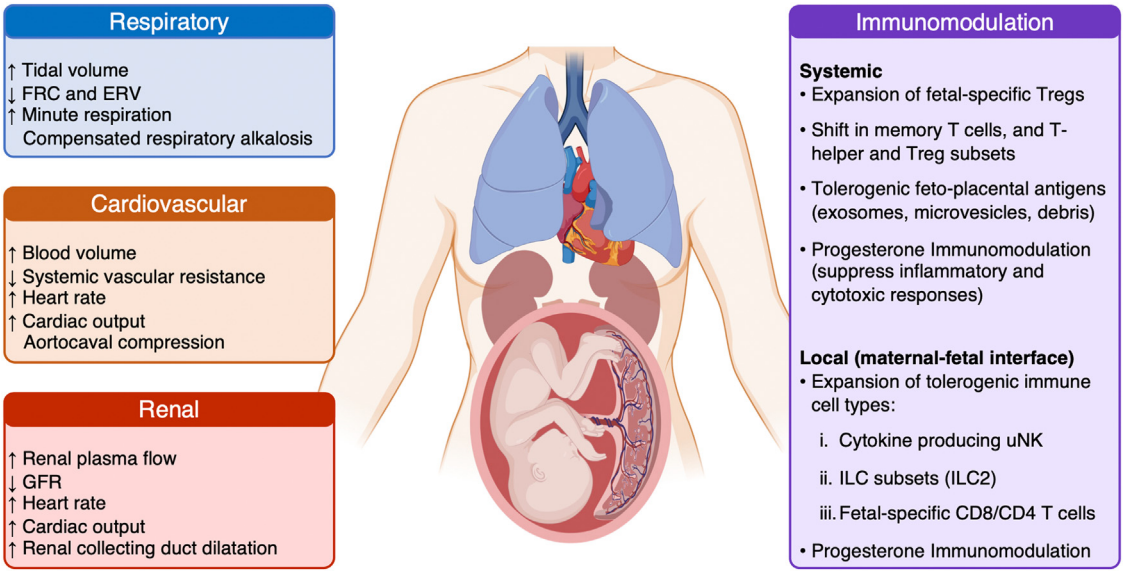

Figure 1. Physiological adaptations in pregnancy. The respiratory, cardiovascular, and renal changes that occur in pregnancy. Immune changes are subdivided into systemic and local changes that enable fetal tolerance. These adaptations contribute to the increased risk of maternal sepsis.
ERV: Expiratory reserve volume; FRC: Functional residual capacity; GFR: Glomerular filtration rate; ILC: Innate lymphoid cells; NK: Natural killer.

antigen-specific cellular responses that are further enhanced during labor.[36,38]

Immune adaptations at the maternal-fetal interface

Modulation of immune responses is also evident locally at the maternal-fetal interface and is seen in both the innate and adaptive arms that include NK cells, innate lymphoid cells (ILCs), and T cells. Importantly, this interface tolerates the semi-allogeneic fetus but can retain an ability to protect against invading pathogens. In fact, 30–40% of decidual cells are leukocytes and this forms a specialized decidual immune system in pregnancy.[53] Uterine NK cells (uNK) from a large portion of innate leukocytes in the endometrium and decidua and they function to facilitate placentation during pregnancy. Crucially, the uNK phenotype changes during early pregnancy from proangiogenic to cytokine producing, thus allowing for extravillous trophoblast invasion.[54,55] Their cytotoxicity is largely limited due to their ability to interact with human leucocyte antigens (HLA) class I molecules expressed by trophoblast (HLA-C, HLA-E, HLA-G). With labour onset, the decidual NK phenotype shifts resulting in a reduction in proportions of cytokine producing $CD56^{hi}$ NK (our unpublished observations). This is consistent with single cell RNA-seq data from the placenta, which has demonstrated an upregulation of NK cell signatures.[56] This suggests that the composition of the uNK compartment is dynamic. Strunz et al.[57] identified a subset of highly proliferative uNK cells that regenerate under the influence of sex hormones and genetic triggers, for example during menstruation and pregnancy. Whilst these cells differentiate locally their origin appears to be from the peripheral circulation and they are transiently tissue-resident.

Another group of tissue resident immune cells important for pregnancy is innate lymphoid cells (ILCs), which have been identified in the uterus and decidua. These have immune modulatory functions and provide protection against pathogens. They are subdivided into group 1 which produces mostly Interferon (IFN)-γ, group 2 which produces Th2 cytokines, and group 3 which produces Interleukin (IL)-22 and IL-17. In the decidua during pregnancy, ILC2 is thought to be the most abundant subset present.[58] However, ILC1 and ILC3 may have key roles during certain pregnancy pathology, including preterm labor (PTL), as well as during physiological labor. Furthermore, during pregnancy, the composition of these cells in the decidua basalis and parietalis is different and may represent a varied immune response. For example, Mendes et al.[59] demonstrated an increase in ILC2 and ILC3 populations in the decidua basalis in PTL, and similarly, Xu et al.[58]saw increases in both basalis and parietalis.

Tissue resident macrophages are situated close to decidual natural killer (dNK) cells. They function to clear debris, present feto-placental antigens and secrete cytokines and chemokines to modulate dNK and T cell responses.[60,61] Both CD8 and CD4 T cells can directly (via HLA-C) or indirectly (via antigen processing cells or APCs) recognize feto-placental antigens. However, antigen specificity provides a means to regulate T cell immune responses to prevent fetal rejection. For example, CD8 T cells expressing inhibitory markers (T cell immunoglobulin and mucin domain-containing protein 3 or Tim-3, Programmed cell death 1 or PD-1) that interact with their ligands (Programmed cell death ligand 1 or PD-L1) on trophoblast are enriched in the decidua in an HLA-C dependent manner.[62] Moreover, the cytotoxic potential of the effector memory CD8 T cell subset is impaired.[63] Further regulation is provided by decidual fetal-specific Tregs that clonally expand during pregnancy.[42] In murine models, these have been shown to have fetal-specific and highly suppressive capabilities.[64] In addition, class-switched memory B cells and IL-10-producing B cells have been found co-localized in clusters with Tregs in pregnancy further enhancing the regulation of local immune responses.[65]

Immune contribution to sepsis

Antenatal responses to infections and vaccines are an opportunity to understand how pregnancy may affect adaptive immunity. Forbes et al.[66]showed impaired *in vitro* antiviral

IFN responses in the second and third trimesters following rhinovirus infection. In contrast, analysis of *ex vivo* responses following influenza vaccine and SARS-CoV-2 infection fare differently, with maintenance of both humoral and antigen-specific responses.[67–69] This suggests that cellular responses are unaffected by pregnancy immune modulation. However, phenotypic data from the same research studies suggest a reduction in the pro-inflammatory cellular compartments and low-level immune regulation.[67,68] With peripartum risks much greater than during the antenatal period, labor, which is itself a process of inflammation, provides an opportunity to understand how inflammatory responses are regulated. Tissue necrosis because of inflammation can release microparticles to interact with innate immune receptors such as toll-like receptors (TLRs) to drive inflammatory signals during labor.[70,71] Interestingly, TLR inhibitors can repress this output.[70] As discussed earlier, in pregnancy many regulatory immune cells are upregulated, including Tregs, and these have a suppressive effect on certain immune responses.[39] Tregs can modify their targets from Th1 to Th2 effector T cells alongside a change in their suppressive activity to either suppress or propagate inflammation. Whilst during sepsis Tregs are thought to have a protective effect by suppressing exaggerated inflammatory immune responses, their abundance in pregnancy may not necessarily be helpful in certain circumstances.[72–74] For example, during labor Treg function is thought to be altered to enable a proinflammatory cytokine response.[38,39] This suggests that immune regulation during the peripartum period may, in fact, result in an augmented inflammatory response to sepsis. In addition to this, leucocyte trafficking may also be altered in pregnancy meaning that important immune cells are less able to clear pathogens at sites of infection. This is shown in murine work using knockout mice which demonstrates that the loss of a monocyte chemoattractant receptor leads to reduced cell trafficking, significantly worse bacteremia, and survival.[25] Furthermore, the migratory potential of important immune cells required during an infection such as neutrophils varies with gestation and during different labor phenotypes.[75,76] These areas of immune modulation are all possible avenues of future research and treatment options.

Cardiovascular

Circulatory adaptations

Cardiac output increases gradually in pregnancy, reaching up to 45% greater than early pregnancy by 24 weeks of gestation.[77,78] This occurs due to changes in stroke volume and heart rate and is associated with both left and right ventricular hypertrophy. Alongside these changes, peripheral vascular resistance falls in the second trimester and reaches a nadir of 40%.[77] Blood pressure (BP) dynamics show similar changes with a fall in both systolic and diastolic, and therefore mean arterial BP in early pregnancy that falls further in the second trimester before increasing in the third.[79] Some of these changes are hormone driven. For example, higher concentrations of progesterone and relaxin are associated with lower systolic BPs.[80]

Renal adaptations

Plasma volume and red cell mass increase with advancing gestation. This is due to activation of the renin-angiotensin-aldosterone (RAA) system that helps to maintain BP. Much of this is due to the fact that progesterone, which also rises in pregnancy, has potent mineralocorticoid effects, and acts as an aldosterone antagonist to inhibit aldosterone binding. This leads to compensatory RAA activation and a rise in serum aldosterone.[81,82] Furthermore, relaxin stimulates vasopressin secretion causing further water retention. The increase in plasma volume and cardiac output alongside renal vasodilatation, lead to an increase in renal plasma flow and glomerular filtration rate.

Kidney size also increases in pregnancy with physiological dilatation of the collecting ducts that causes hydronephrosis in most pregnant women. This hydronephrosis increases with gestation and is greater on the right kidney due to the compressive effect of the gravid uterus.[83]

Cardiovascular contribution to sepsis

Increased levels of prostaglandins and nitric oxide (NO), which are upregulated by oestrogen, encourage smooth muscle relaxation and vasodilatation. During sepsis, further upregulation of NO leads to the development of septic shock.[84] In addition, during sepsis, inflammatory cytokines such as tumor necrosis factor (TNF)-α and IL-1β lead to myocardial depression.[85,86] Furthermore, measurable levels of serum Troponin T and I, and B-type natriuretic peptide (BNP) have been shown to be increased with sepsis-associated myocardial depression.[87–89] These are useful markers for myocardial function and prognosis in sepsis. Considering that cardiac output is increased in pregnancy, a loss of myocardial function has a significant effect on the circulatory system. Downstream complications of severe systemic infections include acute kidney injury, which is associated with significant morbidity and mortality.

Renal contribution to sepsis

Physiological hydronephrosis and the mechanical compression of the ureters by the gravid uterus cause urinary stasis. This alone can increase the risk of bacteriuria and ascending urinary tract infection in pregnancy by up to 40%.[90] Furthermore, renal tubular epithelial cells can interact with inflammatory mediators generated during infections through pattern recognition receptors (PRRs) such as TLRs.[91] This interplay can exacerbate local tissue injury. During sepsis, tissue inflammation, microvascular injury, hypoperfusion, and organ dysfunction ensue as a cascade of events. Local inflammatory responses form an important part of the host's defense against invading organisms. This is mediated by the interaction between pathogen associated molecular patterns (PAMPs) and danger associated molecular patterns (DAMPs) released into the vasculature during the initial innate immune response and TLRs found on immune cells.[92] Renal vascular and tubular epithelial cells also express TLRs and their activation leads to the production of reactive oxygen species (ROS) and cytokine signaling to attract leucocyte infiltrates. The consequent endothelial injury and tubular inflammation lead to microthrombi formation, interstitial oedema, and further tissue injury.[93]

Respiratory

Respiratory adaptations

In pregnancy, there is an increase in oxygen consumption and progressive distension of the uterus that affects both metabolic

demands and lung volume. To try to maintain the total lung capacity, the volume of air remaining in the lungs post-exhalation measured as functional residual capacity (FRC) and expiratory reserve volume (ERV) is reduced.[94] In addition, there is an increase in the tidal volume, which results in greater minute ventilation without increasing the respiratory rate.

Respiratory contribution to sepsis

The adaptations in pregnancy including the physiological hyperventilation result in a state of respiratory alkalosis. This is in part due to progesterone, which increases the sensitivity of the respiratory center to carbon dioxide.[95,96] To maintain acid-base balance, this alkalosis is managed by an increase in renal bicarbonate excretion.[94] Consequently, the pregnant woman's capacity to counter sepsis-related metabolic acidosis may be significantly impaired. This is an important consideration for all forms of sepsis in pregnancy.

During respiratory tract infections, local responses to inflammation are important in the context of pregnancy. As discussed, pregnant women have been disproportionately affected during respiratory pandemics. It is possible that these outcomes are likely to be made worse by the compressive effect of the gravid uterus on the maternal lungs and the greater chance of basal atelectasis during late pregnancy.[94] One of the drivers of clinical severity in these patients is thought to be a heightened cytokine response, which has been observed previously during the H1N1 influenza pandemic.[97] A similar mechanism is thought to be at play during the COVID-19 pandemic. However, acute changes in the lungs may also be affected by pregnancy-specific inflammatory leucocyte sequestering in lung tissue during a cytokine storm, as shown in murine pregnancy sepsis models, eventually causing severe tissue damage.[24]

What are the Neonatal Consequences of Maternal Sepsis?

For the neonate, maternal transmission of bacteria such as GBS or transmission of infections such as chorioamnionitis during the intrapartum period significantly increases the risk of early onset neonatal sepsis (EOS).[98] In addition, neonatal immune function during PTL with chorioamnionitis is associated with greater inflammatory cytokines and leucocyte activation.[99]

Early neonatal sepsis

Unsurprisingly, rather like maternal sepsis, the most common pathogens involved are GBS and *E. coli*, accounting for approximately 70% of cases of EOS.[100,101] Whilst the overall incidence of EOS is 1–2 per 100 live births, mortality from EOS approaches 3% amongst term newborns and 16% in high risk, low birth weight (LBW) neonates.[98] Interestingly, as causative agents identified in neonates, GBS appears to affect more term neonates and *E. coli* predominantly preterm infants, with the latter slowly on the rise. However, other organisms include *Streptococcus* species and *Haemophilus influenzae*.[101]

Significant morbidity from EOS disproportionately affects preterm neonates, who in the acute phases often develop respiratory distress requiring invasive ventilation, and hyper/hypoglycemia. In the long term, these neonates are at risk of bronchopulmonary dysplasia (BPD), poor neurodevelopmental outcome, and cerebral palsy. Term neonates with EOS, commonly by GBS, can have significant neurological sequelae including seizures, blindness, hearing loss, and speech and language delays.[100]

Rates of EOS are higher in some LMICs where the reported incidence of peripartum infection is 4% but symptom reporting suggests a much more plausible 16%. Early neonatal mortality due to puerperal sepsis carries a relative risk of 2-fold when compared to neonatal deaths in the absence of maternal infection. The authors of the study using demographic health survey data from five LMICs suggest that inadequate reporting of maternal sepsis is a significant challenge in the study countries, and improved recognition and treatment of maternal infections may reduce neonatal complications.[102]

Maternal to fetal transmission

During sepsis in pregnancy, vertical transmission to the neonate of the causative organism as well as transmission of maternal colonising organisms (such as GBS) is more likely in the presence of other infectious morbidities. These include risk factors such as prolonged rupture of membranes or intrapartum fever that increase the impact and risk of EOS[98]. Generally, in both these circumstances, the risk of EOS increases 3–4-fold, and 50%–67% of these involve preterm or LBW neonates.[103]The progression of ascending lower genital infections will be further exacerbated by inflammation at the maternal-fetal interface. This causes local immune defenses to be more permeable to invading organisms, and can also lead to infections overwhelming host responses.[104,105]

Other potential sources for vertical transmission of infections are maternal urinary tract infections and respiratory infections. Urosepsis in pregnancy is a potential source of Gram-negative bacteremia and is associated with poor neonatal outcomes includingsepticemiaepticaemia, preterm births, and stillbirths.[106] Although the mechanism for the relationship is not clear, the prevalence of neonatal urinary tract infections in those born to mothers with a corresponding urinary infection is relatively increased.[107,108] Data from LMIC suggest that neonates born to mothers who experienced urinary tract infections during pregnancy are 3.55 times more likely to develop neonatal sepsis when compared to those born to mothers without a urinary tract infection.[109] It is plausible that untreated ascending urinary infections in pregnancy that lead to sepsis may result in fetoplacental transmission through hematogenous spread to infect the neonate.

Respiratory tract infections are another common source of maternal sepsis. Bacterial pneumonia is associated with worse neonatal outcomes that include preterm birth, low birth weight, and pre-eclampsia.[15,110] This is after accounting for comorbidities such as obesity and diabetes. However, the mechanisms for these differences are unknown. While EOS is rare, it remains possible in the presence of maternal bacteremia. Likewise, during COVID-19 infection, pregnant women are more likely to develop severe illness with an increased risk of preterm birth and small for gestational age babies.[111–114] These neonatal complications are more prevalent in moderate to severe COVID-19.[115] However, early neonatal COVID-19 infection is rare and neonatal symptoms are generally mild.[116] The source of vertical transmission remains uncertain and appears to be unlike other viruses such as Zika where trophoblast infection serves

as a route of transmission.[117] Viral entry is possible through the angiotensin converting enzyme-2 (ACE-2) receptor isolated on placental tissue and following placental barrier damage secondary to local inflammation and tissue injury.[118–120] Indeed, the SARS-CoV-2 virus has been detected in syncytiotrophoblast and other placental tissues, and the presence of the virus has been shown to induce a robust immune response.[120–122] In placentas with a high viral load, the maternal space, and fetal chorionic villi are occupied by extensive inflammatory infiltrates that comprise macrophages and T cells, and CD56+ NK cells within the decidua.[121] A similar T cell infiltrate is seen in the fetal chorionic plate. Moreover, ACE-2 receptors which are detectable in fetal kidney, rectum, and ileum, are barely seen in fetal lungs, brain, or heart towards term pregnancy.[123] In fact, surveillance data suggests that postnatal transmission (via respiratory spread, close contact) accounts for most cases of early neonatal infections.

Ultimately the risk of vertical transmission will depend on the maternal system infected, the quality of maternal immune response, the receptiveness of the fetal compartment, and the evasive nature of the organism in question.

Management of early neonatal sepsis

National Institute for Health and Care Excellence (NICE) guidelines for the management and treatment of neonatal infection (NG195), which includes EOS, comprises empirical treatment based on maternal risk factors and neonatal clinical review at birth.[124] Thereafter, the duration of treatment is based on clinical improvement, neonatal blood cultures results, which have notoriously poor sensitivity, and changes in non-specific inflammatory markers, namely C-reactive protein (CRP).[125,126] However, in the era of better antibiotic stewardship, the usefulness of empirical treatment based on maternal risk factors in 'well' infants is debatable, and tools to determine a baby's risk of developing EOS may be helpful in some cases.[125] Having said this, it is important to note that neonatal antibiotic stewardship is mired by challenges, including difficulties in developing unit antibiograms, and a lack of robust antibiotic trials in neonatal populations.[127] There are also challenges with using diagnostic tools in neonatal populations. Research comparing using the Kaiser Permanente sepsis risk calculator (SRC) to standard NICE guidelines across 8 maternity units in Wales by Goel et al.,[125,128] suggests that the use of the tool would have resulted in a 55% reduction in neonates receiving antibiotics. However, in a recent meta-analysis of the current published literature surrounding the SRC (including the study by Goel et al.), the authors found that many EOS cases were missed by the tool. This suggests that whilst the intentions of the SRC are a move in the right direction, research investigating the usefulness of such tools is still in its infancy.[129]

Complications of antibiotic use in neonates

Whatever the case, there is growing evidence that prolonged antibiotic use in this population may be detrimental, especially in preterm neonates without proven infection, increasing the risk of mortality, BPD, necrotizing enterocolitis, retinopathy of prematurity, and periventricular white matter damage.[130] Long-term empirical treatment will also affect the neonatal gut microbiome, and there is evidence that chronic medical problems in later life such as childhood asthma may be influenced by early use of antibiotics.[131] Currently, however, there are insufficient data to make clinical recommendations.[132]

The development and spread of antimicrobial resistance (AMR) in neonatal populations is also a concern. The WHO 2014 annual report of AMR found that the proportions of *E. coli, Klebsiella pneumonia* and *Staphylococcus aureus* resistant to commonly used antibacterial agents, exceeded 50% in many settings.[133] In newborns cared for in neonatal units, genes conferring AMR are detectable in bacteria colonizing the intestines of preterm infants. In the same units, Staphylococcal species resistant to methicillin and vancomycin are becoming more prevalent with a greater mortality associated with infections from these organisms because they are significantly more difficult to treat effectively. Furthermore, other organisms including extended-spectrum β-lactamase (ESBL)-producing Gram-negative pathogens that are resistant to cephalosporins, Gram-negative bacteria resistant to piperacillin-tazobactam, aminoglycosides, and Klebsiella-resistant to carbapenems are slowly emerging.[134] The Neonatal AntiMicrobial Resistance (NeoAMR) launched in 2017 with 39 participating neonatal units across 12 countries, has thus far reported preliminary data over 12 months, showing AMR rates amongst cephalosporins of 26% to 84%, carbapenems of up to 81%, and glycopeptide of up to 45%.[135] These data demonstrate the need for antibiotic stewardship as an increasingly urgent intervention in neonates.

Is There a Role for Antibiotic Stewardship in Maternal and Neonatal Clinical Pathways?

To manage sepsis effectively, clinical pathways have been designed to include recognition, resuscitation, and the timely administration of appropriate antibiotics.[136] Guidance is available for recommended antibiotic regimes for most obstetric indications as well as EOS (Table 1). The overwhelming message of the surviving sepsis campaigns is that the prompt diagnosis of sepsis and initiation of broad-spectrum antibiotics is paramount. Initiatives such as Sepsis Six require that these antibiotics be commenced within 3 h, and these recommendations have significantly reduced mortality rates from sepsis.[137,138] One of the unintended consequences of the sepsis campaigns has been the inappropriate use of clinical sepsis pathways in patients who do not fulfill the criteria for sepsis. Studies have reported that up to 50% of patients treated with broad-spectrum antibiotics for sepsis, did not have sepsis.[139]

The need for maternal antimicrobial stewardship

Clearly, a balance is required between effective treatment and appropriate antibiotic use. Antibiotic stewardship is required to optimize antibiotic usage, including rationalizing and de-escalating or stopping agents, to maintain their effectiveness. This is important because the incidence of AMR and healthcare-associated infections (HCAIs) is rising.[152] In Europe, the AMR in 2018 as reported by the European AMR Surveillance Network (EARS-Net) indicated more than half of the *E. coli* and more than a third of the *Klebsiella pneumonia* isolates were resistant to at least one antibiotic class.[153] In LMIC these figures

Table 1
Common obstetric indications for antibiotics and recommended regimes.

Indication	Causative organisms	Antibiotic recommendations	Important notes	References
		Pregnancy and postnatal for the mother Antibiotic prophylaxis		
GBS prophylaxis	GBS	Benzylpenicillin Penicillin allergy (severe): Vancomycin	Alternative: Cephalosporin	Prevention of early-onset neonatal group B streptococcal disease. Green-top Guideline No. 36. RCOG 2017 [140]
Prophylaxis at caesarean section	Staphylococci Streptococci Gram-negative	Single dose first-generation cephalosporin or penicillin (dose, 30–60 min before surgery)	Avoid amoxicillin plus clavulanate in preterm cases due to risk of necrotizing enterocolitis	WHO recommendation on prophylactic antibiotics for women undergoing caesarean section. Geneva: World Health Organization; 2021 [141]
Prophylaxis at caesarean section	Staphylococci Streptococci Gram-negative	Single dose first-generation cephalosporin (cefazolin) (dose, within 60 min before surgery) Penicillin allergy: Clindamycin + an aminoglycoside	Avoid amoxicillin plus clavulanate in preterm cases due to risk of necrotizing enterocolitis. Azithromycin may be used as an adjunct for non-elective caesareans	ACOG Practice Bulletin No. 199: Use of Prophylactic Antibiotics in labour and Delivery. Obstet Gynecol. 2018 [142]
Prophylaxis for operative vaginal birth	Gram-negative anaerobes Streptococci	Single dose of amoxicillin and clavulanic acid	As soon as possible after birth and no more than 6 h after birth	WHO recommendation on routine antibiotic prophylaxis for women undergoing operative vaginal birth. Geneva: World Health Organization; 2021 [143] Assisted vaginal birth. Green-top Guideline No. 26. RCOG, 2020 [144]
		Antibiotic treatment for suspected sepsis		
Intrapartum pyrexia (suspected sepsis)	Streptococci Gram-negative organisms Anaerobes	Pyrexia with no chorioamnionitis: Cephalosporin with activity against GBS (e.g., cefotaxime) Penicillin allergy: Vancomycin	Pyrexia with chorioamnionitis: add metronidazole.	National Maternity Network: Management of Intrapartum Maternal Pyrexia in Hospital Guideline. NHS Scotland. Scottish Perinatal Network. 2022 [145]
Mastitis causing sepsis	MRSA Streptococci	Flucloxacillin + clindamycin Penicillin allergy: Vancomycin + clindamycin or Clindamycin/teicoplanin	Confirmed MRSA: Vancomycin	Bacterial Sepsis in Pregnancy. Green–top Guideline No. 64a. RCOG 2012 [146] Mastitis and breast abscess. BMJ Best Practise. BMJ 2023 [147]
Caesarean section wound infection causing sepsis	MRSA Streptococci	Flucloxacillin + clindamycin Penicillin allergy: Vancomycin + clindamycin or clindamycin/teicoplanin		Bacterial Sepsis in Pregnancy. Green–top Guideline No. 64a. RCOG 2012 [146]
Endometritis causing sepsis	Gram-negative anaerobes Streptococci	Gentamicin one dose immediately + cefotaxime + metronidazole or gentamicin + clindamycin Penicillin allergy: Gentamicin + clindamycin + ciprofloxacin		Bacterial Sepsis in Pregnancy. Green–top Guideline No. 64a. RCOG 2012 [146] Antibiotic regimens for postpartum endometritis. Cochrane Database Syst Rev. 2015 [148]
Acute pyelonephritis causing sepsis	Gram-negative bacteria Staphylococci and Streptococci	Gentamicin (once only) + cefotaxime or just cefuroxime Penicillin allergy: Gentamicin + ciprofloxacin	ESBLs: gentamicin + meropenem	Bacterial Sepsis in Pregnancy. Green–top Guideline No. 64a. RCOG 2012 [146] Pyelonephritis (acute): antimicrobial prescribing. NICE guideline [NG111]. NICE 2018 [149]
Severe sepsis (with no clear focus)	MRSA, streptococci, Gram-negatives (including ESBL producers + Pseudomonas) and anaerobes	Gentamicin (once only) + meropenem + clindamycin Penicillin allergy: Clindamycin + gentamicin + metronidazole + ciprofloxacin		Bacterial Sepsis in Pregnancy. Green–top Guideline No. 64a. RCOG 2012 [146]
Toxic shock syndrome	Staphylococci Streptococci	Gentamicin (once only) + flucloxacillin + clindamycin or carbapenem (i.e., imipenem/cilastatin or meropenem); a penicillin with a beta-lactamase inhibitor (e.g., ticarcillin/clavulanate or piperacillin/tazobactam); Penicillin allergy: Gentamicin (once only) + vancomycin + clindamycin or gentamicin (once only) + linezolid or just vancomycin	Confirmed Strep: benzylpenicillin and clindamycin. Confirmed methicillin sensitive Staph: clindamycin + oxacillin/nafcillin. Confirmed MRSA: vancomycin instead of flucloxacillin. Regimen must contain an antitoxin agent such as clindamycin or linezolid. Also Consider IVIG	Bacterial Sepsis in Pregnancy. Green–top Guideline No. 64a. RCOG 2012 [146] Toxic shock syndrome. BMJ Best Practise. BMJ 2023 [150]

(*continued on next page*)

Table 1 (*continued*)

Indication	Causative organisms	Antibiotic recommendations	Important notes	References
		Neonatal (EOS)		
Early-onset neonatal sepsis	Streptococcus (GBS); Gram-negative bacteria	Benzylpenicillin with gentamicin		Neonatal infection: antibiotics for prevention and treatment NICE guideline [NG195]. NICE 2021 [151]

ACOG: American College of Obstetricians and Gynecologists; EOS: Early onset neonatal sepsis; ESBLs: Extended-spectrum beta-lactamases; GBS: Group B Streptococcus; IVIG: Intravenous immunoglobulin; MRSA: Methicillin-resistant *Staphylococcus aureus*; NICE: National Institute for Health and Care Excellence; RCOG: Royal College of Obstetricians & Gynaecologists; WHO: World Health Organization.

are much higher. For example, in Sudan up to 92% of urinary *E. coli* isolates are resistant.[154] For Sudanese healthcare, the key drivers of AMR include widespread inappropriate antibiotic use with up to 65% of hospitalized patients receiving antibiotics, and poor access to microbial sensitivity results to guide better prescribing.[155–157] In these resource-limited countries, much of the inappropriate use is due to empirical treatment or the use of antibiotic prophylaxis.[158] AMR is estimated to result in 700,000 deaths each year globally. In 2015 the WHO endorsed a Global Action Plan on Antimicrobial Resistance (GAP) to address the global problem, and in the UK a government document was published in 2019 with the country's 5-year action plan, which amongst other goals, was aimed at reducing antibiotic use by 15% and specified drug-resistant infections by 10% over 5 years.[159] In the maternity setting, patients with peripartum infection have been shown to have resistance to a number of common organisms encountered in obstetrics such as *E. coli*, GBS and GAS, with resistance rates as high as 62% to 81% for *E. coli.*[160] Cohort-specific antibiograms with isolates and their sensitivities may provide a better way to determine resistance patterns to guide antibiotic prescribing in maternity.[161]

Healthcare associated infections

The other consequence of widespread antibiotic use is the development of HCAIs. The HCAI rate in the UK and developed countries ranges between 3.5% and 12%. In the intensive care unit (ICU) up to 30% of patients are affected by at least one episode of HCAI. In comparison, in LMIC the incidence is greater, averaging between 5.7% and 19.1%, and ICU infections could be as high as 88%.[162] Poor reporting and lack of surveillance schemes mean the true incidence may be higher. In the UK, annual counts of hospital-acquired *Clostridioides difficile* and Methicillin-resistant *Staphylococcus aureus* (MRSA) infections have been falling since 2007 and are currently showing a 6 and 7-fold decrease respectively when compared to 2007.[163,164] However, these rates have remained unchanged since 2013 and new efforts are required to ensure a continued decrease.

The need for neonatal antimicrobial stewardship

Antibiotic prescribing in pediatric populations also remains a concern and an area that requires attention. The WHO Access, Watch, and Reserve classification was used in a study across 56 countries to assess the patterns of antibiotic use.[165] The study identified significant variation in antibiotic use in hospitalized neonates and children. One of the key barriers to effective stewardship in neonatal populations remains the lack of metrics for measuring the quality of antibiotic use.[166] Much more effort is needed to establish means of surveillance for effective stewardship programs in vulnerable neonatal populations in different healthcare settings.

Types of antimicrobial stewardship interventions

The WHO has published a framework of antimicrobial stewardship interventions for LMIC, but these are also relevant for resource-rich countries.[167] Similarly, NICE has published guidance for the UK.[168] The interventions are centered around improved education, multidisciplinary working, and better prescribing. In other patient groups, this multifaceted approach has been shown to reduce antibiotic prescriptions without increasing the risk of complications.[169] In addition, appropriate antibiotic use can reduce the rates of hospital acquired infections such as *Clostridium difficile*.[170]

In brief, the proposed recommended interventions comprise [167–169]: (1) basic resources to support antibiotic use including local guidelines for treatment and prophylaxis, access to a microbiology laboratory and clinical expertise on infections, pharmacy overview of dosing and duration of treatments. (2) tools such as the quick sequential (sepsis-related) organ failure assessment (qSOFA) tool for pregnant women, and the Kaiser Permanente SRC for neonates can enable better recognition of sepsis and improve decision-making surrounding the need for antibiotics. (3) education of healthcare professionals to understand indications for treatments, when treatments should be reviewed, use of decision tools, and the importance of auditing and recording antibiotic use, prescribing, and clinical outcomes.(4) use of resources to improve prescribing and effectiveness of antimicrobial stewardship that includes local and regional surveillance of AMR (in common organisms/infections), rapid testing (such as rapid polymerase chain reaction [PCR] as discussed later) and restrictive prescribing of certain antibiotics to prevent resistance.

What Research Gaps Need to be Addressed to Further Improve Clinical Management and Treatment of Maternal Sepsis?

Whilst the overall UK prevalence of sepsis-related maternal deaths remains low, sepsis is still one of the leading causes of direct death in this population. Since 2011, efforts have been made to highlight the importance of better clinical management of sepsis in maternal clinical pathways with early recognition and treatment.[146,171] These have included recommendations from Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries (MBRRACE), NICE and Royal College of Obstetricians & Gynaecologists (RCOG) guidelines as well as screening and action tools from the UK Sepsis trust.[138,146,171,172]

Furthermore, initiatives such as the maternity early warning score (MEWS) and sepsis six have been shown to effectively predict morbidity in maternity patients and reduce inpatient mortality respectively.[137,173,174] This has been relatively effective with a reduction in direct deaths due to sepsis in the UK from 0.63 to 0.44 per 100,000 births from 2009–11 to 2015–17 respectively.[175] Alongside these, rates of EOS have also been falling.[176,177] However, many maternal deaths remain potentially preventable.

Tools to improve recognition of maternal sepsis

Better recognition and prophylactic treatment may provide useful methods to prevent sepsis, particularly during the peripartum period. Similar to SRC, obstetric-modified sepsis scoring tools are useful to objectively risk stratify the severity of sepsis and direct clinical treatment.[178] This includes the qSOFA tool for identifying critically ill obstetric patients.[178,179]

Interventions as prophylaxis

For prophylaxis, the prophylactic antibiotics in the prevention of infection after operative vaginal delivery (ANODE) study and recent Cochrane review on vaginal antiseptic preparation prior to Caesarean section found that such interventions resulted in a 40% reduction in suspected or confirmed infection, and a 64% reduction in post-Caesarean endometritis respectively with likely limited impact on AMR.[20,180] In LMIC, implementing these as part of a series of interventions to reduce maternal and neonatal sepsis would be required in order to be effective.[181]

Immunomodulators

In addition to antibiotics, research to find new methods to enhance either the acute response to infection or the recovery phase during sepsis are potentially important areas for future work. Poor acute immune responses have been associated with an increased risk of developing secondary infections, whilst excessive inflammatory responses are associated with an increased risk of developing downstream complications from sepsis such as cardiovascular collapse.[182,183]

Steroid immune suppression

Respiratory complications during sepsis are likely to benefit most from immunosuppression. Animal study data suggests that this may be particularly relevant in pregnancy. A more recent example of a clinical trial of immunomodulators to modify the host response is the novel Randomised Evaluation of COVID-19 Therapy (RECOVERY Trial) comparing different treatments aimed at altering the host response to SARS-CoV-2 virus (NCT04381936). In patients recruited during the first wave of the pandemic between March and June 2020, dexamethasone treatment significantly lowered 28-day mortality in patients receiving either invasive mechanical ventilation or oxygen alone.[184] Importantly and unlike many other clinical trials, RECOVERY explicitly included pregnant women during recruitment. However, despite showing a clear clinical benefit, far fewer critically ill pregnant women compared to non-pregnant women received steroids (9.3% *vs.* 22.6%).

Immunotherapy agents

The RECOVERY trial collaborative's subsequent work investigating the benefits of Tocilizumab treatment, which is a monoclonal antibody targeted against the interleukin-6 receptor, found that in hospitalized COVID-19 patients with hypoxia and systemic inflammation, Tocilizumab not only improved survival, but it also reduced the likelihood of the composite endpoint of invasive mechanical ventilation or death.[185]

To date, randomized controlled trials conducted using immune-modulators such as Granulocyte-macrophage colony-stimulating factor (GM-CSF) and IgM-enriched immunoglobulin have shown promising results with improved resolution from infection and reduced mortality risk respectively.[186,187] Other potential targets for improved host responses include IFN-γ, IL-7, and IL-15, which have been investigated *ex vivo,* with evidence showing that their use results in improved leucocyte responses.[188–191] Other agents are an IL-1R antagonist (Anakinra), shown to be safe during pregnancy in small studies and used in sepsis in non-pregnant patients (macrophage activating syndrome) to reduce mortality.[192,193] Unfortunately, comparing previous clinical studies to make clear recommendations is difficult due to their heterogeneous study designs with myriad differences including treatment dosing, inclusion and exclusion criteria, supportive treatments, settings, and enlisted study populations. Furthermore, circulating cytokine levels vary during severe sepsis meaning that clinical benefit may only be seen in some patients and suggesting that their use should be reserved for certain situations.[194] Indeed, anti-TNF-α immunotherapy is associated with an overall reduction in mortality and improved survival in patients with high serum levels of IL-6.[195] Observational data from patients taking disease modifying drugs for immune-mediated medical conditions such as rheumatoid arthritis suggest immune suppression may help to prevent unregulated host responses to sepsis.[196]

Clearly in current times with emerging viral pandemics, a significant global incidence of bacterial sepsis, high AMR, and the need for better antibiotic stewardship, novel methods of regulating host responses to infection are an important area of research. A good example is the GBS vaccine, which has thus far been investigated in early clinical trials in pregnancy and shows a great deal of promise.[197] Furthermore, the development of such a vaccine has been identified as a research priority by the WHO.

What is the Evidence for Personalised Approaches to Treat Maternal Infections?

Preterm birth and chorioamnionitis provide an area of clinical research where a personalized approach to the management of infection may reduce the risk of maternal sepsis as well as improve neonatal outcomes. In fact, infection-driven preterm birth is one of the only aetiologies that has a proven direct causal link.

Preterm birth as a model for obstetric infections

It is increasingly perceived that the uterine cavity and amniotic fluid are not sterile, but that they both contain a rich microbiome that is different in each compartment.[198] The uterine microbiome appears synchronous with vaginal bacterial colonies and is affected by age, endometrial inflammation (endometri-

tis), and mode of birth (cesarean section or vaginal birth)[199] whereas the amniotic cavity appears to share its constituent microbiota with the fetus, exposing it to microbes throughout its in-utero development probably by ingestion.[200,201] In almost 60% of cases of PTL is thought to be due to microbial invasion of the amniotic cavity (MIAC). These invading organisms will often include those linked with preterm birth such as *Mycoplasma* and *Ureaplasma* species,[202,203] which are typically not present in mid-trimester pregnancies.[204]

Antibiotics to treat intra-amniotic infection

Professor Sara Kenyon and the ORACLE collaborative group in the early 2000's designed a randomized controlled trial of erythromycin or co-amoxiclav given to pregnant women presenting with PTL and/or preterm ruptured membranes. Importantly, they showed treatment resulted in a significant reduction in maternal infection.[205] Their findings also demonstrated a short-term improvement in neonatal morbidity, but no reduction in perinatal mortality or improvement in the health of the children at age seven.[206–208] However, when administered to the intact membrane group in PTL, treatment with either antibiotic did not improve neonatal outcomes.[209,210]

More recently, in a non-human primate model of preterm birth using an intrauterine injection of *E. coli*, administration of systemic antibiotics 24 h after injecting *E. coli* was significantly effective at eradicating maternal bacteremia. However, treatment did not resolve choriodecidual or amnion tissue inflammation nor preterm birth.[211] These studies suggest that antibiotic prophylaxis, and appropriate treatment of chorioamnionitis can prevent maternal sepsis but they may not improve fetal or neonatal outcomes. So, how can clinical teams rapidly detect bacterial infections and target antibiotic treatments?

New methods to detect pathogens

Whereas traditional microscopy and culture-based methods have often described sterile or culture-negative inflammation in amniotic fluid with preterm birth, new techniques using nucleic acid amplification testing (NAAT) or amplification of prokaryotic 16S subunit ribosomal DNA have proven to be better detection tools, identifying a broad range of organisms as well as those that prove to be more difficult to detect using standard culture-based methods such as *Ureaplasma*.[212]

One of the drawbacks of 16S is the speed of the assay since a reference laboratory is usually required meaning that results can take several days from sample collection. Furthermore, dif-

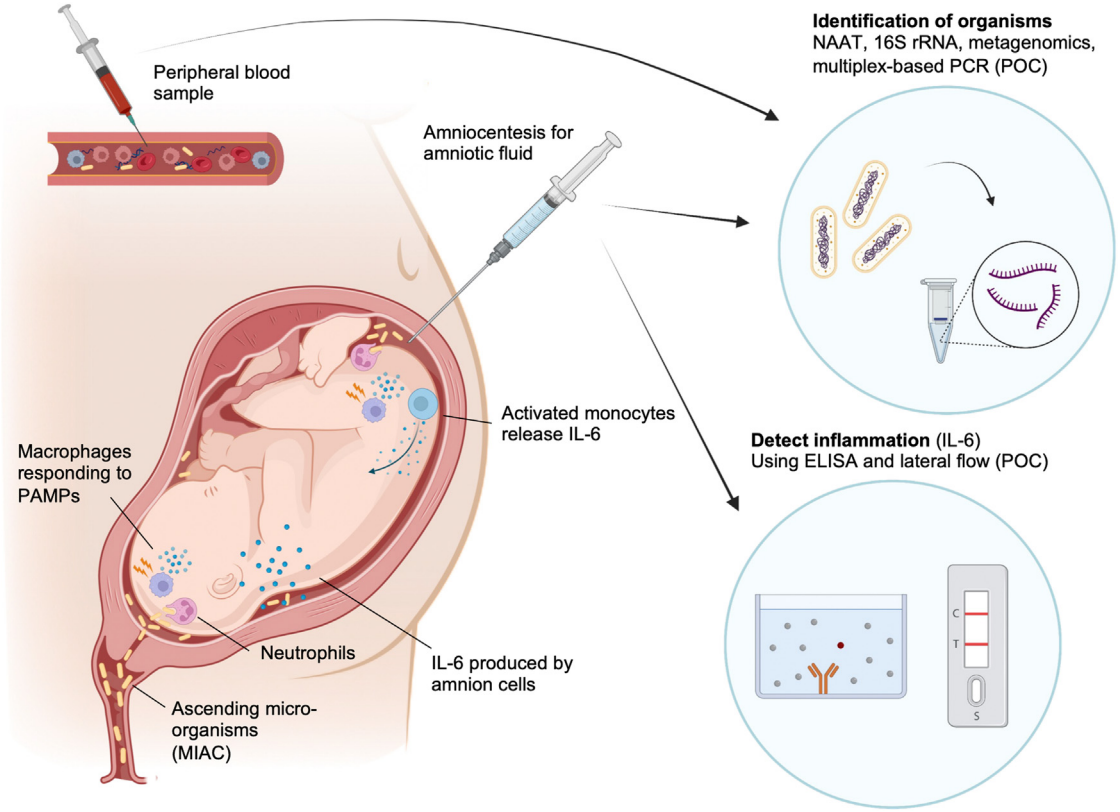

Figure 2. Use of technologies to detect systemic and intra-amniotic infection. Ascending organisms MIAC into the amniotic cavity will be phagocytosed by neutrophils, PAMPs originating from these organisms will activate macrophages causing these cells to release pro-inflammatory cytokines (such as IL-6). IL-6 is also produced by activated monocytes, and amnion cells along with other reproductive/pregnancy tissue as part of an inflammatory immune response. Amniotic fluid can be sampled (by amniocentesis) and used to detect both intra-amniotic infection and inflammation. Systemic infection can be detected from peripheral blood. Traditional NAAT methods can be relatively rapid and are highly sensitive but lack the isolation of AMR. 16S rRNA methods are an alternative, metagenomics gives better coverage, and new methods such as multiplex PCR are rapid and suitable as a POC. Inflammation can be measured by ELISA, rapid chemiluminescent immunoassay and by a lateral flow POC.
AMR: Antimicrobial resistance; ELISA: Enzyme linked immunosorbent assay; IL-6: Interleukin-6; MIAC: Microbial invasion of the amniotic cavity; NAAT: Nucleic acid amplification test; PAMPs: Pathogen associated molecular patterns; PCR: Polymerase chain reaction; POC: Point-of-care test; rRNA: ribosomal RNA.

ferentiating between commensals and colonizing organisms can be difficult. By comparison, culture and sensitivities may take 48 h or more but provide more clinically useful information. New techniques that can identify organisms quickly, and those that also sequence any AMR genes have begun to emerge, which provide a more comprehensive output for clinical application. For example, in the context of labor and birth, NAAT of GBS provides rapid diagnosis with good sensitivity and specificity (91% and 98% respectively) to enable more accurate management of laboring mothers.[213] Methods such as nanopore metagenomic sequencing can genotype without the need for amplification or labeling. Proof of concept studies have demonstrated the feasibility of nanopore technology in respiratory and blood samples with good concordance with traditional culture and sensitivity, thus providing clinical teams the ability to identify organisms, and resistance patterns and rapidly direct appropriate anti-microbial treatments.[214,215]

Improving the precision of identifying clinically relevant infections

However, with early detection at presentation and prior to pregnant women developing overt clinical signs of severe infection, can this technology be further refined to establish a likelihood of severity? Here, cytokine profiling of reservoirs of organisms such as the amniotic cavity may be helpful. Combs et al.[202] investigated amniotic fluid infection in women with spontaneous PTL with intact fetal membranes using amniocentesis alongside standard culture and 16S rDNA methods. They correlated the most prevalent organisms in amniotic fluid with elevated levels of IL-6 and labeled these as infective pathogens. Concentrations of IL-6 in the fluid were combined with the intra-amniotic micro-organisms identified, to create a multivariate regression model for predictors of latency to birth, composite perinatal morbidity, and mortality rates, adjusted for gestational age. Their results showed that IL-6 was a better predictor of poor outcomes than the microbial species alone, which was in keeping with previous reports.[216,217]

Equally, the Premature Rupture Membranes and threatened PTL - a Personalised Approach (PROMPT) will investigate the clinical benefits of rDNA methods using a multiplex-based PCR system to detect bacteria and cytokine profiling of amniotic fluid with the aim of improving latency to birth as well as maternal infection rates in women with ruptured membranes and PTL (Figure 2).[218] Indeed, the use of omics, whereby molecule groups can be assessed from the same biological sample, may provide a comprehensive look at the pathophysiology of the process in question such as with sepsis.[219]

Conclusions

The key strategies discussed in this manuscript are summarised in Figure 3. Maternal sepsis remains a global threat to safe pregnancy, childbirth, and maternal and neonatal outcomes. In the UK, sepsis rates have steadily been falling and emerging research such as the ANODE study and Cochrane review on pre-Caesarean section vaginal preparation will reduce these rates further. Despite this, sepsis remains an important cause of maternal morbidity and mortality in the UK. Initiatives such as the global maternal sepsis study (GLOSS) and NeoAMR,

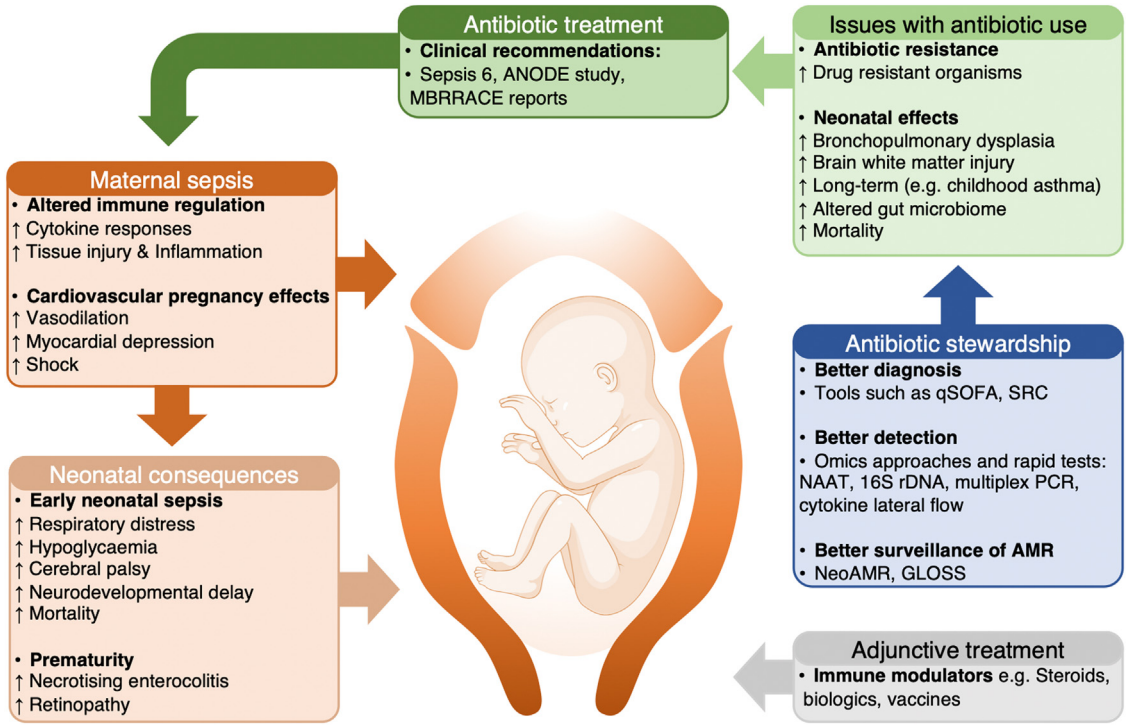

Figure 3. Key strategies for the management of sepsis in pregnancy. This flowchart summaries the maternal neonatal complications, the importance of prompt antibiotic use but the potential issues with the current usage, how antibiotic stewardship can be achieved and the potential for adjunctive treatments.
AMR: Antimicrobial resistance; ANODE: Prophylactic antibiotics in the prevention of infection after operative vaginal delivery; GLOSS: Global maternal sepsis study; MBRRACE: Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries; NAAT: Nucleic acid amplification test; PCR: Polymerase chain reaction; qSOFA: quick Sequential organ failure assessment; rDNA: ribosomal DNA; SRC: Sepsis risk calculator.

will help to provide a framework for reporting maternal infections as well as reflecting the burden of neonatal unit-level AMR worldwide. This will guide the development of core practices for managing maternal and neonatal infections. Early and appropriate detection of both maternal and neonatal infections is key and tools such as qSOFA and SRC have the potential to influence antibiotic stewardship and thus clinical care in the acute setting. However, further research is required on their use. Adjunctive immunotherapy is another potential avenue for research in sepsis whereby the host response can be altered to fit the patient's needs in terms of both clinical deterioration and immune response. This introduces the concept of personalized medicine where combinations of antibiotics and immunotherapy agents are used together to improve the clinical outcome. Individualized risk stratification rather than the use of population-based scores and protocols will help to achieve this. There is still some way to go before this is a clinically viable option but research to date has yielded promising results. It remains critical in the current climate where patients often face multi-organism infection and widespread antibiotic drug resistance, to investigate novel methods to diagnose and manage sepsis.

Author Contributions

Nishel M Shah was responsible for the conception of the article topic, undertook the primary literature search, reviewed, and summarised current evidence, was responsible for writing the initial and revised drafts based on comments and suggestions from co-authors and submitted the final version. **Esmita Charani, Damien Ming and Fook-Choe Cheah** all reviewed each draft with critical revision of intellectual content, reviewed the current literature and incorporated this into the article. **Mark R Johnson** was involved in the conception of the article topic, critically revised the intellectual content, and advised on the structure of the article, content, and current areas of debate. All authors read and approved the final version.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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