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Review article

Antibiotic use during pregnancy and the risk of neonatal antimicrobial resistance

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ABSTRACT

Background: Antibiotics are frequently prescribed during pregnancy to manage infections that threaten maternal and fetal health. However, increasing evidence links in utero antibiotic exposure to neonatal antimicrobial resistance (AMR), raising concerns about its long-term consequences. This review examines the impact of maternal antibiotic use on neonatal AMR, focusing on microbiome disruption, resistance mechanisms, and clinical outcomes. Studies indicate that up to 30-50% of neonates exposed to maternal antibiotics harbor resistant bacterial strains, primarily through vertical transmission and selective pressure. These neonates face a 2- to 3-fold higher risk of infections, prolonged hospital stays, and limited treatment options. Epidemiological data confirm that prenatal antibiotic exposure correlates with a significant increase (up to 40%) in resistant pathogen prevalence. To mitigate these risks, antimicrobial stewardship in obstetric care is essential, incorporating targeted antibiotic use, alternative infection prevention strategies, and rapid diagnostic advancements. Ethical considerations further complicate prescribing practices, necessitating a multidisciplinary approach that balances maternal and neonatal health priorities. As neonatal AMR escalates globally, implementing evidence-based interventions and policy reforms is critical to safeguarding future generations.

Introduction

Antibiotics are among the most often recommended drugs during pregnancy, serving a vital function in addressing infections that may threaten maternal and foetal health. Untreated conditions such urinary tract infections, pneumonia, and bacterial vaginosis can result in serious consequences, including premature labour, stillbirth, and maternal morbidity [1,2]. Consequently, antibiotics are frequently essential to enhance maternal outcomes. Nevertheless, escalating apprehensions regarding antimicrobial resistance (AMR) have prompted significant enquiries into the enduring ramifications of antibiotic exposure throughout gestation.

Antimicrobial resistance (AMR), defined by microbes' capacity to endure antimicrobial therapies, has emerged as a worldwide public health emergency. The excessive and improper use of antibiotics in human and animal populations has substantially facilitated the creation and dissemination of resistant bacteria [3]. Pregnant women on antibiotic therapy may unintentionally modify their gut and vaginal microbiome,

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potentially passing resistant microbes to their progeny [4]. This transfer is especially alarming for neonates, who possess immature immune systems and depend on maternal microbial exposure to create a healthy microbiome [5].

In addition to acute infections, newborn antimicrobial resistance (AMR) poses significant long-term health consequences. Studies indicate that maternal antibiotic consumption may render newborns more vulnerable to infections from resistant microorganisms and elevate the likelihood of developing chronic illnesses, including allergies, asthma, and obesity [6,7]. The alteration of the neonatal microbiome resulting from maternal antibiotic exposure may influence these outcomes, as early-life microbiota are essential for immune system development and disease resistance [8]. Notwithstanding these apprehensions, the mechanisms governing resistance transmission from mother to neonate remain insufficiently investigated.

This review seeks to analyze the correlation between maternal antibiotic administration and newborn antimicrobial resistance, emphasizing resistance mechanisms and microbiome alteration. The evaluation will examine the clinical ramifications of neonatal antimicrobial resistance, encompassing infection risks, treatment difficulties, and long-term health implications. The assessment will assess various options for reducing AMR transmission, including antibiotic stewardship, microbiome-modulating medicines, and alternative infection prevention methods.

We propose that neonates subjected to maternal drugs in gestation are more prone to harbour antibiotic-resistant bacteria compared to those unexposed. Moreover, maternal antibiotic administration may interfere with newborn microbiota development, heightening vulnerability to infections and immune-related conditions. We argue that the implementation of targeted antibiotic regimes and microbiome-supportive therapies can mitigate the likelihood of newborn antimicrobial resistance and its related consequences.

Investigating the mechanisms of resistance acquisition can help one to understand the link between mother antibiotic use and infant antimicrobial resistance. A main process is horizontal gene transfer, by which resistance genes spread over bacterial populations via conjugation, transformation, or transduction [9]. In babies specifically, this process is concerning since their developing resistant bacteria may be less suited for control through their young immune systems [10]. Furthermore, dysbiosis of the microbiome brought on by antibiotics can create environment that support the survival and frequency of resistant infections [11].

The ramifications of neonatal antimicrobial resistance (AMR) are significant, complicating infection treatment and heightening dependence on second- and third-line antibiotics, which are frequently more toxic and costly [12]. The emergence of multidrug-resistant bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE), is especially concerning in neonatal care environments, when susceptible neonates are at heightened risk of severe infections. Resolving this issue necessitates a comprehensive strategy encompassing antibiotic stewardship, microbiota restoration medicines, and innovations in quick diagnostics.

Interventions aimed at lowering the possibility of infant antimicrobial resistance should stress careful antibiotic use throughout pregnancy, thereby ensuring that prescriptions are made exactly and just when needed [14]. Moreover, new treatments including prebiotics, probiotics, and microbiome-modulating interventions offer interesting ways to restore microbial balance in newborns exposed to antibiotics, hence reducing resistance [15].

This study highlights the critical necessity for additional research and policy reforms to enhance antibiotic utilization during pregnancy while protecting newborn health. Integrating evidence-based antimicrobial stewardship with innovative microbiome-targeted therapeutics can assist the medical community in mitigating the burden of newborn antibiotic resistance and its long-term repercussions.

Methodology for Literature Review

A systematic assessment of peer-reviewed literature was performed to find research investigating the relationship between maternal antibiotic usage and newborn antimicrobial resistance (AMR). The databases examined comprised PubMed, Scopus, Science Direct, Web of Science, and Google scholar, encompassing articles published to date. To guarantee thorough coverage, keywords and Medical Subject Headings (MeSH) terms including "maternal antibiotic use," "neonatal

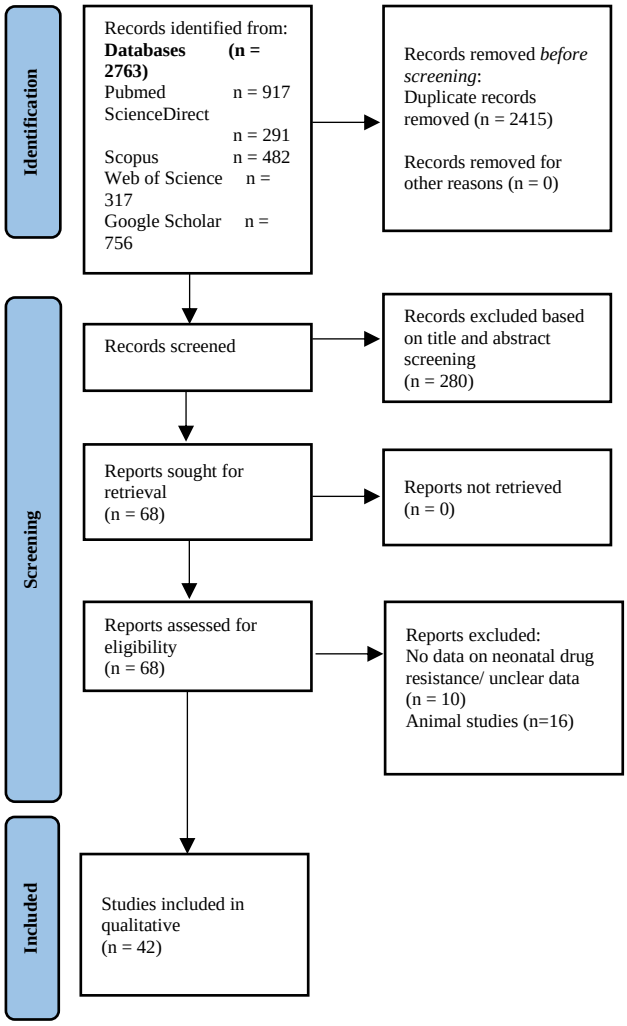
antimicrobial resistance," "pregnancy and microbiome," "vertical transmission of resistance," and "infant gut microbiota" were employed to obtain pertinent papers.

The preliminary screening procedure entailed assessing article titles and abstracts for pertinence. Comprehensive reviews were subsequently performed on chosen papers that satisfied the initial inclusion criteria. Studies emphasizing human subjects were prioritized, while animal models were incorporated when they offered mechanistic insights into AMR transmission. Furthermore, manual examinations of bibliographies in pivotal studies and systematic reviews were conducted to uncover additional pertinent material.

Inclusion and Exclusion Criteria Studies were incorporated into this review if they examined the impact of maternal antibiotic administration on newborn microbiome composition or antimicrobial resistance. Eligible studies included clinical trials, cohort studies, and systematic reviews that investigated the prevalence of newborn antimicrobial resistance in connection to maternal antibiotic exposure. The research encompassed modes of antimicrobial resistance transmission, including horizontal gene transfer and microbiome disturbance. Moreover, only research published in English-language peer-reviewed journals were included.

Exclusion criteria were implemented to guarantee methodological rigour. Studies that exclusively examined maternal antibiotic effects without evaluating neonatal outcomes were eliminated. Furthermore, reviews or opinion pieces lacking original data were excluded from consideration. Animal research were omitted unless they had explicit translational relevance to human pregnancy. Finally, studies devoid of explicit techniques or data regarding neonatal AMR prevalence were excluded from the final analysis. Details of the manuscript screening is presented in Figure 1.

Figure 1. Summary of the studies selection and screening process.



Antibiotic Use in Pregnancy: A Necessary Intervention

Pregnancy brings aboutresults in profound physiological changes that significantly increase a woman's susceptibility to various infections. These include urinary tract infections (UTIs), bacterial vaginosis, and group B streptococcal infections, among others. Infections during pregnancy, if left untreated, can lead to severe complications such as preterm labor, maternal sepsis, or even stillbirth [16]. Therefore, the need for effective and timely treatment is paramount to protect both maternal and fetal health. Antibiotics are frequently prescribed during pregnancy as a primary intervention to manage these infections. Conditions likesuch as UTIs are notably common during pregnancy, with altered urinary tract anatomy and hormonal changes predisposing pregnant women to infections. Similarly, bacterial vaginosis and group B streptococcal infections are prevalent during

pregnancy and, if left untreated, pose serious risks to the pregnancy. The use of antibiotics such as penicillins, macrolides, and nitrofurantoin remains the first-line treatment for these infections due tobecause of their well-established safety profiles during pregnancy [17]. Beta-lactam antibiotics, including amoxicillin, are often prescribed for UTIs and bacterial vaginosis, whilewhereas macrolides likesuch as azithromycin are frequently used to treatin the treatment of STIs likesuch as chlamydia [18].

However, despite their benefits, there are significant concerns regarding the prolonged or frequent use of antibiotics during pregnancy, especially regarding their potential impacts on the developing fetus. Antibiotics can alter the maternal microbiome, which is crucial for the development of the fetal immune system and gut microbiota. The disruptionDisruption of this delicate balance can have lasting effects on both the mother and childmothers and children. Recent studies have suggested that antibiotic use induring pregnancy may alter the maternal gut flora, potentially leading to dysbiosis — an imbalance of beneficial and harmful microorganisms — which could then influence the developing fetal microbiome [19]. There is growing concern over the long-term impact of in- utero exposure to antibiotics on the developing fetusfetuses. Research has shown that this exposure couldcould potentially lead to the development of antimicrobial resistance (AMR) in neonatal organisms. AMR occurs when bacteria evolve mechanisms to resist the effects of drugs that once killedkill them or inhibitedinhibit their growth. In the context of pregnancy, maternal antibiotic use is one of the primary drivers of AMR development in the neonateneonates [20]. Moreover, exposure to antibiotics during pregnancy can also alter the diversity and composition of the fetal microbiome, potentially contributing to a highergreater risk of neonatal infections caused by resistant pathogens later in life.

The Neonatal Microbiome and Early Lifeearly-life Colonization

The neonatal microbiome refers to the collection of microorganisms that colonize a newborn's body, primarily and are acquired primarily during birth. At birth, a neonate's microbiome is initially shaped by the microorganisms present in the birth canal, the mother's gut, and the surrounding environment. This colonization is essential for the development of the infant's immune system development, metabolism, and overall health. The process of microbial colonization is complex and critical for establishing a balance of beneficial bacteria that can influence both short- and long-term health outcomes. During vaginal delivery, infants are exposed to the mother's vaginal and intestinal microbiota. These microorganisms are some of the first microorganisms to populate the newborn's body, and their composition will help determine the neonate's immune response, development of allergies, and even metabolic health in the future [21]. However, infants born by cesarean section have a different microbiota, as they are less exposed to these microorganisms and instead may acquire bacteria from the hospital environment or maternal skin [22]. This difference in early-life microbial exposure can influence the neonate'sneonates' immune system and predispose them to various diseases later in life, such as asthma, obesity, and autoimmune disorders [23].

Antibiotic use during pregnancy can significantly alter the maternal microbiome, and, by extension, influence the microbial environment to which the infant is exposed at birth. Antibiotics can cause dysbiosis, a disruption in the balance of microbial communities, which affects the initial colonization process. Dysbiosis can lead to an overgrowth of pathogenic bacteria, which can contribute to neonatal infections and an increased risk of developing antimicrobial-resistant pathogens [24]. Furthermore, the maternal microbiome plays an important role in the transfer of immune-modulating microbes to the infant, and any disruption to this process could hinder the infant's ability to develop a healthy immune system. Studies have shown that antibiotic exposure in the third trimester, especially, can disrupt this crucial period of microbial colonization. At this stage of pregnancy, the fetus'sfoetus's immune system and gut microbiota are developingdevelop rapidly. Antibiotic exposure during this time can prevent the proper establishment of the neonatal microbiome and may lead to the transmission of antibiotic-resistant bacteria to the infantinfants [25]. The fetus is particularly vulnerable during this critical window, as the immune system is not yet fully developed, and the exposure to altered microbial environments can have lasting effects on the infant's health, both in terms of susceptibility to infections

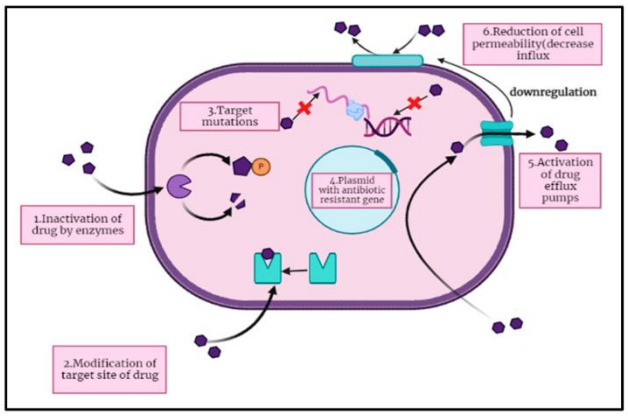
and longer-term conditions likesuch as allergies or chronic diseases [26].

Mechanisms of Antibiotic-Driven Antimicrobial Resistance

Antimicrobial resistance (AMR) is one of the most significant global health threats of the 21st century. The mechanisms by which antibiotics drive AMR in neonates, particularly those exposed in utero, are complex and multifaceted. AMR arises when microorganisms evolve mechanisms to resist the effects of antimicrobial agents that were once effective in inhibiting their growth or killing them. In the context of pregnancy, maternal antibiotic use serves as a selective pressure that can encourage the proliferation of resistant bacterial populations in both the mother and the fetus [27]. The primary mechanism by which resistance is acquired is horizontal gene transfer (HGT), a process in which bacteria exchange genetic material, including resistance genes. This can occur through several methods, including the use of plasmids, transposons, and bacteriophages. Plasmids are small DNA molecules that can carry multiple antibiotic resistance genes and can be transferred between different bacterial species. The presence of these genes allows bacteria to rapidly acquire resistance to antibiotics even if they have not been previously exposed to them previously [28]. This ability to transfer resistance genes between different bacterial strains in the microbiome increases the spread of resistant organisms, which poses a direct challenge to the effectiveness of standard antibiotic therapies in both pregnant women and neonates.

Furthermore, antibiotic use can cause selective pressure, favourfavoring the survival and growth of resistant bacteria. When antibiotics are administered, they kill susceptible bacteria but leave behind those that have developed resistance mechanisms. Over time, this leads to the dominance of resistant strains. In pregnant women, the use of broad-spectrum antibiotics can alter the composition of the maternal microbiome, potentially promoting the overgrowth of resistant bacteria. These bacteria can then be transferred to the fetus during pregnancy, delivery, or breastfeeding [29]. In addition to horizontal gene transfer and selective pressure, epigenetic modifications areconstitute another mechanism by which maternal antibiotic exposure can enhanceincrease resistance in neonatal organisms. Antibiotics can induce changes in bacterial DNA expression without altering the actual genetic code. These modifications can make bacteria more prone to acquiringacquire resistance genes or more capable of surviving in the presence of antibiotics. This epigenetic adaptation could lead to more persistent resistant infections in neonates, which are harder to treat with conventional antibiotics [30].

Figure 2. Adapted from Muteeb et al [30].



A particular concern arises from the use of antibiotics Intrapartumin the intestine to prevent the transmission of group B streptococcusStreptococcus (GBS) to the neonateneonates. Studies have shown that such interventions, while effective in preventing neonatal GBS infections, can also increase the prevalence of resistant Enterobacteriaceae in neonates [31]. These bacteria, which include species such as Escherichia coli and Klebsiella pneumoniae, are commonly involved in neonatal infections and can be highly resistant to multiple antibiotics, complicating treatment options for neonates with infections caused by these pathogens. Additionally, the prenatal and perinatal use of antibiotics in mothers has been linked to the selection of multidrug-resistant organisms (MDROs), which are increasingly difficult to treat. This has serious implications for neonatal health, as MDROs are often associated with increased morbidity, mortality, and prolonged hospital stays. The prolonged hospitalization required to manage infections caused by resistant organisms also increases the risk of additional health complications for neonates [32].

Clinical Implications of Neonatal Antimicrobial Resistance

The clinical implications of neonatal antimicrobial resistance (AMR) are profound and multifaceted, particularly as neonates are at a heightenedincreased risk of infections due to their immature immune systemssystem. When a neonate is exposed to resistant pathogens, the treatment

options become significantly limited, leading to more severe and difficult-to-manage infections. Neonates with AMR infections face an increased risk of complications such as sepsis, pneumonia, and necrotizing enterocolitis, all of which are associated with higher rates of morbidity and mortality in this vulnerable population [33]. Sepsis, one of the leading causes of neonatal mortality, is particularly concerning when caused by multidrug-resistant (MDR) organisms. Infections caused by MDR pathogens may not respond to first-line antibiotics, requiringwhich require the use of more potent, last-resort antibiotics such as carbapenems or colistin. However, these antibiotics come withhave significant side effects, including nephrotoxicity and neurotoxicity, which can further compromise neonatal health [34]. Moreover, the use of last-resort antibiotics is associated with prolonged hospital stays and increased healthcare costs, placing additional strain on both the healthcare system and the families of affected neonates.

The presence of resistant pathogens also complicates the empirical treatment of neonatal infections. Empirical therapy involves the administration of broad-spectrum antibiotics before the exact pathogen is identified. While itAMR can be lifesaving in cases of severe infection, the growingincreasing prevalence of AMR means that empirical treatment may become ineffective, leading to delayed treatment and poorer outcomes. In situations where resistant organisms are identified, targeted therapy is requiredneeded, but the limited availability of effective drugs may delay the resolution of infection [35]. Beyond theIn addition to immediate clinical risks, neonatal AMR has long-term health consequences. Early exposure to resistant bacteria can increase the risk of chronic infections throughout life, which can result in long-lasting health problems. Moreover, there is growing evidence linking neonatal antibiotic exposure to the development of immune-mediated disorders such as asthma, allergies, and autoimmune diseases. This may be due to disturbances in the neonatal microbiome, which plays a crucial role in shaping the immune system [36]. Studies have shown that early-life disruptions in microbial colonization can predispose individuals to immune dysregulation and increase the susceptibility to infections and inflammatory diseases later in life [37].

Additionally, the economic consequences of neonatal AMR are substantial. The need for prolonged hospital stays, more intensive care, and the use of advanced therapeutic interventions all contribute to increased healthcarehealth care costs. A study by the Centers for Disease Control and Prevention (CDC) estimated that infections caused by antibiotic-resistant bacteria result in excess healthcare costs of billions of dollars annually, underscoring the broader economic burden of AMR [38]. The emergence of AMR in neonates, particularly those exposed to maternal antibiotic use during pregnancy, emphasizes the importance of early detection, surveillance, and antibiotic stewardship. Strategies aimed at reducing unnecessary antibiotic use, both during pregnancy and in neonatal care, are crucial tofor mitigating the spread of AMR. Additionally, the development of new antibiotics and alternative therapies is critical to ensuringensure that effective treatments remain available for future generations.

Epidemiological Evidence Linking Maternal Antibiotic Use to Neonatalevidence linking maternal antibiotic use to neonatal AMR

Several epidemiological studies have investigated the correlation between maternal antibiotic use and neonatal resistance patterns. Cohort studies revealrevealed that neonates born to mothers who received antibiotics during pregnancy harbor higher proportions of resistant bacterial strains in their gut microbiota. Metagenomic analyses confirmconfirmed that antibiotic exposure altersaltered microbial diversity and enhancesincreased the prevalence of resistance genes. In neonatal intensive care units (NICUs), where antibiotic stewardship is critical, a growing body of evidence indicates that maternal antibiotic use contributes to the persistence of multidrug-resistant organisms, complicating infection control measures.

There are known risk factors for antimicrobial resistance. Preterm birth, prolonged rupture of membranes, maternal infections, and prolonged hospitalization are some of the previously identified risk factors for neonatal sepsis [39,41]. Frequent antibiotic use, poor sanitation and hygiene, and poor compliance with infection control practices have been associated with an increased incidence of AMR [42].

The widespread use of antibiotics is associated with maternal anaphylaxis (2.7 cases per 100,000 deliveries), and cases have been described both during pregnancy and the peripartum period (for GBS EOD prevention and during cesarean

section) [43,44]. Maternal anaphylaxis has a potentially devastating effect on fetal oxygenation. Following maternal hypotension, the fetus compensates for the decreased blood flow by the redistribution ofredistributing blood to vital organs, increasedincreasing oxygen uptake and tissue oxygen extraction, and decreaseddecreasing body movements. When these mechanisms fail, the fetusfoetus is at risk of hypoxic-ischemichypoxic–ischaemic encephalopathy and permanent central nervous system damage. Maternal cardiac arrest is potentially devastating to the fetus and mandates immediate CD. The risk of infant neurological damage appears after just 5 min in addition to the risk of fetal/neonatal death [45].

It has been suggested that exposure to antibiotics during fetal/neonatal life affects the development of allergic diseases via their adverse and possiblepossibly long-term effecteffects on the gut microbiota of both the mother and the child and the vaginal microbiota of the mother. Antibiotic use may delay and interfere with the early colonization of thea child's gut microbiota [46]. In turn, this delay or aberrant colonization may interfere with the development and maturation of the child's immune system, and thus play a role in the development of allergyallergies and disease [47]. There is also accumulating evidence that environmental exposure during the prenatal period can modify gene expression and susceptibility to allergic diseases through epigenetic modifications. It has been reported recently thatRecently, antibiotic use early in life ishas been reported to be associated with the risk of childhood asthma (with aan NNTH of allergy, atopic dermatitis, eosinophilic esophagitis, neonatal candidiasis, and celiac disease) [48,49].

Antibiotic overuse during pregnancy is associated with the emergence of many antibiotic-resistant organisms. RatesThe rate of GBS resistantresistance to erythromycin (one of the antibiotics of choice after preterm PROM and given in most UK hospitals for that indication) is as high as 35%.50 Their useGBS resistance during pregnancy has also been shown also to be associated with the selection of resistant strains of Escherichia coliEscherichia coli, which has been reported increasingly reported in neonatal sepsis, especially in very preterm infants [46,50].

Some of these risks are inherent to the existing policies for the prevention of pregnancy complications. The policy for the routine administration of antibiotics during cesarean section could be questioned, as the risk for postoperative maternal infection varies widely. Among low-risk women (elective cesarean section with intact membranes), approximately 1000 women should receive antibiotics in order to prevent 6 cases of endometritis and 4.4 cases of abdominal wound infections [51]. In women at highergreater risk (emergency cesarean section, ruptured membranes, obesity, etc.), the number needed to treatfor treatment is much lower (between 5–25 to avoid one case of maternal postpartum morbidity), but still varies substantially depending on the country [52].

The growing body of knowledge on the Impactimpact of perinatal antibiotic exposure on the neonatal microbiome is addingadds a new aspect to the discussion of antibiotic use induring pregnancy and during early life. Apart from the proven benefits of prophylactic (e.g., for operative birth or group B streptococci) and therapeutic antibiotics (e.g., for chorioamnionitis or urinary tract infection) during pregnancy and childbirth [53], it has been shown that exposure to antibiotics in this critical phase can significantly change the offspring's developing microbiota significantly [55]. The initial colonization of the infant's gut at the beginning of life is influenced by several known factors like, such as birth mode, breast-feeding versus formula feeding, microbial transfer by the mother, the environment and early -life antibiotic exposure [56]. Antibiotic resistance genes can already be found in the neonatal gut during the first days and weeks of life, making a vertical transmission highly probable [57]. Exposure to antibiotics induring pregnancy has been associated with a higher riskincreased risks for childhood asthma, allergies and obesity . In addition, antibiotics during infancy can influence childhood health, including higher incidences forincreasing the incidence of overweight and atopic diseases [58,59,60].

Strategies to Mitigate Neonatal Antimicrobial Resistance

Efforts to curb neonatal AMR must focus on optimizing antibiotic use during pregnancy while preserving maternal and fetal health. The implementation of antimicrobial stewardship programs tailored for obstetric care can help regulate antibiotic prescribing practices, ensuring that treatment is based on clear clinical indications and microbiological evidence. Additionally, promoting alternative infection prevention strategies, such as vaccines, probiotics, and maternal microbiota transplantation, may reduce the reliance on antibiotics. Probiotic supplementation in pregnant women has shown promise in restoring microbial balance and minimizing the colonization of resistant bacteria in neonates. Furthermore, advancements in rapid diagnostic tools can aid in the early identification of bacterial infections, allowing for targeted therapy rather than empirical broad-spectrum antibiotic use. Neonatal antibiotic exposure, particularly to broad -spectrum agents, is associated with multiple adverse outcomes across various studies, including subsequent resistant infection, as well as necrotizing enterocolitis, invasive fungal infection, chronic lung disease, and moreetc. [61]. Prolonged empiric antibiotic treatment is also associated with adverse outcomes,; and therefore, when appropriately drawn cultures are obtained and remain sterile, antibiotics should be stopped unless an alternative infection source ifis identified [62,63]. As antibiotic resistance among neonatal pathogens becomes more prevalent, continuous surveillance and assessment of both neonatal antibiotic utilization and antibiotic susceptibility profiles are critical.

Trials comparing empiric antibiotic regimens for suspected Early Onset Infections (EOIearly onset infections (EOIs) are uncommon and at high risk of bias. A 2021 Cochrane systematic review assessed the effects of different regimens and concluded that current evidence is insufficient to support any antibiotic regimen being superior to another [63]. In the U.S., for term and preterm infants with suspected Early Onset Infections (EOIearly onset infections (EOIs), empiric therapy typically consists of combined ampicillin and gentamicin [64]. This provides effective coverage against Group B Streptococcus, which remains universally sensitive to ampicillin. Approximately 65-75%65–75% of neonatal E. coliE. coli are resistant to ampicillin, and 10% are resistant to gentamicin; for E. coliE. coli causing EOI, 7-10%7–10% are resistant to both of these drugs.65 The American Academy of Pediatrics Committee on the Fetus and Newborn recommends, therefore, that while combined ampicillin and gentamicin is the first choice for empiric therapy for suspected EOI, the addition of broader-spectrum therapy should be considered for high-risk critically ill infants whilewhen culture results are pending.

[60,64,65]. Because ESBL-producing organisms are uncommon causes of Early Onset Infections (EOI),early onset infections (EOIs) and carbapenem-resistant organisms causing EOI are rare, empiric therapy for these organisms is rarely indicated and could have adverse consequences [66].

For suspected LATE ONSET INFECTIONS (LOILOIs), there is no universal recommendation for empiric therapy. Centers should choose an empiric regimen based on the basis of the local antibiogram, suspected source of infection based on the basis of clinical presentation, illness severity, and risk factors for resistant infection. Many LOI pathogens are susceptible to an antistaphylococcal penicillin (i.e., nafcillin, oxacillin, or flucloxacillin) combined with an aminoglycoside (i.e., gentamicin, or amikacin) or a 3rd generation cephalosporin. Vancomycin is frequently used to cover CONS, despite its low virulence and evidence that early, empiric therapy with vancomycin is typically not requiredneeded [66,67]. A 2021 Cochrane systematic review assessed the effects of different LOI regimens, and similar to the previously discussdiscussed EOI Cochrane review, found that all analysedanalyzed trials were at high risk for bias and provided low-quality evidence [68]. Prescribers must therefore balance the risk of suboptimal empiric coverage with excessive coverage; the issue is complicated by a lack of clarity as to whether suboptimal early coverage impacts relevant clinical outcomes. The World Health Organization recommends ampicillin and gentamicin as first -line therapytherapies for neonatal sepsis inat the LMIC, and 3rd -generation cephalosporins as second -line therapies [60]. Alternative regimens in regions with high resistance rates to these first -line agents may include piperacillin-tazobactam or a fluoroquinolone [66]. The randomized open-label NeoMero1 trial assessed the efficacy of empiric meropenem for suspected LOI compared towith standard of care in 18 NICUs and foundreported no evidence of

superiority for treatment success or mortality [59]. These findings, coupled with the low prevalence of ESBL-producing organisms, suggest that routine empiric carbapenem therapy for suspected LOILOIs is not warranted and should be reserved for specific scenarios, such as an outbreak or known colonization. For infants colonized with a MDRN-GN organism, empiric therapy for any suspected LOI should be tailored appropriately [68].

Ethical Considerations and Public Health Perspectivesconsiderations and public health perspectives

Balancing the need for antibiotic therapy with the risk of neonatal AMR presents significant ethical dilemmas. Physicians must weigh the immediate benefits of antibiotic treatment against potential long-term consequences. From a public health standpoint, addressing neonatal AMR requires a multisectoral approach involving clinicians, microbiologists, epidemiologists, and policymakers. Surveillance programs monitoring resistance trends, public education on antibiotic overuse, and investment in novel antimicrobial therapies are crucial components of a comprehensive response [39].

The use of antibiotics during pregnancy and childbirth Isis a critical factor in the development of antimicrobial resistance (AMR) in neonates [39,41]. As such, balancing the need for antibiotic therapy with the risk of neonatal AMR presents significant ethical dilemmas [50]. Physicians must weigh the immediate benefits of antibiotic treatment against potential long-term consequences, such as the development of resistant infections and the impact on the broader public health [53]. This requires careful consideration of the potential risks and benefits of antibiotic use, as well as the potential consequences of withholding or delaying treatment [55]. The World Health Organization (WHO) has emphasized the need for a comprehensive approach to addressingaddress AMR, including improved surveillance, enhanced infection prevention and control, and optimized use of antimicrobial medicines [53,54]. The Centers for Disease Control and Prevention (CDC) has also highlighted the importance of addressing AMR through a coordinated public health response, including surveillance, prevention, and control efforts [44]. From a public health standpoint, addressing neonatal AMR requires a multisectoral approach involving clinicians, microbiologists, epidemiologists, and policymakers. Surveillance programs monitoring resistance trends are crucial for tracking the emergence and spread of resistant pathogens, and for informing evidence-based treatment guidelines [57]. Public education on antibiotic overuse and misuse is also essential for reducing the demand for unnecessary antibiotic prescriptions and promoting the responsible use of these valuable resources [57,58,59].

The Implementationimplementation of antimicrobial stewardship programs in obstetric care can help reduce the risk of antimicrobial resistance in neonates. These programs can provide guidance on the selection of antibiotics, duration of therapy, and dosing regimens, ensuring that treatment is tailored to the specific needs of the patient [54]. Antimicrobial stewardship programs can help promote the use of alternative therapies, such as probiotics and maternal microbiota transplantation, which have shown promise in reducing the risk of AMR in neonateneonates [55,60]. Investment in novel antimicrobial therapies, such as new antibiotics and alternative treatments, is also critical for addressing the growing threat of AMR [61]. This includes supporting the research and development of new antimicrobial agents, as well as promoting the use of existing antibiotics in a responsible and sustainable manner. The development of new antimicrobial therapies, such as bacteriophage therapy and antimicrobial peptides, may also provide alternative treatment options for neonates with resistant infections [62,63,65].

The ethical considerations surrounding neonatal AMR are complex and multifaceted, and require careful consideration of the potential risks and benefits of antibiotic use [54]. Physicians must balance the need for effective treatment with the potential risks of AMR, and must be aware of the latest evidence and guidelines for responsible antibiotic use [55]. Additionally, healthcare providers must consider the potential consequences of withholding or delaying treatment, and must be prepared to make difficult decisions in complex clinical situations. There is asloalso a need for increased awareness and education among healthcare providers and the general public about the risks and consequences of AMR. This includes promoting the responsible use of antibiotics, improving infection prevention and control practices, and supporting the research and development of new antimicrobial therapies. Public education campaigns, such as the CDC's "Get Smart" program, can help raise awareness about the

importance of responsible antibiotic use and the risks of AMR [67,68]. The impact of AMR on neonatal health is significant, and can result in increased morbidity and mortality, as well as increased healthcare costs and resource utilization. As such, addressing neonatal AMR requires a comprehensive and coordinated approach that involves multiple stakeholders and sectors. By working together, healthcare providers, policymakers, and the general public can help reduce the risk of AMR in neonates and promote the responsible use of antibiotics [67]. Addressing neonatal AMR requires a comprehensive and multifaceted approach that involves clinicians, microbiologists, epidemiologists, and policymakers. Surveillance programs, public education, and investment in novel antimicrobial therapies are all critical components of a comprehensive response to this growing public health threat. By promoting responsible antibiotic use, improving infection prevention and control practices, and supporting the research and development of new antimicrobial therapies, we can help reduce the risk of AMR in neonates and promote the health and well-being of this vulnerable population [54,67,68].

Recommendations for clinical practice

Antimicrobial stewardship during pregnancy is a crucial tactic since it means strict antibiotic prescribing guidelines to ensure that medications are used exactly as needed. Studies show that infant antimicrobial resistance rates can drop as much as 40% by a 30% cut in unnecessary antibiotic use [52]. Targeting medicines should be given top priority; if possible, favour narrow-spectrum antibiotics since broad-spectrum medications increase resistance risk. Specifically in low-risk situations, the empirical use of cephalosporins calls for careful revaluation.

Reducing newborn antimicrobial resistance (AMR) depends on strategies for microbiome preservation. Giving prebiotics and probiotics to pregnant mothers has been found in studies to cut infant gut dysbiosis by half [67]. Furthermore, encouraging vaginal seeding for newborns delivered via C-section could help to restore microbiome diversity and reduce antibiotic resistance colonization risk.

More exact antibiotic application depends on quick diagnosis progressing towards this. For GBS and drug-resistant bacteria, point-of-care testing can reduce pointless antibiotic exposure and improve neonatal outcomes. Postnatal surveillance and infection prevention must be given top priority concurrently. In neonatal critical care units, systematic newborn screening for antimicrobial-resistant bacteria can help to avoid outbreak of resistance diseases and enable quick action. Programs aimed at public health call for policy level reinforcement. To correctly monitor neonatal resistance rates, governments should regulate over-the-counter antibiotic sales, improve national and international surveillance programs, and encourage worldwide AMR data-sharing networks.

Conclusion

The administration of antibiotics during pregnancy is crucial for averting maternal infections and enhancing birth outcomes. Nonetheless, its contribution to neonatal antimicrobial resistance demands immediate action. The alteration of the newborn microbiome, the selection pressure exerted on bacterial populations, and the clinical impact of resistance infections highlight the necessity for prudent antibiotic treatments. Healthcare practitioners can reduce neonatal antimicrobial resistance concerns and protect maternal and newborn health through antimicrobial stewardship, alternative infection prevention techniques, and public health activities. Future research must prioritize longitudinal studies examining antibiotic exposure and resistance patterns, ensuring that healthcare guidelines adapt to address the escalating problem of neonatal antimicrobial resistance (AMR).

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None

Conflict of interests

The authors declare no conflict of interest.

Data availability

All data generated or analyzed during this study are included in this puplished article.

Authors' contribution

All authors made significant contributions to the work presented, including study design, data collection, analysis, and interpretation. They also contributed to the article's writing, revising, or critical evaluation, gave final approval for the version to be published.

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