REVIEW Open Access

Effectiveness of interventions to screen and manage infections during pregnancy on reducing stillbirths: a review

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associated with an infection, while only 2% of term stillbirths were infection-related [4]. Direct infection, placental damage, and severe maternal illness are the most commonly reported mechanisms by which infections may cause stillbirths [5].

Among infections, various organisms have been implicated as causing stillbirth, including bacteria, viruses, protozoa, helminthes and fungi [6]. Syphilis remains an avoidable cause of infection related stillbirths Plasmodium falciparum malaria has been associated with stillbirth especially in primigravidas owing to its high prevalence and extensive placental damage [7]. TORCH infections, which include Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes infections, are infections during pregnancy that are associated with congenital anomalies and possibly stillbirths [8,9]. Most of the TORCH infections cause mild maternal morbidity, but have serious fetal consequences [8]. Periodontal disease is another important chronic infectious disease of humans which is commonly present in pregnancy [10]. It's prevalence range from 35 to 100%

overall quality of evidence of an outcome was also assessed and graded according to the CHERG adaptation of the GRADE technique [20]. This assessment was based on three components: 1) the volume and consistency of the evidence; 2) the size of the effect, or risk ratio; and 3) the strength of the statistical evidence for an association between the intervention and outcome, as reflected by the p-value [20,21].

Quantitative data synthesis

We performed meta-analyses where data were available from more than one study for an outcome. The primary outcomes of interest were stillbirths and perinatal mortality. The reason for including perinatal mortality as an outcome was based on the fact most of the studies do not report disaggregated data for stillbirths but do that by combining stillbirths with early neonatal deaths (i.e. perinatal mortality). This exercise is in accordance with the basics of CHERG rules which take into account the biological plausibility of the intervention and limitations of measured outcomes [20]. For example studies may not collect the outcome of interest (e.g., pneumonia mortality) but may collect data on severity of disease (e.g. hospital admission). CHERG rules will thus consider a range of outcomes (where necessary) and choose a point estimate which is the most conservative and represent the expected effect of the intervention based on biological plausibility [20].

We used dichotomous values for pooling the data, except for insecticide-treated mosquito nets (ITNs) where data were pooled by generic inverse variance method of meta-analysis. The summary estimates were described as relative risk (RR) or Odd ratios (OR) with 95 % confidence interval (CI). The assessment of statistical heterogeneity among trials pooled data was done by visual inspection (i.e. the overlap of the confidence intervals among the studies), Chi square (P-value) and I^2 values. An I^2 value greater than 50% was taken to represent substantial heterogeneity in the pooled data. In case of substantial heterogeneity, causes were explored by sensitivity analysis. A random effects model was used for the meta-analysis in case of substantial heterogeneity. All the analyses were conducted using Review Manager 5 [22]. We applied the CHERG Rules for Evidence Review to recommend a final estimate for reduction in stillbirth from interventions for a specific maternal infection during pregnancy [20].

Results

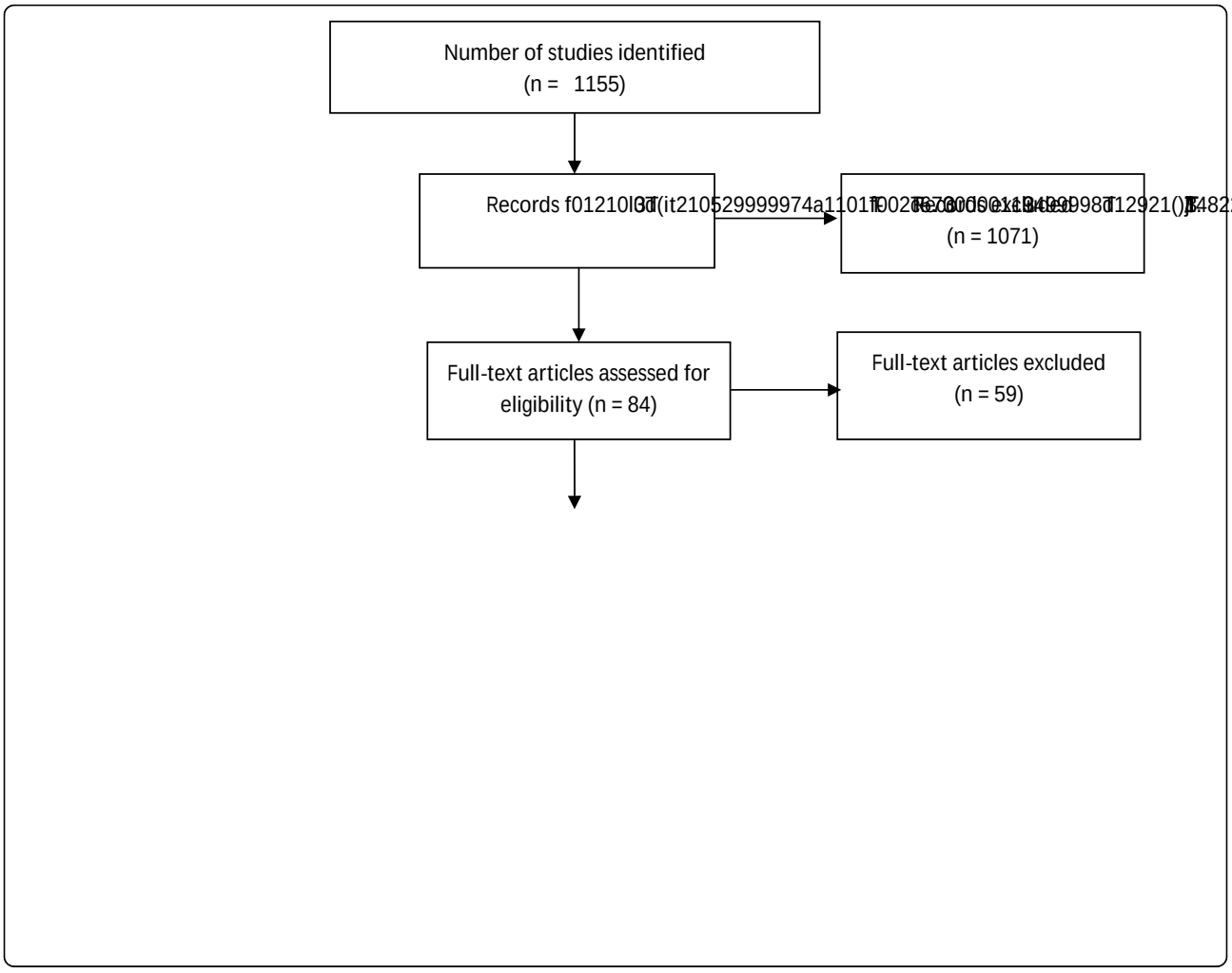
A total of 1155 hits were identified from our search strategies (Figure 1). After screening the titles and abstracts, 84 studies were initially considered eligible. We thoroughly reviewed the abstracts and full texts, where available and 25 studies were selected for inclusion in the meta-analyses (Additional file 3). Additional File 4 outlines the characteristics of included studies.

Syphilis

No randomized trials were found for treatment of syphilis and its effect on prevention on stillbirths. However, a random-effects meta-analysis of 8 observation studies by Blencowe et al. in this supplement has shown an estimated reduction of 80 % (RR 0.20, 95% CI 0.12 - 0.34) in syphilis related stillbirths with use of penicillin [23]. It is however important to note that none of the included studies in this meta-analysis made any attempt to control for systematic differences between treated and untreated women (confounding). For example women not attending antenatal clinic and/ or not complying with complex penicillin treatment regimens may differ in their risk profiles for stillbirth, preterm delivery and neonatal death from fully compliant infected women.

Malaria

There were 6 randomized controlled trials that addressed prevention of malaria during pregnancy by IPTp or ITN. As the effects of IPTp and ITNs used during pregnancy have similar causal pathways for preventing stillbirth, and as there is no evidence of a synergistic effect between them [24], the data were pooled irrespective of method used. The combined results show 22% reduction in stillbirths (RR = 0.78; 95% CI: 0.59 – 1.03) (Figure 2). A subgroup analysis of three trials [25-27] that evaluated the impact of IPTp with sulfadoxine-pyri-



Chorioamnionitis

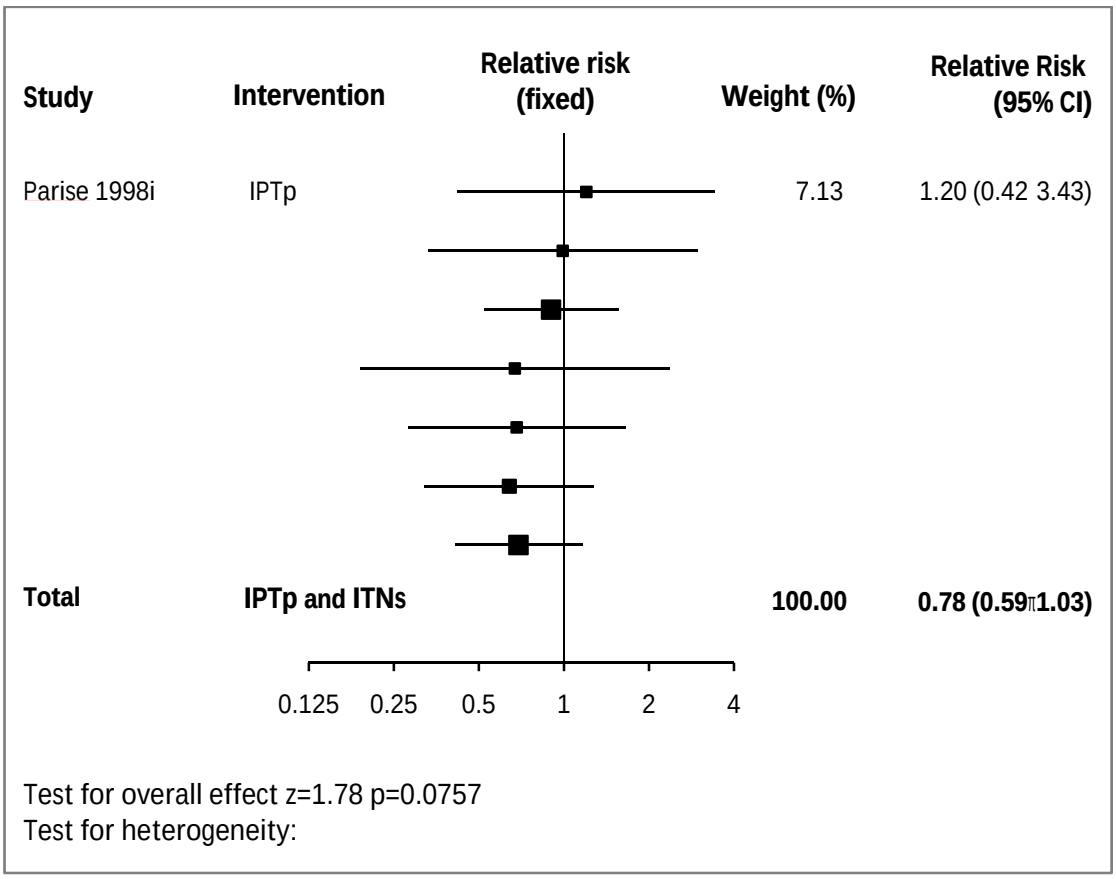
The Cochrane review by Kenyon et al. [38] studies the use of antibiotics for preterm premature rupture of membrane (pPROM) and reports a statistically significant 43% reduction in risk of chorioamnionitis (RR = 0.57; 95% CI: 0.37 – 0.86). There was however no impact on perinatal mortality/or fetal death before discharge (RR = 0.90; 95% CI: 0.74 – 1.10). Another Cochrane review by Flenady and King [39] on antibiotics for PROM at or near term showed no impact of antibiotics on chorioamnionitis (RR = 0.60; 95% CI: 0.30 – 1.18) nor on perinatal mortality (RR = 0.98; 95% CI: 0.14 – 6.89). There were no separate data on stillbirth.

Asymptomatic bacteriuria

Studies have looked at the association between asymptomatic bacteriuria during pregnancy and perinatal mortality. In a study performed from 1972 to 1979, pregnant women with asymptomatic bacteriuria had a significantly higher perinatal mortality (64.9 vs. 15.6, p < 0.001) [40]. However, a more recent population-based retrospective study by Sheiner et al. showed that patients with asymptomatic bacteriuria, in whom antibiotic treatment was recommended, had similar perinatal mortality rates compared to women without asymptomatic bacteriuria (1.5% vs. 1.4%, P = 0.707) [41]

Periodontal disease

While published data convincingly display a link between periodontal disease and stillbirth incidence [10,15,42-44], there is limited literature on interventions for periodontal disease and impact on stillbirths. The systematic review by Polyzos et al. [14] studied the impact of periodontal care during pregnancy and found a non-significant effect on abortions and stillbirths (OR = 0.73; 95% CI: 0.41 to 1.31). In a recent randomized controlled trial, 1082 pregnant women with periodontal disease were allocated either to receive periodontal treatment in mid-pregnancy or after delivery. There were four unexplained stillbirths in the control group


Study
Intervention
Relative risk (fixed)
Weight (%)
Relative Risk (95% CI)
Parise 1998i
IPTp
7.13
1.20 (0.42 3.43)
Total
IPTp and ITNs
100.00
0.78 (0.59π1.03)
0.125
0.25
0.5
1
2
4
Test for overall effect z=1.78 p=0.0757
Test for heterogeneity:

and no losses in the treated group, but the results were non-significant (P = 0.12) [45]. A meta-analysis on periodontal care during pregnancy versus treatment after birth based on two studies [13,45] has shown a 70% sig-

Herpes simplex infections have also been described as a cause of fetal death [54]. However, Herpes simplex viruses rarely, if ever, cause stillbirth, likely because the virus rarely causes an intrauterine infection. Neonatal infections are acquired during fetal passage through an infected birth canal. There is a paucity of evidence with regards to the significance of Herpes virus in causing stillbirths. Also, whether treatment and prevention have a significant positive impact on adverse pregnancy outcomes remains elusive.

Tables 1 - 4 outline the quality grading of the overall evidence of all the interventions considered in this review and described below in the same order.

Discussion

Syphilis remains a major cause of avoidable perinatal death in many countries despite being treatable, and despite the WHO recommendation that all pregnant women be tested as part of routine antenatal care. Most studies report syphilis to have a relative risk of stillbirth in the range of 2 to 5; however, a Tanzanian study reported a relative risk of 18 for women with active syphilis [55]. In some areas of sub-Saharan Africa, about 25% to 50% of all stillbirths were associated with syphilis [56]. Syphilis also contributes to stillbirths in other areas of the world including Russia, Asia and South America [57]. The findings of a meta-analysis by Blencowe et al. correlate with the above observations and shows that treatment of syphilis during pregnancy can significantly reduce syphilis related stillbirths by up to 80 % [23]. This

death were ranked as having a ‘moderate’ grade of evidence. Included studies had limitations, including a low recruitment response and unclear allocation concealment. The evidence to date does not suggest any benefit of screening and treating all pregnant women for asymptomatic BV to prevent stillbirths. Although antibiotic treatment targeting bacterial vaginosis may be of value in some women [37], further research needs to be

The review employs a comprehensive search strategy thus increasing the chance of retrieving all relevant studies. Mainly randomized controlled and quasi randomized trials have been considered that provide a high quality level of evidence. It is however important to note that data from interventional studies were scarce. A high quality research agenda addressing the contribution of infections to stillbirth, especially in developing countries, is needed to reduce stillbirths worldwide. At present, large gaps exist in the growing list of stillbirth risk factors, especially those that are infection related [72]. The clearest evidence of impact on stillbirth prevention is adequate prevention and treatment of infections such as syphilis and possibly malaria. Other potential causes of stillbirth including HIV, bacterial vaginosis, ascending infections and TORCH infections need to be investigated further to help establish the role of prevention/treatment and its subsequent impact on stillbirth reduction [72]. Efficacious interventions exist for certain maternal infections and conditions for which the evidence of plausible benefit is not very clear. Therefore, efforts need to be geared to conduct high quality trials for us to ascertain the full extent of the relation between interventions and their potential to reduce stillbirths.

Conclusions

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