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# Maternal Exposure to Medications and the Risk of Congenital and Early-Onset Hearing Loss in Children: A Systematic Review and a Meta-Analysis

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**Keywords:** congenital hearing loss | intrauterine drug exposure | pregnancy | reproductive toxicology | systematic review

## ABSTRACT

**Background:** Congenital hearing loss (CHL) affects approximately 1–2 in 1000 children and significantly impacts development. Exposure to medications during pregnancy may impact offspring hearing; however, the ototoxic effects of different drugs have not been systematically investigated.

**Methods:** This systematic review and meta-analysis was conducted following PRISMA guidelines and analysed 21 experimental and observational studies examining 60 drugs across various categories.

**Findings:** Magnesium sulphate and systemic steroids, alone or in combination, showed potential protective effects towards CHL. Specific antibiotics (e.g., gentamicin and metronidazole) and non-steroidal anti-inflammatory drugs were associated with an increased risk of CHL. Modest evidence indicated that low-dose acetylsalicylic acid increased risk, whereas higher doses did not. Other drugs, such as anti-neoplastic agents and valproic acid, showed weaker associations with CHL. Most studies had methodological limitations.

**Conclusion:** Our findings highlight the urgent need for robust research to minimise preventable hearing loss in children.

**Summary**

Hearing loss present at birth or in early childhood can significantly affect a child's development. Some medications taken during pregnancy may potentially influence the risk of hearing loss in infants, but this has not been thoroughly studied. We reviewed 21 studies investigating 60 different drugs to gain a better understanding of their effects. We found that certain medications, such as magnesium sulphate and steroids, might offer protection against hearing loss. Conversely, others, including some antibiotics and anti-inflammatory drugs such as acetylsalicylic acid, may increase the risk. Our findings underscore the need for further research to inform safer medication use during pregnancy and reduce preventable hearing loss in children.

## 1 | Introduction

Congenital hearing loss (CHL) affects 1–2 in 1000 children worldwide [1, 2] and negatively affects language development, academic performance and social and emotional well-being [3]. Several recognised risk factors for CHL in children include hereditary HL, in utero infection with cytomegalovirus (CMV) and prolonged neonatal intensive care [4]. However, the aetiology remains unknown for 25%–40% of affected children [3, 5–7].

The development of the inner ear begins around the fourth gestational week. By the sixth gestational week, formation of the cochlear duct commences; the bony labyrinth is ossified by the 23rd week and fetal hearing commences by approximately 27 weeks gestation. The inner ear, however, remains vulnerable to external stimuli throughout pregnancy and postnatally until the age of 4 years, as several structures of the inner ear, such as hair cells and neurons, continue development [8, 9].

Pregnancy exposure to drugs may contribute to CHL. In adults, several classes of drugs can potentially damage or impair the function of the inner ear, including some classes of antibiotics, loop diuretics, salicylates and antimalarial drugs [10–13]. For example, aminoglycosides are known to generate reactive oxygen species (ROS), leading to apoptosis in cochlear hair cells [14]. Salicylates impact outer hair cell electromotility and cochlear blood flow, causing reversible hearing changes [15, 16]. Loop diuretics impair endolymph production by disrupting ion transport in the stria vascularis of the cochlear duct, leading to a collapse of the endocochlear potential and causing transient, reversible hearing loss [17]. Finally, some antineoplastic agents accumulate in cochlear structures, leading to excessive ROS production and DNA damage in cochlear cells [18]. As most drugs cross the placental barrier [4], specific drugs may affect the development of the fetal inner ear, resulting in CHL. Importantly, the majority of pregnant women are exposed to medications during pregnancy; in 2018, 63.3% of pregnant Danish women redeemed at least one prescription during pregnancy [19] and worldwide prescription drug use during pregnancy ranged from 27% to 93% [20].

There has been no systematic data reviewing the relationship between pregnancy drug exposure and CHL. This knowledge is crucial to reduce preventable causes of HL, allow for early diagnostics and optimise treatment should exposure occur. We aimed to systematically review the literature on the potential association between maternal drug exposure and CHL in children.

## 2 | Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21, 22] and registered at the International Prospective Register of Systematic Reviews (PROSPERO) on 14 February 2023 (registration number CRD42023399514).

### 2.1 | Eligibility Criteria

#### 2.1.1 | Study Designs

Randomised controlled trials (RCTs), cohort studies and case–control studies were included. Reviews, systematic reviews, meta-analyses, editorials, case reports, case series, cross-sectional studies, descriptive studies, poster presentations and conference abstracts were excluded due to risk of bias, inability to establish causality and insufficient data.

#### 2.1.2 | Participants

Studies on pregnant women of all ages were included. Animal studies were excluded.

#### 2.1.3 | Intervention

Studies on the use of all prescribed and over-the-counter drugs, regardless of trimester and indication, were included, as were findings on combinations of drugs. Studies of all recreational drugs, alcohol, caffeine, vitamins/supplements or complementary medicine were excluded.

#### 2.1.4 | Outcome

Studies reporting on sensorineural CHL in children as their primary or secondary outcome were included, defined as mild, moderate and severe hearing impairment diagnosed in early childhood due to damage to inner ear structures or central auditory pathways. Studies on hearing loss of all degrees of severity were included. Studies on children with congenital infections or genetically induced hearing loss were excluded.

#### 2.1.5 | Imprecise Reporting

Studies where intrauterine and postnatal drug exposure in children were reported as combined exposures rather than individually were excluded. Studies reporting hearing loss in conjunction with other outcomes, such as neurodevelopmental outcomes, were also excluded.

#### 2.1.6 | Language

As the first author is proficient in English, Danish, Swedish, Norwegian and Turkish, studies published in these languages were evaluated.

#### 2.1.7 | Full-Text Articles

If only an abstract were available, the study was excluded.

### 2.2 | Information Sources

PROSPERO and Cochrane Database of Systematic Reviews (CDSR) were searched to identify ongoing or recently completed systematic reviews. The systematic literature search was conducted following the PRISMA guidelines [21, 22].

A database search was conducted on Embase, PubMed and Web of Science on 25 January 2023. A second search was conducted on the same databases on 5 September 2024. The search string used in PubMed is shown in Appendix A. A flow diagram of the search and screening process is shown in Figure 1.

### 2.3 | Search Strategy

The specific search strategies were created with assistance from a Health Sciences Librarian with expertise in systematic review searching, with input from the project team. No lower limit for publication dates was applied. Literature search strategies were developed using the medical subject headings (MeSH) and text words related to the subject. The search strings were performed following the PICO strategy [23], using pregnancy (patient), drug exposure (intervention) and HL in children (outcome). Three major medical electronic databases were used: PubMed, Embase and Web of Science. To ensure literature saturation, the reference lists of included studies were scanned. See Appendix A for the search string used in PubMed.

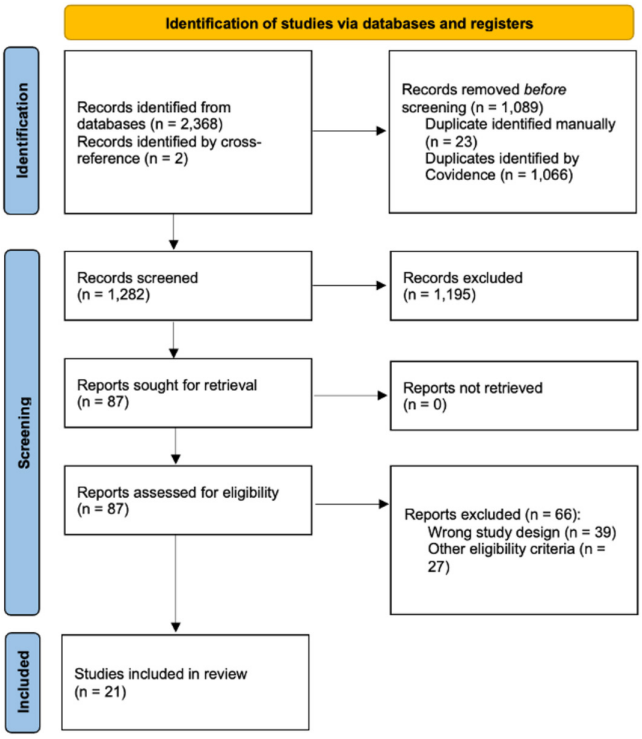


**FIGURE 1** | Flow diagram of the systematic review process.

### 2.4 | Search Results

Search results were imported to the reference program EndNote 20 (Clarivate, London, UK), where duplicates were deleted automatically. The literature was then imported into the online program Covidence (Melbourne, Australia) to check for missed duplicates and to support the screening and selection process.

Two reviewers (A.S.K. and M.Ø.T.) independently screened all titles and abstracts using Covidence. The study was excluded if the title and abstract failed to fulfil the predefined eligibility criteria. If the title and abstract met the predefined eligibility criteria, or if eligibility was uncertain, the article was included for full-text screening. Disagreement between the reviewers was resolved through discussion. Reviewers were not blinded to the journal titles, authors, or institutions. Microsoft Excel was used as the primary data management tool.

### 2.5 | Data Items

Study characteristics (author, publication year, study design, study size, year of conduct, country or continent), patient characteristics (maternal diseases, trimester of exposure and exclusion/matching/adjusting criteria/randomisation method), exposure characteristics (type of drug, dose of drug, number of exposed and non-exposed pregnant people), outcome characteristics (gestational age at birth, weight at birth, number of children with and without hearing loss), hearing loss characteristics (type of hearing loss, method of diagnosis and age at diagnosis) were extracted by the first author. Data from all included studies reporting effect estimates (odds ratios (OR), risk ratios (RR) or mean differences) for the outcome CHL was extracted, along with corresponding confidence intervals. Studies where OR were either directly reported or where sufficient information (number of participants in each group) was provided to allow us to calculate OR were used to conduct a meta-analysis.

### 2.6 | Data Synthesis

We present a quantitative analysis using forest plots where sufficient data were available in the included studies, complemented by a narrative of key findings of the included studies in text and tables. We prioritised using the adjusted estimates when they were presented in the studies; if not, we utilised raw estimates. If none were provided but there was sufficient data about exposed and non-exposed, we calculated the estimates ourselves. We employed a random-effects model to account for heterogeneity and calculated pooled effect sizes with 95% confidence intervals.

### 2.7 | Quality Assessment and Risk of Bias

The methodological quality and the risk of bias within the included studies were assessed by the first author using the Newcastle-Ottawa Scale (NOS) [24] for non-randomised trials and the Cochrane risk-of-bias (ROB2, August 2019 version) [25] for randomised trials. The NOS includes three categories of criteria, giving a total maximum score of 9 points to each study. The ROB2 includes five domains used to grade the risk of bias in the studies, where studies are either graded 'high risk', 'some concerns' or 'low risk'.

The quality of evidence for all outcomes was assessed by the first author using The Oxford Centre for Evidence-Based Medicine 2011 (OCEBM) Levels of Evidence [26], where each study is given a score from 1 to 5, with 1 being the highest level of evidence (systematic review or [RCTs]) and 5 being the lowest level of evidence (expert opinion without critical appraisal).

The quality assessment scores were used to contextualise the strength of individual studies; but did not influence inclusion or weighting in meta-analyses. Sensitivity analyses by study quality were not conducted.

## 3 | Results

A search on PROSPERO did not identify any relevant systematic reviews.

### 3.1 | Study Selection

A total of 1414 publications were identified through the databases Embase ($n = 856$), PubMed ($n = 408$) and Web of Science ($n = 160$). We removed 132 duplicates using Endnote and Covidence, leaving 1282 publications for the initial screening of titles and abstracts. Furthermore, 1195 publications were excluded as they were deemed irrelevant to the specific focus of this systematic review, leaving 85 studies for full-text screening. We excluded 66 studies due to eligibility criteria; 39 studies due to study design, nine due to participant group, eight studies due to wrong outcome, six studies were imprecise and four did not meet language criteria. A list of excluded but possibly relevant case reports and case series found through the screening process or screening of references is provided in Appendix B. A list of excluded but possibly relevant studies in other languages found through the screening process or screening of references is provided in Appendix C. We included two studies through cross-reference. A total of 21 studies were included in this systematic review and meta-analysis.

### 3.2 | Study Characteristics

We included four RCTs, 12 cohort studies [27–37] and five case–control studies [38–42] (Table 1). Four studies were conducted in Asia, three in South America, three at multiple centres worldwide, three in Europe, three in North America, two in Australia/New Zealand and one in Africa.

There were four publications from the 2000s, eight from the 2010s and four from the 2020s.

The 21 studies examined a total of 60 drugs from 13 different categories: corticosteroids alone [32, 33, 36, 41–45], magnesium sulphate alone or in combination with corticosteroids [32, 33, 40–42, 47], antibiotics [28, 33, 39–41], antimalarials [27, 34, 35, 39], non-steroidal anti-inflammatory drugs (NSAIDs) [39, 46], antiretrovirals [29], antineoplastic drugs [30], neurological drugs [39], diuretics [39], topical agents [39], attention deficit hyperactivity disorder (ADHD) medication [37], drugs not specified [38].

Twelve [27–36, 38, 42] of 21 (57%) studies reported the assessment method used to diagnose hearing loss. The methods included otoacoustic emissions (OAE), transient evoked otoacoustic emissions (TEAOE/TOAE), auditory brainstem response (ABR), automated auditory brainstem response (AABR/A-BAEP) and pure tone audiometry (Table 2). In fifteen [27, 30, 32–37, 39, 42–47] of 21 (71%) studies, drug intake was the primary exposure (Table 3).

The age at hearing loss diagnosis was provided in 18 studies [27, 29–34, 36, 38–41, 43–47] and ranged from a non-specified age ('newborn') to 11 years of age.

### 3.3 | Summary of Effect Estimates

An OR or adjusted OR estimate together with 95% confidence intervals was reported for 37 drugs or drug combinations (adjusted factors are presented in Table 2). Additionally, the OR for 16 drugs in 10 studies [27, 28, 30, 34, 35, 37–39, 43, 46] could be calculated using the reported numbers of exposed and non-exposed cases and controls. A RR estimate together with 95% confidence intervals was reported in two publications for two drug or drug combinations. Results for all studies are summarised in Table 1. Whenever ORs were reported or calculated, they were used to perform a meta-analysis, which was visually displayed using forest plots using the software package R and a random-effects model.

### 3.4 | Drug-Specific Meta-Analyses

#### 3.4.1 | Studies on Magnesium Sulphate and/or Systemic Steroids

The overall effect estimate of the meta-analysis on magnesium sulphate with or without steroids was OR 0.65 (95% CI: 0.42–1.00) in favour of magnesium sulphate or magnesium sulphate in combination with steroids [32, 33, 41, 42, 47] (Figure 2). The overall effect estimate of the meta-analysis on betamethasone and systemic corticosteroids given alone was OR 0.86 (95% CI: 0.69–1.08) in favour of systemic corticosteroids [32, 33, 36, 39, 41, 43, 44] (Figure 3). One study found an adjusted OR of 1.16 (95% CI: 0.62–2.16) for dexamethasone compared to betamethasone [45].

#### 3.4.2 | Studies on Acetylic Salicylic Acid and Other NSAIDs

We identified only two studies on NSAIDs including acetylsalicylic acid (ASA). Foch et al. [39] first studied the association for

**TABLE 1** | Characteristics of included studies on drug exposure and congenital hearing loss.

| Author, publication year | Country | Study design | Drug investigated | Trimester of exposure | Reported estimate | # Children antenatally exposed to drug with hearing loss | # Children antenatally exposed to drug without hearing loss | # Children antenatally non-exposed to drug with hearing loss | # Children antenatally non-exposed to drug without hearing loss |
|---|---|---|---|---|---|---|---|---|---|
| Asztalos et al. 2013 [43] | 20 countries in North- and South America, Europe and Asia | RCT | Betamethasone | 2nd or 3rd | Calculated OR 1.80 (95% CI: 0.71–4.56) | 11 | 862 | 6 | 849 |
| Azizi et al., 2016 [38] | Iran | Case–control | Ototoxic drugs (not specified) | Not specified | Calculated OR 1.66 (95% CI: 1.11–2.47) | 75 | 300 | 49 | 326 |
| Bang Madsen et al. 2023 [37] | Denmark | Cohort | ADHD medication (Methylphenidate, Amphetamine, Dexamphetamine, Lisdexamphetamine, Modafinil, Atomoxetine and Clonidine) | Throughout pregnancy or new users some time during pregnancy | Adjusted HR 1.04 (95% CI: 0.67–1.62), Calculated OR 1.29 (95% CI: 0.92–1.81) | 35 | 863 | 32430 | 1032867 |
| Borba et al. 2004 [27] | Brazil | Cohort | Chloroquine diphosphate | Four mothers during 1st and five mothers during 1st, 2nd and 3rd | $p = 0.55$ | 0 | 9 | 0 | 10 |
| Crowther et al. 2007 [44] | Australia and New Zealand | RCT | Betamethasone | 2nd and 3rd | OR 0.77 (95% CI: 0.19–3.06), $p = 0.71$ | 4 | 517 | 5 | 521 |
| Crowther et al. 2019 [45] | Australia and New Zealand | RCT | Dexamethasone vs. Betamethasone | 2nd or 3rd | OR 1.16 (95% CI: 0.62–2.16), $p = 0.65$ | 21 | 593 | 18 | 595 |

(Continues)

**TABLE 1** | (Continued)

| Author, publication year | Country | Study design | Drug investigated | Trimester of exposure | Reported estimate | # Children antenatally exposed to drug with hearing loss | # Children antenatally exposed to drug without hearing loss | # Children antenatally non-exposed to drug with hearing loss | # Children antenatally non-exposed to drug without hearing loss |
|---|---|---|---|---|---|---|---|---|---|
| Fakhim et al. 2010 [28] | Iran | Cohort | Ototoxic drugs, Aminoglycosides (especially Amikacin) were the most common | Not specified | Calculated OR 25.75 (2.98–240.08), $p = 0.086$ | 1 | 17 | 4 | 1819 |
| Fasunla et al. 2014 [29] | Nigeria | Cohort | HAART with efavirenz + lamivudine + tenofovir or atazanavir + ritonavir + tenofovir + zidovudine + lamivudine or other combination therapies including lopinavir or abacavir. | Not specified | RR 0.13 (95% CI: 0.05–0.32), $p = 0.002$ | Not reported | Not reported | Not reported | Not reported |
| Finch et al. 2021 [30] | USA, Canada and Europe | Cohort | Cisplatin | 2nd | Not reported | 3 | 16 | 0 | 264 |
| | | | Oxaliplatin | 2nd and 3rd | Not reported | 0 | 11 | 0 | 264 |
| | | | Carboplatin | 2nd and 3rd | Not reported | 1 | 12 | 0 | 264 |
| | | | Platinum agents vs. non-platinum-containing agents | 2nd and 3rd | OR 60.3, $p = 0.0003$ | 4 | 43 | 0 | 264 |
| Foch et al. 2018 [39] | France | Case–control | Valproic acid/valpromide | 1st (100%), 2nd (60%), 3rd (60%) | Adjusted OR 5.20 (95% CI: 1.93–14.00) | 5 | 20 | 1166 | 25875 |
| | | | Systemic corticosteroids | 1st (51%), 2nd (35%), 3rd (34%) | Adjusted OR 0.75 (95% CI: 0.61–0.93) | 102 | 1069 | Not reported | 24826 |
| | | | Peripheral vasodilators | 3rd | Univariate OR 3.58 (95% CI: 1.77–7.24) | 9 | 57 | 1236 | 27989 |
| | | | Dihydroergocryptine | 3rd | Adjusted OR 3.71 (95% CI: 1.75–7.89) | 8 | 48 | 1163 | 25847 |
| | | | Fusafungine and bacitracin/tixocortol | Not specified | Adjusted OR 2.55 (95% CI: 1.32–4.93) | 10 | 86 | 1161 | 25809 |

(Continues)

**TABLE 1** | (Continued)

| Author, publication year | Country | Study design | Drug investigated | Trimester of exposure | Reported estimate | # Children antenatally exposed to drug with hearing loss | # Children antenatally exposed to drug without hearing loss | # Children antenatally non-exposed to drug with hearing loss | # Children antenatally non-exposed to drug without hearing loss |
|---|---|---|---|---|---|---|---|---|---|
| | | | Antithrombotic agents | Not specified | Univariate OR 1.42 (95% CI: 1.02–1.99) | 37 | 591 | 1208 | 27455 |
| | | | ASA ≤ 300 mg | Not specified | Adjusted OR 1.53 (95% CI: 1.12–2.11) | 43 | 625 | 1128 | 25270 |
| | | | NSAIDs: ASA > 300 mg and other NSAIDs | Not specified | Adjusted OR 1.00 (95% CI: 0.81–1.12) | 102 | 2281 | 1069 | 23614 |
| | | | Antihaemorrhagics | Not specified | Univariate OR 3.48 (95% CI: 1.47–8.23) | 6 | 39 | 1239 | 28007 |
| | | | Tobramycine | Not specified | Not significant | Not reported | 2 | | 28044 |
| | | | Gentamicine | Not specified | Calculated OR 3.22 (95% CI: 0.43–24.48) | 1 | 7 | 1244 | 28039 |
| | | | Netilmicine | Not specified | Not significant | Not reported | 12 | | 28034 |
| | | | Erythromycine | Not specified | Calculated OR 1.11 (95% CI: 0.81–1.52) | 46 | 937 | 1199 | 27109 |
| | | | Chloroquine | Not specified | Not significant | Not reported | 6 | | 28040 |
| | | | Quinine | Not specified | Not significant | 1 | 6 | 1244 | 28040 |
| | | | Furosemide | Not specified | Calculated OR 1.18 (95% CI: 0.16–8.60) | 1 | 19 | 1244 | 28027 |
| | | | Emollients and protectives | Not specified | Univariate OR 1.28 (95% CI: 1.03–1.58) | 94 | 1687 | 1151 | 26359 |
| | | | Cream composed of glycerol, paraffin and vaseline | 1st, 2nd and 3rd | Adjusted OR 1.28 (95% CI: 1.00–1.64) | Not reported | Not reported | 1236 | Not reported |
| Gazia et al. 2019 [31] | Italy | Cohort | Not specified | Not specified | OR 0.91 (95% CI: 0.20–4.16), $p = 0.9$ | 2 | 16 | 32 | 234 |
| Kasapoglu et al. 2020 [32] | Turkey | Cohort | Magnesium sulphate (+ betamethasone if needed) | 2nd and 3rd | OR 0.23 (95% CI: 0.05–1.19), $p = 0.08$ | 3 | 89 | 16 | 131 |

(Continues)

**TABLE 1** | (Continued)

| Author, publication year | Country | Study design | Drug investigated | Trimester of exposure | Reported estimate | # Children antenatally exposed to drug with hearing loss | # Children antenatally exposed to drug without hearing loss | # Children antenatally non-exposed to drug with hearing loss | # Children antenatally non-exposed to drug without hearing loss |
|---|---|---|---|---|---|---|---|---|---|
| | | | Betamethasone | 2nd and 3rd | OR 1.59 (95% CI: 0.39–6.43), $p = 0.51$ | Not reported | Not reported | Not reported | Not reported |
| Leung et al. 2016 [33] | USA | Cohort | Magnesium sulphate | 2nd and 3rd | OR 0.38 (95% CI: 0.2–0.74) | 25 | 186 | 20 | 58 |
| | | | Betamethasone and magnesium sulphate | 2nd and 3rd | OR 0.31 (95% CI: 0.16–0.60), $p < 0,001$ | 32 | 209 | 25 | 69 |
| | | | Betamethasone | 2nd and 3rd | OR 0.41 (95% CI: 0.2–0.86), $p = 0.018$ | 20 | 175 | 13 | 35 |
| | | | Ampicillin | Not specified | OR 0.63 (95% CI: 0.33–1.19), $p = 0.15$ | 21 | 141 | 24 | 103 |
| | | | Ampicillin and sulbactam | Not specified | OR 2.3 (95% CI: 1.08–4.9), $p = 0.03$ (after adjusting for GA $p = 0.12$) | 12 | 33 | 33 | 211 |
| | | | Clindamycin | Not specified | OR 0.99 (95% CI: 0.36–2.74), $p = 0.99$ | 5 | 27 | 40 | 217 |
| | | | Gentamicin | Not specified | OR 1.8 (95% CI: 0.68–4.48), $p = 0.28$ | 6 | 19 | 39 | 225 |
| | | | Metronidazole | Not specified | OR 1.77 (95% CI: 0.6–5.1), $p = 0.29$ | 5 | 16 | 40 | 228 |
| | | | Azithromycin | Not specified | OR 0.92 (95% CI: 0.1–7.6), $p = 0.9$ | 1 | 6 | 44 | 238 |
| | | | Amoxicillin and clavulanate | Not specified | OR 0.66 (95% CI: 0.1–5.4), $p = 0.7$ | 1 | 8 | 44 | 236 |
| | | | Penicillin | Not specified | $p = 0.22$ | 0 | 8 | 45 | 236 |
| | | | Nitrofurantoin | Not specified | $p = 0.25$ | 0 | 7 | 45 | 237 |
| | | | Erythromycin | Not specified | $p = 0.39$ | 0 | 4 | 45 | 240 |

(Continues)

**TABLE 1** | (Continued)

| Author, publication year | Country | Study design | Drug investigated | Trimester of exposure | Reported estimate | # Children antenatally exposed to drug with hearing loss | # Children antenatally exposed to drug without hearing loss | # Children antenatally non-exposed to drug with hearing loss | # Children antenatally non-exposed to drug without hearing loss |
|---|---|---|---|---|---|---|---|---|---|
| | | | Maternal antibiotics | Not specified | OR 0.55 (95% CI: 0.28–1.11), $p=0.095$ | 30 | 191 | 15 | 53 |
| | | | Other (sulfamethoxazole and trimethoprim, cefotetan, ceftriaxone, cephalexin and cefazolin) | Not specified | OR 1.05 (95% CI: 0.5–2.2) | 11 | 57 | 34 | 187 |
| Patatt et al. 2021 [34] | Brazil | Cohort | Antimalarial drugs (chloroquine, coartem, quinine + clindamycin and primaquine) | 1st, 2nd and 3rd | $p<0.001$ | 0 | 32 | 21 | 474 |
| Silva et al. 2015 [35] | Amazonas | Cohort | Antimalarial drugs (chloroquine (66.7%), primaquine, coartem, quinie or unknown) | 1st (33.3%), 2nd (26.7%), 3rd (30.0%) and unknown (13.3%) | RR 5.64 (95% CI: 1.17–27.3), $p=0.031$ | 2 | 28 | 3 | 251 |
| Soraisham et al. 2011 [46] | Canada | Cohort | Indomethacin | 2nd | Calculated OR of 1.32 (95% CI: 0.27–6.49), $p=0.74$ | 2 | 73 | 5 | 241 |
| The MAGPIE Follow Up Trial. 2006 [47] | 19 countries in Africa, Asia, North- and South America and Europe | RCT | Magnesium sulphate | 3rd | Calculated OR 2.02 (95% CI: 0.2–20.72) | 2 | 1633 | 1 | 1647 |
| Tsao et al. 2023 [40] | Taiwan | Case–control | Gentamicin and furosemid | Not specified | adjOR 1.01 (95% CI: 0.96–1.07) | 2599 | 11 336 | 10 273 | 53 029 |
| Tsao et al. 2024 [41] | Taiwan | Case–control | Gentamicin and furosemid | Not specified | adj OR 0.97 (95% CI: 0.89–1.06) | 1585 | 2011 | 6852 | 11 128 |
| | | | Steroids | Not specified | adj OR 0.99 (95% CI: 0.90–1.09) | 655 | 2941 | 2177 | 15 803 |

(Continues)

**TABLE 1** | (Continued)

| Author, publication year | Country | Study design | Drug investigated | Trimester of exposure | Reported estimate | # Children antenatally exposed to drug with hearing loss | # Children antenatally exposed to drug without hearing loss | # Children antenatally non-exposed to drug with hearing loss | # Children antenatally non-exposed to drug without hearing loss |
|---|---|---|---|---|---|---|---|---|---|
| | | | Magnesium sulphate | Not specified | adj OR 1.01 (95% CI: 0.90–1.14) | 435 | 1216 | 3161 | 16 674 |
| | | | Steroids + magnesium sulphate | Not specified | adj OR 0.79 (95% CI: 0.67–0.93) | 276 | 3320 | 880 | 17 100 |
| Wang et al. 2023 [42] | China | Case–control | Dexamethasone | < 28 weeks, 28–32 weeks or > 32 weeks | OR 1.1 (95% CI: 0.62–1.96) | 57 | 50 | 242 | 249 |
| | | | Dexamethasone + magnesium sulphate | < 28 weeks, 28–32 weeks or > 32 weeks | OR 0.98 (95% CI: 0.61–1.57) | 196 | 249 | 103 | 91 |
| Waters et al. 2008 [36] | USA | Cohort | Betamethasone or dexamethasone | Not specified | Multivariate OR = 0.83 (95% CI: 0.5–1.4) | 63 | 417 | 32 | 162 |

Abbreviations: ASA: acetylsalicylic acid, ADHD: attention deficit hyperactivity disorder, adjOR: adjusted odds ratio, CI: confidence interval, HR: hazard ratio, HAART: highly active antiretroviral therapy, NSAID: non-steroidal anti-inflammatory drug, OR: odds ratio, RCT: randomised controlled trial, RR: risk ratio, USA: United States of America.

**TABLE 2** | Detailed characteristics and methodological features of included studies.

| Author, publication year | Patient recruitment, year of conduct | Maternal diseases | Exclusion/matching/adjusting/ randomisation method | Type of hearing loss and method of diagnosis |
|---|---|---|---|---|
| Case–control studies | | | | |
| Azizi et al. 2016 [38] | Newly born infants seen at the social welfare centre of Kermanshah 2013 | Not specified | Exclusion: Missing information in the files, lost-to-follow up. Matching: One control selected for each case through a systematic sampling method. | HL or deafness diagnosis based on TEOAE and ABR. |
| Foch et al. 2018 [39] | EFEMERIS database 2004–2015 | Chronic disease, diseases during pregnancy, congenital infection, diabetes, arterial hypertension and pre-eclampsia | Exlusion: Gene related deafness, children not attending 24-month health certificate. Adjustment: Prematurity, gender, congenital infection, ear malformation, birth asphyxia and recurrent otitis at 24 months. | HL diagnosis based on hearing examination on the 24-month certificate. |
| Tsao et al. 2023 [40] | Nationwide Taiwan databases, 2002–2015 | Not specified | Multivariate conditional logistic regression analysis, adjusted for potential confounders (not specified) | Hearing impairment registered as ICD-9-CM 389 and 794.15 |
| Tsao et al. 2024 [41] | Nationwide Taiwan databases, 2004–2015 | Not specified | Multivariate conditional logistic regression analysis, adjusted for potential confounders (not specified) | Hearing impairment registered as ICD-9-CM 389 and 794.15 |
| Wang et al. 2023 [42] | West China Second University Hospital, Sichuan University from 2018 to 2020 | Premature birth | Exlusion: congenital brain defects, neural tube defects, ear malformations or family history of hereditary deafness. Matching: difference in GA between case and control group was within 1 week and IVF or no IVF was performed at the same time. Adjustment: age of the mother, chorioamnionitis, treatment with antenatal magnesium sulphate. | Hearing screening failure, defined as hearing level exceeded 30 dB NHL in one or two ears during AABR. |
| Cohort studies | | | | |

(Continues)

**TABLE 2** | (Continued)

| Author, publication year | Patient recruitment, year of conduct | Maternal diseases | Exclusion/matching/adjusting/ randomisation method | Type of hearing loss and method of diagnosis |
|---|---|---|---|---|
| Bang Madsen et al. 2023 [37] | Data from Danish nationwide registers, 1998–2015 | ADHD | Exclusion: missing/unlikely gestational age, chromosomal abnormalitis, missing paternal links, mothers prescribing other psychotropic medications, mothers with only one prescribed ADHD medication. Adjustment: maternal age, parity, maternal psychiatric history, in- or outpatient admission to psychiatric ward within 2 years prior to pregnancy and until delivery, use of other psychotropic medications during pregnancy, number of hospitalisations during pregnancy not related to psychiatry, smoking during pregnancy, living alone, education, birthyear and psychiatric history of the father. | ICD-codes H90, H91.0, H91.8, H91.9, H93.2, Z03.7A |
| Borba et al. 2004 [27] | Data from structured questionnaires and medical records of children of patients with SLE at the Rheumatology Division of University of Sao Paulo. | SLE | Exclusion: history of recurrent otitis, acoustic trauma or ototoxic antibiotic treatment (aminoglycosides, macrolides, furosemide, ethacrynic acid and acetyl salicylic acid), no exposure during first trimester, children < 4 years of age. | Sensorineural HL diagnosis based on PTA including analysis of high-frequency and low-frequency PTA. |
| Fakhim et al. 2010 [28] | High risk infants selected from ICU ward of Kodakan, Alzahra and Talegani hospitals, low risk infants selected from women hospitals (not specified), 2004–2006 | Not specified | Exclusion: not specified, infants with blood bilirubin moren than 20 mg/dL or requiring blood exchange possibly excluded. | All with a risk score (including in utero drug exposure) were screened with OAE. In case of impairment, the children were treated with antibiotics for two weeks and a second OAE was performed. In case of continuous impairment, ABR was performed and diagnosis of HL was given if hearing treshold was > 30 dB at ABR in one ear. If the child had blood bilirubin > 20 mg/dL or required blood exchange, ABR was done initially. |

(Continues)

**TABLE 2** | (Continued)

| Author, publication year | Patient recruitment, year of conduct | Maternal diseases | Exclusion/matching/adjusting/ randomisation method | Type of hearing loss and method of diagnosis |
|---|---|---|---|---|
| Fasunla et al. 2014 [29] | Newborns at the postnatal HIV clinics at the University College Hospital, Ibadan and Adeoyo Maternity Hospital, 2012–2013 | HIV | Exclusion: stillborn, unhealthy child at 1 month old. | Sensorineural HL diagnosis based on ABR. |
| Finch et al. 2021 [30] | The Cancer and Pregnancy Registry enrolling pregnant women with cancer, 1995–2018 | Cancer | Exclusion: women diagnosed with cancer within the first year after giving birth, temporary hearing issues secondary to ear canal fluid or recurrent otitis media. | Sensorineural HL diagnosis (according to the Clark classification of HL) based on initial screening with OAE. After failing OAE, AABR was conducted to classify the level of HL. |
| Gazia et al. 2019 [31] | NICU infants at The Department of Audiology of Palermo University, 2010—unknown end date | Not specified | Matching: for age and gender. | Sensorineural HL diagnosis based on ABR (treshold > 40 dB), TEOAE and tympanometry. |
| Kasapoglu et al. 2020 [32] | Medical records of preterm infants at a tertiary university hospital, 2015–2017 | Indications: neuroprotection, tocolysis or prophylaxis for eclampsia | Exclusion: newborns with history of intrauterine infections, lethal congenital abnormalities, craniofacial anomalies and newborns dying after birth. Adjustment: GA at delivery, magnesium sulphate and betamethasone. | HL defined as pass/fail ABR (Madsen Accuscreen). If stimulus to produce a response did not exceed 30 dB in both ears, they passed. |
| Leung et al. 2016 [33] | Medical records of preterm neonates from the NICUs of University of Maryland Medical Centre and Mercy Medical Centre, 1999–2003 | For Betamethasone and Magnesium Sulphate: Premature birth, preeclampsia/ eclampsia. For antibiotics: Group B streptococcus, latency, suspected chorioamnionitis and maternal infection | Exclusion: Congenital brain/neural tube defects, congenital infections, no available cord blood or venous sample within 12 h of birth. Adjustment: for GA. | Initial screening with AABR (treshold > 30 dB). If failed screen, AABR repeated. HL defined as two AABR screen failures in one or both ears. |

(Continues)

**TABLE 2** | (Continued)

| Author, publication year | Patient recruitment, year of conduct | Maternal diseases | Exclusion/matching/adjusting/ randomisation method | Type of hearing loss and method of diagnosis |
|---|---|---|---|---|
| Patatt et al. 2021 [34] | Interviews and records from medical files, HBAP NHS database, Clinica Limiar database, the newborn's vaccination card, the pregnant woman's card and data collection form used to include and study patients from HBAP and Clíníca de Avaliacao e Reabilitacao da Audicao—Limiar, 2014–2015 | Malaria (*P. vivax* and P. falciparum) | Exclusion: newborns with other risk indicators for HL, non-Brazilian mothers, birth at the hospital, not complete follow-up, not recieving prenatal care, not participating in the hearing screening program and no consent. | HL diagnosis based on initial TEOAE testing of newborns and retesting after 15 days if initial TEOAE failed. Newborns of mothers who recieved antimalarial drugs and newborns who failed the second TEOAE was tested with A-BAEP. |
| Silva et al. 2015 [35] | Data from medical records and/or interviews through a NHS program conductet at a tertiary referral hospital including high-risk pregnant women and newborns at high risk, 2011–2013 | Malaria (plasmodium vivax and plasmodium falciparum) | Exclusion: children not completing the NHS program, if variables of interest abscent, if communication difficulties with parents, parent/guardians not signing a consent form. Matching: GA, birth weight, risk factors for HL in childhood (toxoplasmosis, rubella, CMV, herpes, syphilis and family history of HL) | HL based on screening with TOAE for low risk newborns those without (RFHL, such as toxoplasmosis, rubella, CMV, herpes, syphilis, newborns of women recieving antimalaria drugs during pregnancy and family history of HL in childhood) and combined TOAE/AABR for those with RFHL. HL defined as probability of HL due to fail in hearing screening. |

(Continues)

**TABLE 2** | (Continued)

| Author, publication year | Patient recruitment, year of conduct | Maternal diseases | Exclusion/matching/adjusting/ randomisation method | Type of hearing loss and method of diagnosis |
|---|---|---|---|---|
| Soraisham et al. 2011 [46] | Data from maternal charts, a regional NICU, 2000–2003 | Premature birth | Exclusion: stillborn, children dying after birth, loss to follow up, children with birth weight > 1250 g and GA < 28 weeks, children with major congenital or chromosomal anomalies, no neurodevelopmental assessment, no consent. Adjustment: GA, surgical PDA ligation, IVH, BPD and postnatal steroid use. | Sensorineural HL diagnosis based on examination by an audiologist. Deafness defined as sensorineural HL requiring amplification. |
| Waters et al. 2008 [36] | Neonatal database at Christiana Hospital, July 1998–July 2004 | Infants < 1500 g | Exclusion: infants with a partial/inadequate exam, patients reviecing only partial therapy or more than one course of steroids, infants labelled as 'suspect' on OAE. Adjusting: multivariate analysis with logistic regression performed to control for confounding variables. | HL defined as 'fail' on OAE. |
| Randomised controlled trials | | | | |
| Asztalos et al. 2013 [43] | Participating centres, enrollment 2001–2006 and follow-up 2006–2012 | Risk of preterm birth | Central randomisation with stratification according to centre and GA at enrollment. Exclusion: GA not 25–32 weeks, women not remaining pregnant 14–21 days following therapy, women not remaining at risk of preterm birth after therapy and lost-to-follow up. | Deafness. |
| Crowther et al. 2007 [44] | Newborns of women in ACTORDS trial | Risk of preterm delivery | Women randomly assigned through a central telephone randomisation service with stratification according to centre, GA and number of foetuses. Adjustment: GA at trial entry, antepartum haemorrhage and preterm prelabour rupture of the membranes. Exclusion: stilborn, children dying before discharge, children dying before follow-up and no paediatric/psychological examination. | Deafness defined as requirement of hearing aids at follow-up at 2 years corrected age. |
| Crowther et al. 2019 [45] | Data from medical records, examination by paediatrics and questionnaires, 14 maternity hospitals that provide care for preterm babies, 2009–2013 | Risk of preterm birth | Randomised through a central randomisation service. Adjustment: for hospital, GA at entry, number of foetuses, language spoken at home, mother's education, gender of child. Exclusion: Contraindications to antenatal corticosteroids, no consent, chorioamnionitis, women already recieved antenatal corticosteroids in second stage or labour, known fetal lung maturation, dead child before discharge and dead child before follow-up. | Deafness defined as requirement of hearing aids or worse at 2 years corrected age. |

(Continues)

**TABLE 2** | (Continued)

| Author, publication year | Patient recruitment, year of conduct | Maternal diseases | Exclusion/matching/adjusting/ randomisation method | Type of hearing loss and method of diagnosis |
|---|---|---|---|---|
| The MAGPIE follow up trial. 2006 [47] | Data from questionnaires filled by a health professional (shortened if language or culture demanded it) filled at clinic or at home visit, register data from UK cases on pregnant women from 125 centres in 19 countries in Africa, Asia, North- and South America and Europe, 1998–2001 | Pre-eclampsia | Randomly assigned participants. Exclusion: stillborn, lost-to-follow up (no response or died). Adjustment: GA, maternal anticonvulsant before trial entry, gender of the child, women with multiple pregnancies and children admitted to a special care baby unit. | HL defined as requirement of hearing aids. |

Abbreviations: ABR: auditory brainstem response, AABR: automated auditory brainstem response, ADHD: attention deficit hyperactivity disorder, A-BAEP: automated brainstem auditory evoked potential, BPD: bronchopulmonary dysplasia, CMV: cytomegalovirus, dB: decibel, GA: gestational age, HL: hearing loss, HIV: human immunodeficiency virus, ICD: international classification of diseases, IVH: intraventricular haemorrhage, IVF: in vitro fertilisation, ICU: intensive care unit, NHL: normal hearing level, NHS: newborn hearing screening, NICU: neonatal intensive care unitOAE: otoacoustic emission, PDA: patent ductus arteriosus, PTA: pure tone audiometry, RFHL: risk factors for hearing loss, SLE: systemic lupus erythematosus, TEOAE: transient evoked otoacoustic emission, UK: United Kingdom.

**TABLE 3** | Critical appraisal and quality assessment of included studies.

| Author | Limitations presented by the study authors | Other shortcomings of the study | CEBM levels of evidence (max = 1, min = 5) | NOS (min = 0, max = 9) /ROB2 scaling | Was drug exposure the primarily investigated exposure |
|---|---|---|---|---|---|
| Case–control studies | | | | | |
| Azizi et al. 2016 [38] | False positive cases. | • Unclear whether all cases and controls are examined by same methods (TEOAE and ABR). TEOAE conducted at different time points (early birth, first month, first to third month, third month onward). 375 children considered as cases after initial TEOAE screening, although only 72 children had HL/deafness after repeated examination (the method of repetition not specified).<br>•The authors have defined the study as a cross-sectional study, but the study design suggests that it is a case–control study. The cases and controls have hovewer not been matched and potential confounders have not been adjusted for in the analysis. | **5** | **1** | No |
| Foch et al. 2018 [39] | • Database does not contain information on type or degree of HL.<br>• Risk factors for HL (gene mutations, family history, hyperbilirubinaemia) not systematically recorded.<br>• Only prescribed and dispensed drugs taken into account—over-the-counter drugs dispensed during hospitalisation not taken into account.<br>• No information on the mothers' compliance. | • Age at diagnosis (2 years) may be too early to diagnose all with HL.<br>• No systematic distinguish between sensorineural and conductive HL.<br>• Method of diagnosis is described as 'hearing examination on the 24-month certificate' but not further specified. | **4** | **9** | Yes |
| Tsao et al. 2023 [40] | •Retrospective, observational study based on a large population database with risk of introducung selection bias.<br>•Uses ICD-9-CM codes, which lack specificity regarding labouratory data, disease severity, HL subtypes.<br>•Possible underestimation of genetic components due to the expenses of genetic testing. | • Method of diagnosis of HL not reported but based on ICD-codes, which might underestimate the true number of children with HL.<br>• Gentamicin and Furosemid reported as one category. | **4** | **5** | No |

(Continues)

**TABLE 3** | (Continued)

| Author | Limitations presented by the study authors | Other shortcomings of the study | CEBM levels of evidence (max = 1, min = 5) | NOS (min = 0, max = 9) /ROB2 scaling | Was drug exposure the primarily investigated exposure |
|---|---|---|---|---|---|
| Tsao et al. 2024 [41] | •Retrospective, observational study based on a large population database with risk of introducung selection bias.<br>•Majority of cases are Asian.<br>•Used ICD-9-CM codes, which lack specificity regarding severity of morbidities associated with preterm birth and other diseases.<br>•No information on incidence of uni−/bilateral HL and outcome data.<br>•Possible underestimation of genetic components. | •Method of diagnosis of HL not reported but based on ICD-codes, which might underestimate the true number of children with HL.<br>•Gentamicin and Furosemid reported as one category. | **4** | **5** | No |
| Wang et al. 2023 [42] | •The study can not exclude the effect of abnormal hearing screening due to incomplete development of the newborn on HL.<br>•The study did not explore the effect of antenatal steroid use of different doses on development of HL. | • Age at diagnosis was from 48 h after birth to before discharge from NICU, which is too early to diagnose all with HL and will include both false positives and false negatives. | **4** | **6** | Yes |
| Cohort studies | | | | | |
| Bang Madsen et al. 2023 [37] | •Low number of antenatally exposed children and sample size insufficient to evaluate associations for different types of drugs.<br>•Based on registry data and cannot include subclinical conditions and does not contain information on alcohol or illegal drug use.<br>•Risk of misclassification when using redeemed prescriptions to define status of exposure.<br>•Did not include doses of ADHD medication, which can underestimate exposure time. | • Method of diagnosis of HL not reported but based on ICD-codes, which might underestimate the true number of children with HL. | **3** | **8** | Yes |

(Continues)

**TABLE 3** | (Continued)

| Author | Limitations presented by the study authors | Other shortcomings of the study | CEBM levels of evidence (max = 1, min = 5) | NOS (min = 0, max = 9) /ROB2 scaling | Was drug exposure the primarily investigated exposure |
|---|---|---|---|---|---|
| Borba et al. 2004 [27] | None presented. | • Inclusion criteria for outcome was age above 4, which could lead to survival bias.<br>• Small study size, only $n = 9$ in exposed and $n = 10$ in non-exposed group and no children with HL in either group.<br>• No adjustment for several potential confounders (GA, familiar disposition, perinatal asphyxia, NICU stay, hyperbilirubinaemia, intrauterine infections or genetic HL).<br>• Four of nine mothers in the exposed group discountinued their drugs during pregnancy but no detailed information on durage of drug use. | **3** | **5** | Yes |
| Fakhim et al. 2010 [28] | None presented. | • No information on age of diagnosis.<br>• High-risk and low-risk infants selected from two different centres, potentially leading to selection bias.<br>• Small study size of exposed group ($n = 18$). No information on or adjustment for several potential confounders (GA, familiar disposition, perinatal asphyxia, NICU stay, postnatal aminoglycoside use, intrauterine infections or genetical HL).<br>• All infants with impaired initial OAE have been treated with unspecified antibiotics for 2 weeks but a possible causal relationship between postnatal antibiotic treatment and HL has not been taken into account. | **5** | **2** | No |

(Continues)

**TABLE 3** | (Continued)

| Author | Limitations presented by the study authors | Other shortcomings of the study | CEBM levels of evidence (max = 1, min = 5) | NOS (min = 0, max = 9) /ROB2 scaling | Was drug exposure the primarily investigated exposure |
|---|---|---|---|---|---|
| Fasunla et al. 2014 [29] | No data on toxoplasmosis, CMV and rubella. Small study. | • Age at diagnoses (2.87 years +/−1.05 years) may be too early to diagnose all with HL.<br>• Study size not reported.<br>• The study mainly investigates differences in outcomes in newborns of HIV exposed and HIV non-exposed mothers, but they also compare the hearing of newborns in the treated vs. non-treated HIV exposed group. There is therefore no control group of mothers without HIV. Unhealthy children at 1-month old were excluded, potentially leading to both selection and information bias.<br>• No information on or adjustment for potential confounders (familiar disposition, perinatal asphyxia, NICU stay, hyperbilirubinaemia, postnatal aminoglycoside use, intrauterine infections and genetic HL). | **3** | **3** | No |
| Finch et al. 2021 [30] | None presented. | • Small study ($n = 19$, $n = 11$, $n = 13$ exposed, respectively).<br>• Three of the 4 newborns that failed the initialt screening with OAE had a normal AABR but were still included as HLcases.<br>• No information on or adjustment for potential confounders (familiar disposition, perinatal asphyxia, NICU stay, hyperbilirubinaemia, postnatal aminoglycoside use, intrauterine infections and genetic HL).<br>• The majority of this study is descriptive. | **3** | **5** | Yes |

(Continues)

**TABLE 3** | (Continued)

| Author | Limitations presented by the study authors | Other shortcomings of the study | CEBM levels of evidence (max = 1, min = 5) | NOS (min = 0, max = 9) /ROB2 scaling | Was drug exposure the primarily investigated exposure |
|---|---|---|---|---|---|
| Gazia et al. 2019 [31] | None presented. | • Age at diagnosis was 4–20 weeks at first diagnostic ABR and may be too early to diagnose all with HL.<br>• Only few included in exposed group ($n = 18$).<br>• Sample includes only NICU infants, who have an apriori higher risk of HL.<br>• No information on or adjustment for potential confounders (familiar disposition, perinatal asphyxia, hyperbilirubinaemia, postnatal aminoglycoside use, intrauterine infections and genetic HL). | **3** | **4** | No |
| Kasapoglu et al. 2020 [32] | Suggest larger and well-designed studies for future research. | • Age at diagnosis was newborn stage, which may be too early to diagnose all with HL.<br>• Only few included in exposed group ($n = 19$). Only preterm newborns, who have an apriori higher risk of HL, are included and the results can therefore not be extrapolated to general population.<br>• No adjustment made for several potential confounders (familiar disposition, perinatal asphyxia, hyperbilirubinaemia, postnatal aminoglycoside use or genetic HL). | **3** | **5** | Yes |

(Continues)

**TABLE 3** | (Continued)

| Author | Limitations presented by the study authors | Other shortcomings of the study | CEBM levels of evidence (max = 1, min = 5) | NOS (min = 0, max = 9) /ROB2 scaling | Was drug exposure the primarily investigated exposure |
|---|---|---|---|---|---|
| Leung et al. 2016 [33] | Lack of follow-up confirmation of hearing screen results. Only studies a high-risk population (premature infants). | • Age of diagnosis was prior to discharge from NICU, which may be too early to diagnose all with HL.<br>• Study size only reported for exposed group.<br>• Only children at NICU, who have an apriori higher risk of HL, are included and the results can therefore not be extrapolated to general population.<br>• No information of or adjustment for several confounders (familiar disposition, perinatal asphyxia, hyperbilirubinaemia or genetic HL). | **3** | **6** | Yes |
| Patatt et al. 2021 [34] | Change of study design to case–control more appropriate because of low incidence of malaria infection in pregnancy. | • Age of diagnosis was before or up to 22 days after discharge, which may be too early to diagnose all with HL.<br>• Only few included in the exposed group ($n = 32$).<br>• All exposed mothers' children were tested with A-BAEP, but only the children in the non-exposed group who failed the TEOAE twice was tested with A-BAEP, which could lead to information bias.<br>• No adjustment made for GA. | **3** | **5** | Yes |
| Silva et al. 2015 [35] | None presented. | • No information on age of diagnosis.<br>• Only few included in exposed group ($n = 30$).<br>• The data is collected from newborns at a high-risk centre, and the results can therefore not be extrapolated to general population. | **3** | **2** | Yes |

(Continues)

**TABLE 3** | (Continued)

| Author | Limitations presented by the study authors | Other shortcomings of the study | CEBM levels of evidence (max = 1, min = 5) | NOS (min = 0, max = 9) /ROB2 scaling | Was drug exposure the primarily investigated exposure |
|---|---|---|---|---|---|
| Soraisham et al. 2011 [46] | • Retrospective study, risk of selection bias.<br>• Pregnancy induced hypertension significantly higher in non-exposed group (indomethacin).<br>• No data on use of magnesium sulphate.<br>• Mothers not recieving indomethacin might have presented with advanced preterm labour or delivered due to maternal or fetal indications. | • Age of diagnosis was 30–42 months, which may be too early to diagnose all with HL.<br>• Only preterm newborns, who have an apriori higher risk of HL, are included and the results can therefore not be extrapolated to general population.<br>• No adjustment made for several confounders (GA, familiar disposition, perinatal asphyxia, hyperbilirubinaemia, postnatal aminoglycoside use, intrauterine infections and genetic HL).<br>• Some pregnant women in the exposed- and non-exposed groups have also been exposed to antihypertensive drugs and steroids but the results are not adjusted for intake of these or other drugs. | **4** | **5** | Yes |
| Waters et al. 2008 [36] | •Limited power to detect small changes in failed hearing screen bas on exposure due to small study size.<br>•Not possible to control for all confounders, including family history of HL, aminoglycoside og diuretic usage.<br>•Outcome based on OAE results, which is only a screening test.<br>•Exposure was limited to only single course or no course administration. | • Study only based on a single hospital database.<br>•Age at diagnosis was prior to discharge from the NICU, which is too early to diagnose all children with HL. | **3** | **5** | Yes |
| Randomised controlled trials | | | | | |
| Asztalos et al. 2013 [43] | Analysis not prespecified in the study. | • Age of diagnosis was before or after 2 years, which may be too early to diagnose all with HL.<br>• The authors calculate no estimates for the risk of the investigated drug on HL but only all neuromotor disabilities. | **2** | Some concerns | Yes |
| Crowther et al. 2007 [44] | Neurosensory examination in 2 years of age may be too early for detecting HL and need follow-up later on. | • Age of diagnosis was 2 years, which may be too early to diagnose all with HL. | **2** | Some concerns | Yes |

(Continues)

**TABLE 3** | (Continued)

| Author | Limitations presented by the study authors | Other shortcomings of the study | CEBM levels of evidence (max = 1, min = 5) | NOS (min = 0, max = 9) /ROB2 scaling | Was drug exposure the primarily investigated exposure |
|---|---|---|---|---|---|
| Crowther et al. 2019 [45] | Data not collected on the use of postnatal corticosteroids and might have differed in the exposed vs. non-exposed group. | • Age of diagnosis was 2 years or before, which may be too early to diagnose all with HL. | 2 | Low risk | Yes |
| The MAGPIE Follow Up Trial. 2006 [47] | Use of several different assessment tools, some neurodevelopmental assesments not complete, not all childrenf from the primary study included in this follow-up study (those included were usually more low risk. Those excluded usually from families in countries with high PNM). | • Age of diagnosis was 18 months, which may be too early to diagnose all with HL.<br>• Lost-to-follow up was predominantly in developing countries.<br>• Only one exposed was deaf. | 2 | High risk | Yes |

Abbreviations: ABR: auditory brainstem response, ADHD: attention deficit hyperactivity disorder, AABR: automated auditory brainstem response, A-BAEP: automated brainstem auditory evoked potential, PNM: perinatal mortalityCEBM: Centre for Evidence-Based Medicine, CMV: cytomegalovirus, GA: gestational age, HL: hearing loss, HIV: human immunodeficiency virus, ICD: international classification of diseases, NDS: Newcastle-Ottawa Scale, NICU: neonatal intensive care unit, OAE: otoacoustic emission, RoB2: Risk of Bias 2, TEOAE: transient evoked otoacoustic emission.

antithrombotics as a group and found an overall OR of 1.42 (95% CI: 1.02–1.99). In a subgroup analysis, they found an OR of 1.53 (95% CI: 1.12–2.11) for a daily dosage of ASA ≤ 300 mg and an OR of 1.00 (95% CI: 0.81–1.12) for a daily dosage of ASA > 300 mg and other NSAIDs. An OR of 1.32 (95% CI: 0.27–6.49) for indomethacin was calculated using the numbers reported in the study of Soraisham et al. [46]; a meta-analysis of ASA and NSAIDs at all doses yields an overall point estimate of OR 1.21 (95% CI: 0.87–1.68) (Figure 4).

#### 3.4.3 | Studies on Antibiotics

Six studies investigated the relationship between antenatally administered antibiotics and CHL in children. A number of antibiotics in pregnancy indicated a possible association with HL. A meta-analysis of all antibiotics together yielded an overall point estimate of OR 1.23 (95% CI: 0.97–1.57) [28, 31, 33, 39–41] (Figure 5).

#### 3.4.4 | Studies on Other Drugs

An odds ratio was reported or could be calculated for a number of other classes of drugs investigated in seven studies [27, 29, 30, 34, 35, 37–39] (Figure 6). Additionally, one study investigated the effect of antiretroviral therapy combinations and found an RR of 0.13 (95% CI: 0.05–0.32) [29].

## 4 | Discussion

This systematic review and meta-analysis identified 21 studies on antenatal drugs and CHL. The studies were heterogeneous in terms of study design and exposure. Given the observational design of most studies, causal relationships cannot be inferred due to the inherent risk of confounding, selection bias and lack of randomisation. Therefore, any observed association should be interpreted cautiously.

### 4.1 | Classes of Drugs Considered

Key drugs investigated were magnesium sulphate, systemic steroids, ASA and other NSAIDs and antibiotics. Magnesium sulphate and systemic steroids, either alone or in combination, showed potential protective effects. There was modest evidence of an increase in the risk when ASA was given at lower doses but not at higher doses. Several antibiotics, including gentamicin and metronidazole, showed some evidence of an increased risk. Several other drugs showed weaker evidence of an association with CHL, including anti-neoplastic agents and valproic acid.

### 4.2 | Corticosteroids

Antenatally administered systemic corticosteroids in infants subsequently born preterm are associated with reductions in cerebral palsy, lower risk of neurodevelopmental impairment and lower incidence of bronchopulmonary dysplasia, possibly due to

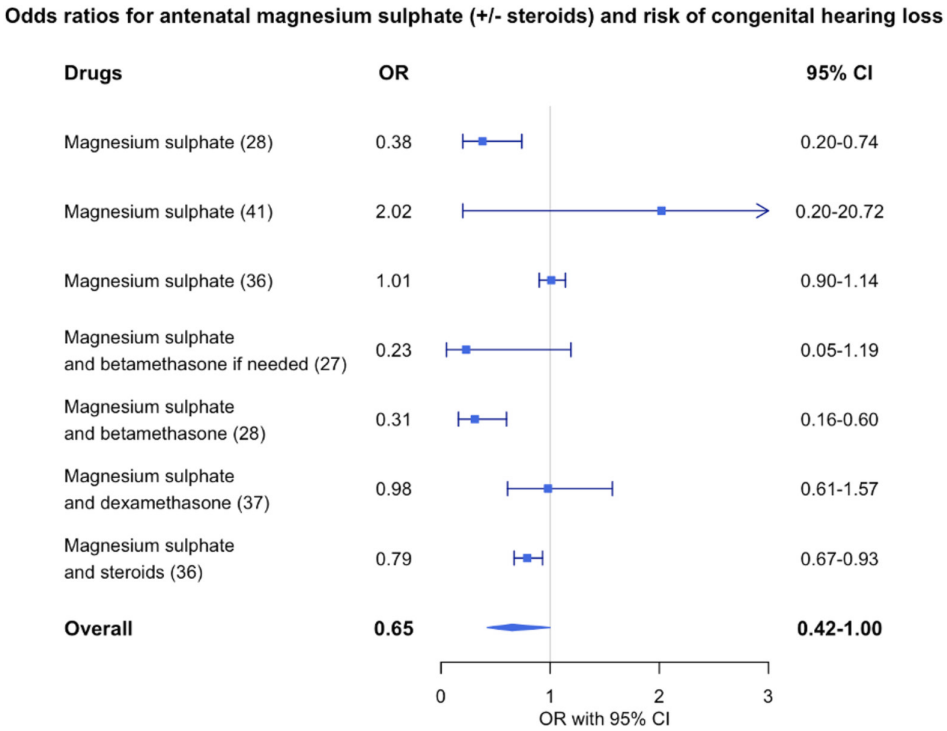


**FIGURE 2** | Forest plot of odds ratios for magnesium sulphate alone or in combination with systemic steroids and congenital hearing loss. Studies included in the forest plots reported either an OR or an adjusted OR and 95% confidence intervals, or these could be calculated using reported raw numbers. Numbers in parentheses correspond to individual study identifiers. OR: odds ratio. CI: confidence interval. NI: no information.

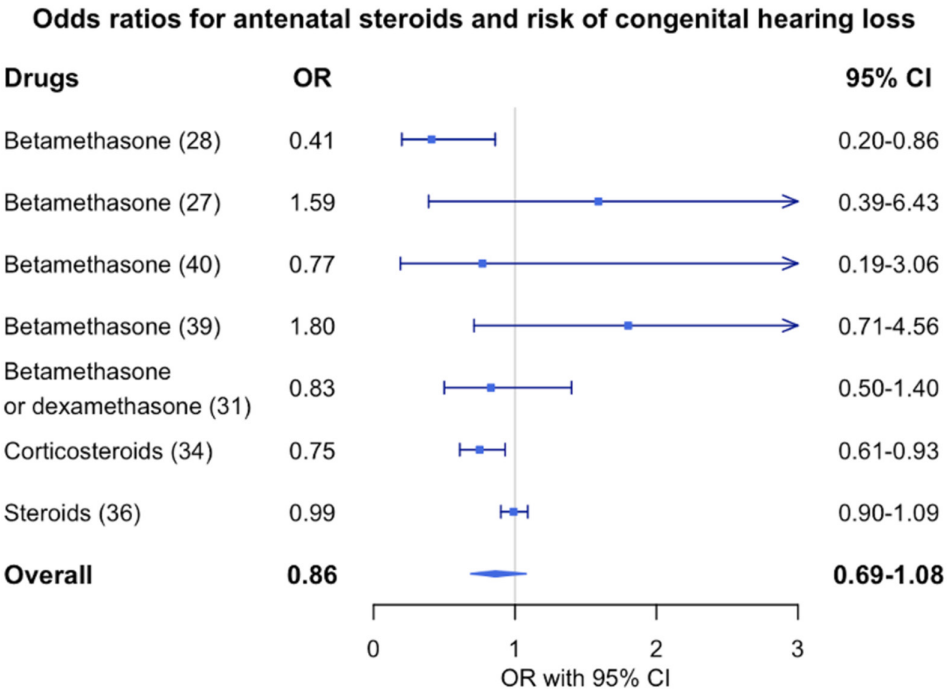


**FIGURE 3** | Forest plot for systemic steroids where an OR or an adjusted OR and 95% confidence intervals were reported or could be calculated using reported raw numbers. Numbers in parentheses correspond to individual study identifiers. OR: odds ratio. CI: confidence interval.

improved respiratory function and lower rates of intraventricular haemorrhage [48–50]. Antenatal corticosteroids may directly protect against congenital sensorineural CHL by reducing inflammation caused by chorioamnionitis [51] and by improving blood circulation to inner ear cells and brain areas regulating hearing. However, antenatal administration of antenatal

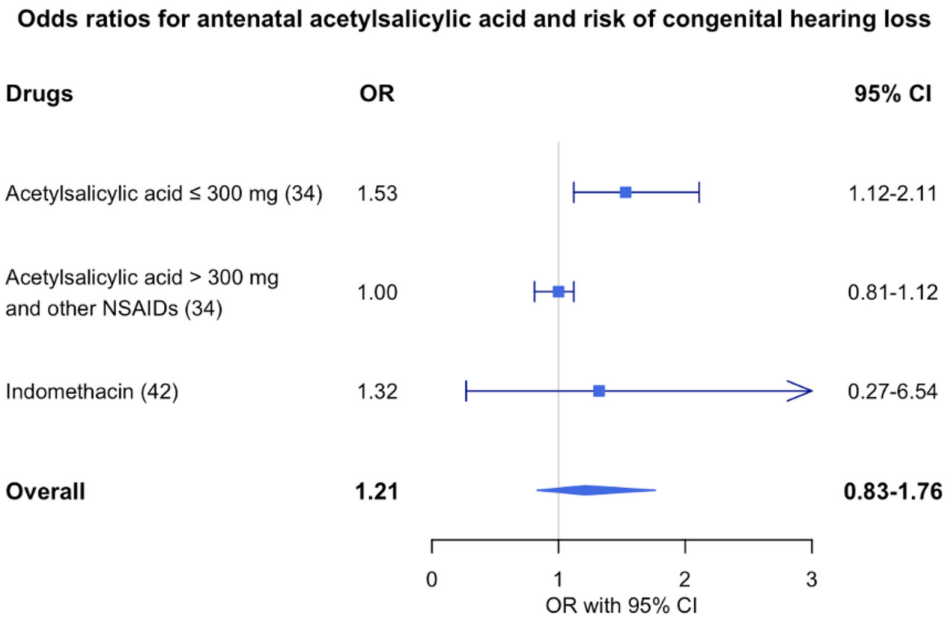


**FIGURE 4** | Forest plot for acetylsalicylic acid and other NSAIDs where an OR or an adjusted OR and 95% confidence intervals were either reported or could be calculated using reported numbers. Numbers in parentheses correspond to individual study identifiers. OR: odds ratio. CI: confidence interval.

steroids to women who subsequently deliver at term has been associated with mental and behavioural disorders in children in the long term [52].

### 4.3 | Magnesium Sulphate

Magnesium sulphate, often given with corticosteroids, is used as a neuroprotectant for pregnancies at risk of preterm delivery [53]. Studies on magnesium sulphate primarily focus on mortality and cerebral palsy [54], but magnesium alone has been shown to reduce hearing damage caused by acoustic trauma in guinea pigs [55–57]. We speculate that the potential mechanism could be due to its ability to preserve inner hair cells and cochlear function and protect these areas from damage related to prematurity. Another possible mechanism is that magnesium lowers the risk of complications of prematurity and therefore protects against the development of HL in the newborn.

### 4.4 | Acetylsalicylic Acid

Our systematic review found that low doses (ASA ≤ 300 mg/day), but not high doses (> 300 mg/day) of ASA were associated with hearing loss, based on the study by Foch et al. [39]. This is in contrast with evidence from adults, where high doses of salicylates, commonly used as an analgesic, can induce reversible hearing loss [12, 58] through vasoconstriction and ischaemic damage [59]. We hypothesise that this discrepancy may be due to the timing and duration of the exposure, rather than the daily dosage itself. High doses of ASA are typically discontinued in the third trimester due to an increased risk of premature ductal closure [60, 61], whereas low doses are typically administered from before the 16th gestational week and throughout the pregnancy to women at risk of preeclampsia. The extended exposure and possibly higher cumulative doses during critical developmental periods could influence fetal physiology, contributing to the higher risk of CHL.

### 4.5 | Antibiotics

Several antibiotics have well-documented ototoxic effects in children and adults [58, 62]. Aminoglycosides are toxic to inner hair cells of the cochlea, the stria vascularis, marginal cells and spiral ganglion neurons and damage to these structures may contribute to hearing loss [58]. This is in accordance with our findings, which provide some evidence for an association between specific antibiotics, including gentamicin and metronidazole and CHL.

### 4.6 | Antimalarials

Evidence linking antimalarial drug usage in utero to CHL is limited. A systematic review concluded that it might be the case for not all but for some antimalarials, through loss of outer cochlear hair cells and damage of the neural cells in the cochlea [63]. This could explain the varied results, underlining the necessity of examining these drugs separately rather than as a group.

### 4.7 | Antineoplastic Agents

Previous studies have found an association between treatment with platinum analogues for cancer in children and adults that increases the risk of hearing loss [64, 65] through oxidative stress, DNA damage and apoptosis in cochlear cells [66, 67]. A similar mechanism could affect the foetus when exposed antenatally.

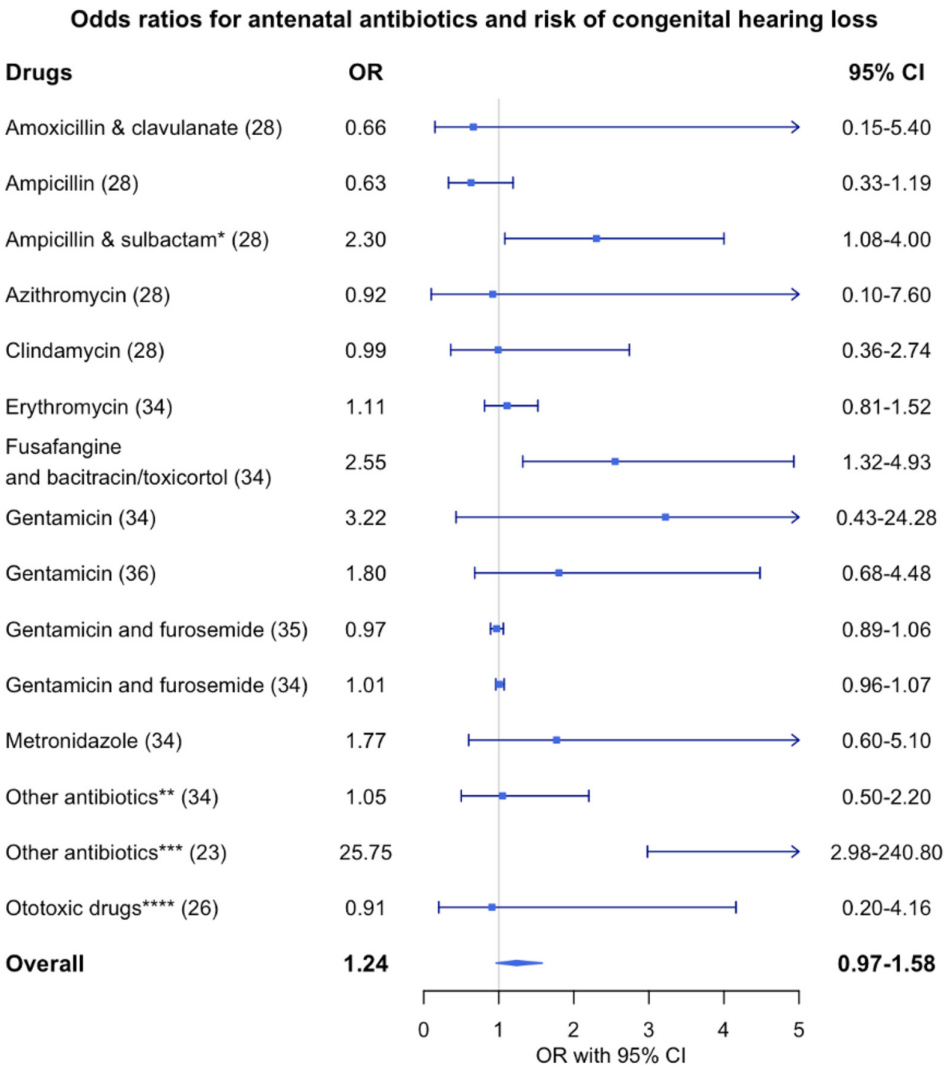


**FIGURE 5** | Forest plot for antibiotics where an OR or an adjusted OR and 95% confidence intervals were either reported or could be calculated using reported numbers. Numbers in parentheses correspond to individual study identifiers. *Reporting that it was no longer significant when adjusted for GA, but without reporting adjusted OR or CIs. **Sulfamethoxazole and trimethoprim, cefotetan, ceftriaxone, cephalexin, cefazolin. ***The authors reported that in this group aminoglycosides (especially amikacin) were the most common. ****Furosemide, dexamethasone, vancomycin, gentamicin, tobramycin. OR: odds ratio. CI: confidence interval.

### 4.8 | Valproic Acid

Valproic acid is teratogenic through possible mechanisms, such as oxidative stress, folate antagonism and histone deacetylase inhibition [68, 69]. However, there is a lack of evidence of its effect on the development of the inner ear and hearing. We identified only one study [39] investigating this association, suggesting strong evidence of increased risk of CHL following pregnancy exposure to valproic acid.

### 4.9 | Dihydroergocryptine

Dopamine receptors expressed in the cochlea indicate they have a role in auditory function; however, evidence on how they affect hearing development is unclear [70]. This could explain why antenatal exposure to dihydroergocryptine could alter hearing.

### 4.10 | Antiretroviral Therapy

For highly active antiretroviral therapy in HIV/AIDS treatment, the study by Fasunla et al. [29] found a strong protective effect (RR = 0.13, 95% CI: 0.05–0.32). We speculate that this is due to a direct therapeutic effect on HIV/AIDS, limiting the negative impact of the disease on the development of the fetal ear.

## 5 | Limitations of the Evidence Included in This Review

### 5.1 | Study Design

The studies in this systematic review were highly heterogeneous in terms of study size, study design and methods of analysis, making it difficult to systematically compare the studies across all parameters. For some of the exposures, the combined

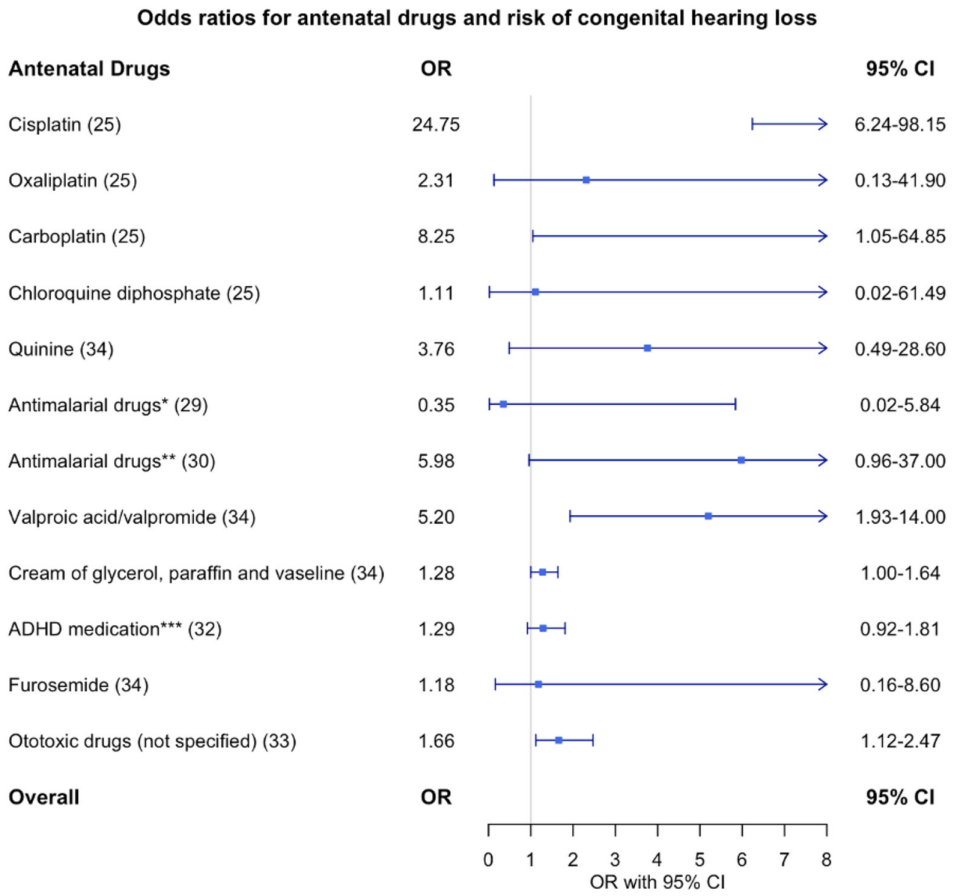


**FIGURE 6** | Forest plot of other drugs or drug combinations where an OR or an adjusted OR and 95% confidence intervals were reported. Numbers in parentheses correspond to individual study identifiers. *Chloroquine, coartem, quinine + clindamycin, primaquine. **66.7% was chloroquine. ***Methylphenidate, amphetamine, dexamphetamine, lisdexamphetamine, modafinil, atomoxetine, clonidine. OR: odds ratio. CI: confidence interval.

evidence was based on very few exposed, limiting the power of the analyses.

Only four of the 16 studies [43–45, 47] were RCTs; 12 were cohort studies [27–37, 46] and five were case–control studies [38–42]. Although RCTs are often considered the gold standard for drawing causal inferences due to their better control for confounders [71], they are not feasible or ethical for investigating antenatal drug exposure and hearing loss as the primary outcome in children.

In studies where HL and/or drug exposure are not the primary outcomes, the study design and methods might be more prone to using less specific and thorough methods for assessing these variables, leading to both misclassification and underreporting—for example, in the study by Azizi et al. [38] it is unclear whether all cases and controls were examined by the same diagnostic methods.

## 5.2 | Age and Method of Diagnosis of Hearing Loss and Follow-Up

This systematic review included studies from 47 different countries. A global survey on newborn hearing screening [72] found that, among these countries, 18 (38.3%) had a universal newborn hearing screening program, 19 (40.4%) did not and for 10 countries (21.3%) the status was unknown. The absence of newborn hearing screening in many countries creates a critical gap in early hearing loss detection. While maternal records often provide detailed information about medical exposures during pregnancy, the lack of early screening means that HL in newborns frequently goes undetected until later in childhood or adulthood. This delay postpones intervention and makes it difficult to link hearing loss to prenatal drug exposure. Over time, this connection becomes less likely to be considered, as other postnatal factors may arise that could contribute to hearing loss.

The definition of hearing loss in all studies ranged from unspecified hearing loss to more specific criteria, such as hearing screening in newborns with OAE and AABR, to more definitive methods like diagnostic ABR and pure-tone audiometry. The test method also varied, from only using single screening methods (e.g., OAE) to using several diagnostic methods in combination. The age of diagnosis ranged from shortly after birth up to several years. The lack of standardisation in defining and diagnosing cases could cause an over- or underrepresentation of cases in each study. Several studies relied on screening tools (e.g., OAE or AABR); this might have produced false positives and very

few of the studies followed up with confirmatory audiometry or ABR to confirm sensorineural hearing loss. The inconsistent follow-up increases the likelihood that some reported cases reflect false-positive findings rather than true CHL. Conversely, these screening tools may also yield false negatives, potentially underestimating the true prevalence of CHL. Further, as diagnosis of hearing loss may be difficult in newborns and younger children and if diagnosed later may be affected by postnatal contributors to hearing impairment, i.e., traumatic hearing loss, a potential bias may have been introduced in studies with longer follow-up.

### 5.3 | Dose and Timing

Teratogenicity may be dose-dependent and related to timing in pregnancy [73], data on drug dosage were limited in the included studies. Furthermore, for the majority of the investigated drugs in the included studies, the trimester of exposure was not reported.

These limitations are likely to have contributed to the inconsistent findings. The prevalence of CHL in the included RCTs ranged from 0.09% to 3% and in the other study designs from 0% to 16.5%. In comparison, the prevalence of CHL requiring treatment is 0.4% in Danish children [74].

### 5.4 | Confounders

To accurately assess the impact of specific drug exposures on hearing, known risk factors for hearing loss must be considered and controlled for in the analysis. Several pre-, peri- and postnatal risk factors associated with early childhood hearing loss include genetic disposition, neonatal intensive care over 5 days, hyperbilirubinaemia requiring exchange transfusion, aminoglycoside administration for over 5 days, congenital infections and several congenital malformations [3]. Many studies included in this systematic review did not systematically assess or exclude children with genetic hearing loss, anatomic malformations or congenital infections, such as CMV. Most included studies adjusted for few or no risk factors (Table 2). Genetic hearing loss and congenital infections were exclusion criteria in this review; however, only one study was excluded based on this criterion and most studies did not investigate these causes, potentially inadvertently including these patient groups. The lack of proper adjustment for known confounders in most studies could lead to spurious associations between antenatal drug exposure and CHL.

Many of the drugs administered perinatally are related to the risk of premature birth. Of 21 included studies, seven studies only included preterm infants or children with low birth weight [31–33, 36, 41, 42, 46]; 13 included either only term or both term and preterm children [27–30, 34, 35, 37, 39, 40, 43–45, 47] and one included children of unknown gestational age at birth [38]. Several studies have found a negative association between gestational age, birth weight and neurodevelopmental impairment [75, 76]. Drugs like steroids, magnesium sulphate and antibiotics, administered to manage preterm birth risks, may therefore be subject to confounding by indication. For all antenatally administered drugs studied, it is crucial to differentiate between the drug's effects and those of the treated condition on CHL, to avoid confounding by indication. This potential for confounding by indication, particularly in high-risk pregnancies requiring medical treatment, is a major inherent limitation in evaluating drug-specific effects.

A further important limitation is that not all studies reported adjusted effect estimates and we therefore used unadjusted effect estimates or calculated crude estimates from available data, potentially increasing the risk of residual confounding. As the unadjusted effect estimates and calculated estimates do not account for known risk factors, the pooled estimates should be interpreted with caution and observed associations may potentially be explained by unmeasured confounders.

### 5.5 | Socioeconomic Factors

None of the included studies considered socioeconomic factors, although this may influence health-seeking behaviour and health literacy, access and drug use in pregnant people and affect child health outcomes.

### 5.6 | Polypharmacy

Most of the included studies did not mention the use of multiple drugs in the interpretation of their results. However challenging, polypharmacy is an important factor when conducting studies on the effects of drug use, as many patients consume multiple medications, either prescribed or over-the-counter. Some associations could therefore possibly be due to drug–drug interactions known to be related to polypharmacy.

In this systematic review and meta-analysis, only 21 studies fulfilled the eligibility criteria; many of these studies were of too small a size to detect an association with a rare outcome such as CHL. Although some found associations between the investigated drugs and CHL, none of these results are unfortunately sufficient to draw clinical conclusions.

## 6 | Strengths and Limitations of the Review Process

### 6.1 | Language Criteria

While screening and evaluating studies in several different languages stated in the Methods section minimises language bias within those languages, it introduces a potential limitation by excluding studies published in other major languages, such as French, Chinese and Spanish. This restriction may potentially have led to the exclusion of relevant findings, reducing the global representativeness of the review. We were able to identify 11 possibly relevant publications that could not be included in the systematic review due to language criteria (Appendix C). Several non-analytical studies that could potentially contain additional important information were excluded due to study design.

## 6.2 | Effect Estimates Not Reported

An important limitation in our meta-analysis was the lack of reporting of effect estimates in some included studies. While the necessary numbers of study participants were provided, we calculated an effect estimate to include in our meta-analysis. This allowed for a more comprehensive inclusion of available data but also led to unadjusted effect estimates, as we were not able to account for potential confounders that the original studies might have adjusted for in their analyses. Therefore, the pooled effect estimates may overestimate the effect of antenatal exposure to the investigated drug on the development of CHL.

## 6.3 | Future Perspectives

The limitations of the review process highlight the need for a cautious interpretation of our results and underline the need for research using population-linked data from multiple countries, although this approach cannot account for over-the-counter drugs or all confounders. Alternatively, conducting cohort or case–control studies using large registries on sensorineural hearing loss or deafness could be considered, recognising that this method may be prone to bias. Future larger clinical studies should account for the many factors associated with exposure (dosage of drug, trimester of exposure) and outcome (other known risk factors associated with CHL) and explicitly adjust for potential confounders, such as congenital CMV, genetic predisposition, maternal infections and socioeconomic factors. Confounding by indication should also be considered, especially in high-risk pregnancies where drug exposure is more common. The methods used to diagnose hearing loss should be standardised, e.g., by performing newborn hearing screening and follow up as indicated using gold standard methods and there should be a sufficient time window for follow up, diagnosing all childhood hearing loss cases while excluding cases caused by other factors later in life. Finally, international collaboration using standardised data collection methods could improve sample sizes and generalisability.

# 7 | Conclusion

This systematic review and meta-analysis identified several antenatal drugs potentially related to CHL and some that may protect against it, including magnesium sulphate and systemic steroids. We found a reverse dose–response effect of ASA, which may be explained by a cumulative dosage effect or that the fetal ear is more susceptible in the late part of the pregnancy. Several antibiotics, including gentamicin, metronidazole and aminoglycosides, may increase the risk of CHL but part of these associations might be explained by confounding by indication due to the underlying disease. Given the widespread use of drugs during pregnancy and the negative impact of hearing loss on child development, large, rigorous studies are warranted.

### Author Contributions

A.S.K., C.Z.S., T.O. and L.H.P. conceptualised the systematic review and designed the methods; L.H.P. supervised the project. The literature screening was carried out by A.S.K. and M.Ø.T. A.S.K. wrote the paper with support from M.Ø.T., C.Z.S., D.P.B., J.E.M., T.O. and L.H.P. All authors approved the final version of this paper.

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### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Appendix A

### Search String Used in PubMed—Search Performed on 25 January 2023 and 5 September 2024

('pregnancy'[MeSH Terms] OR 'pregnan*'[Text Word] OR 'gestation*'[Text Word] OR 'matern*'[Text Word]) AND ('chemically induced disorders'[MeSH Terms] OR 'drug therapy'[MeSH Terms] OR 'maternal exposure'[MeSH Terms] OR 'teratogens'[MeSH Terms] OR 'teratogenesis'[MeSH Terms] OR 'teratology'[MeSH Terms] OR 'maternal fetal exchange'[MeSH Terms] OR 'ototoxicity'[MeSH Terms] OR 'abnormalities, drug induced'[MeSH Terms] OR 'chemically induced'[MeSH Subheading] OR 'pharmacotherap*'[Text Word] OR 'teratolog*'[Text Word] OR 'maternal exposure*'[Text Word] OR 'intrauterine exposure*'[Text Word] OR 'in utero exposure*'[Text Word] OR 'transplacental exposure*'[Text Word] OR 'maternal fetal exchange*'[Text Word] OR 'vestibulotoxic*'[Text Word] OR 'ototoxic*'[Text Word] OR 'cochleotoxic*'[Text Word] OR 'drug related'[Text Word] OR 'drug induced'[Text Word] OR 'medication induced'[Text Word] OR 'chemically induced'[Text Word] OR 'drug exposure*'[Text Word]) AND ('hearing loss'[MeSH Terms] OR 'hearing loss, unilateral'[MeSH Terms] OR 'hearing loss, bilateral'[MeSH Terms] OR 'hearing loss, sensorineural'[MeSH Terms] OR 'deafness'[MeSH Terms] OR 'ear, inner'[MeSH Terms] OR 'hearing impair*'[Text Word] OR 'deafness*'[Text Word] OR 'hearing loss*'[Text Word] OR 'hypoacus*'[Text Word]) AND ('infan*'[Text Word] OR 'newborn*'[Text Word] OR 'new born*'[Text Word] OR 'perinat*'[Text Word] OR 'neonat*'[Text Word] OR 'baby'[Text Word] OR 'babies'[Text Word] OR 'toddler*'[Text Word] OR 'minors*'[Text Word] OR 'boy'[Text Word] OR 'boys'[Text Word] OR 'boyhood'[Text Word] OR 'girl*'[Text Word] OR 'kid'[Text Word] OR 'kids'[Text Word] OR 'child'[Text Word] OR 'child*'[Text Word] OR 'children*'[Text Word] OR 'schoolchild*'[Text Word] OR 'school child'[Text Word] OR 'school child*'[Text Word] OR 'juvenil*'[Text Word] OR 'youth*'[Text Word] OR 'teen*'[Text Word] OR 'underage*'[Text Word] OR 'paediatrics'[MeSH Terms] OR 'paediatric*'[Text Word] OR 'paediatric*'[Text Word] OR 'peadiatric*'[All Fields] OR 'school'[Text Word] OR 'school*'[Text Word] OR 'prematur*'[Text Word] OR 'preterm*'[Text Word])

## Appendix B

### Possibly Relevant Case Reports and Case Series

1. Barbero P, Lotersztein V, Bronberg R, Perez M, Alba L. Acitretin embryopathy: a case report. Birth Defects Res A Clin Mol Teratol. 2004;70 [10]:831–3.

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## Appendix C

### Possibly Relevant Reports in Other Languages

#### German

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#### Spanish

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#### Polish

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#### Romanian

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